CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-306

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	NDA
Application Number(s)	21-306
Material Submitted	Safety Update Safety Analysis of Late Onset Application Site Skin Reactions
Submit Date	29 March 2010
Received Date	29 March 2010
Division / Office	Division of Anesthesia and Analgesia Products
Reviewer	Robert A. Levin, M.D.
Team Leader	Robert Shibuya, M.D.
Project Manager	Matt Sullivan
Review Completion Date	08 April 2010
Established Name	Buprenorphine Transdermal System
(Proposed) Trade Name	Butrans™
Therapeutic Class	Opioid
Indication(s)	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
Applicant	Purdue Pharma L.P.

Background

NDA 22-306, buprenorphine transdermal system (Butrans) for the indication for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time was submitted September 25, 2009. Subsequent to completing my review of this NDA, the applicant submitted on March 29, 2010 the Safety Update.

In addition a postmarketing safety analysis of late onset application site reactions was conducted in response to a report of severe, late onset application site reactions associated with use of Norspan/Butrans in the United Kingdom.

Safety Update

This addendum includes a review of the safety update comprised of new data from three sources:

1. Safety data from study BUP3025, the only clinical study that was ongoing at the time of the database cutoff for the ISS. The clinical study has now been completed.
2. Case reports from literature published between March 1, 2009 (the cutoff date for the ISS) and September 30, 2009 (the cutoff date for this update)
3. Reports of postmarketing safety data received between May 1, 2009 and September 30, 2009.

BUP3025

No new deaths were reported in BUP3025; the one death that occurred was previously reported and reviewed. The incidence of nonfatal SAEs was similar to that previously observed with no significant change in incidence in any major diagnostic category with the exception of one SAE due to an allergic reaction described below.

Allergic Reaction SAE

Subject 0008030, a 47 year old woman enrolled in Study BUP3025 due to osteoarthritis of the left knee developed an allergic reaction consisting of hives on her face and neck with pruritus and slight left eyelid swelling six days after starting Butrans. The Butrans was stopped and the subject was treated with Benadryl and appeared to improve. However, the next day she was admitted to the hospital with a swollen tongue and treated with IV steroids. She was discharged on oral steroids and her allergic reaction resolved.

Impression

Local skin reactions related to the use of Butrans are not new or unexpected. However, the occurrence of the above anaphylactic/anaphylactoid type reaction is potentially life-threatening and warrants inclusion in the label.

Postmarketing Safety Data

The applicant reports that the available worldwide postmarketing experience with transdermal formulations of buprenorphine was reviewed for the period of 01-May-2009 to 30-Sep-2009. The most frequently reported adverse events included: application site reactions, nausea, vomiting, pruritus, dizziness, somnolence and drug ineffective. The applicant provided table below summarizes the most frequently reported application site AEs (an individual may have more than one preferred term).

Table 69. Most Frequently Reported Postmarketing Application Site AEs for the period of 01-May-2009 through 30-Sep-2009 Associated with the Use of BuTrans, Norspan and Transtec

Preferred Term	No. of Cases
Application site erythema	87
Application site pruritus	65
Application site rash	40
Erythema	34
Pruritus	31
Skin reaction	26
Rash	24
Application site reaction	21
Application site irritation	20
Application site vesicles	20
Application site pain	19
Skin irritation	17
Application site hypersensitivity	13
Application site inflammation	12
Application site dryness	11
Dermatitis contact	11

The latency between time of product exposure and event onset was reported in 29 cases:

- 10 cases occurred within 1 week
- 3 cases occurred within 1-2 weeks
- 6 cases occurred within 2-3 months
- 3 cases occurred within 6-12 months
- 5 cases occurred within 6-12 months
- 2 cases occurred after12 months

The postmarketing reports did not reveal any new safety issues not already known to be associated with buprenorphine. The development of late onset application reactions is discussed at the end of this review.

Case Reports from the Worldwide Literature

The applicant reports that a review of 13 case report publications from 01-March-2009 through 30-Sep-2009 revealed no unexpected adverse events. From my review of the summaries of these 13 case reports, I find no new unexpected safety information.

Late Onset Application Site Reactions

A postmarketing safety analysis of late onset application site reactions was conducted in response to a report of severe, late onset application site reactions associated with use of Norspan/Butrans in the United Kingdom. The safety analysis dated 12-Feb-2010 identified 1,335 cases (through 27-Aug-2009) involving 2,637 skin associated adverse events in patients treated with buprenorphine in the international drug safety database. According to the applicant the majority of the cases lacked latency data but some which were severe occurred weeks to months after initiating patch. Many of the cases were consistent with allergic contact dermatitis. The applicant also identified four articles describing a total of nine case reports of allergic contact dermatitis, confirmed by patch testing.

Of the 1335 cases, 183 cases contained latency information. Approximately 45% of the cases with latency data had skin reactions within the first 10 days and 36% within the first day. However, 55% of patch site reactions occurred after 10 days and approximately 24% occurred after 100 days of buprenorphine treatment. The most frequent patch reactions included application site erythema and pruritus. The applicant noted that there were cases where more than three inflammatory type events occurred indicating symptoms typical for contact dermatitis.

The applicant concluded that the Company Core Data Sheet (CCDS) be updated to include two additional adverse events, “application site dermatitis” and “contact dermatitis.” The CCDS should also be updated with the statement, “In some cases delayed local allergic reactions occurred with marked signs of inflammation. In such cases treatment with Butrans should be terminated.”

The applicant has recommended the following changes to the package insert:

- Addition of two adverse events: “application site dermatitis” and “contact dermatitis”

- Addition of following precaution: (b) (4) [redacted] ."

Conclusion

Review of the Safety Update does not change my overall impression of the safety adverse event profile. However, an allergic reaction in one subject appeared to be potentially life-threatening and required treatment with IV steroids. The symptoms appeared to progress even after removal of the patch and treatment with benadryl. In my initial review of the NDA many cases of local skin reactions were identified but there were no cases of anaphylaxis/anaphylactoid reactions reported. The possibility of life-threatening anaphylaxis/anaphylactoid reactions should be included in the label.

In addition I concur with the recommendations of the applicant to include under adverse events: "application site dermatitis" and "contact dermatitis." And the following precaution: (b) (4) [redacted]

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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

/s/

ROBERT A LEVIN
05/20/2010

ROBERT B SHIBUYA
05/20/2010
I concur with Dr. Levin's review.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-306
Priority or Standard	Standard
Submit Date(s)	25 September 2009
Received Date(s)	30 September 2009
PDUFA Goal Date	30 March 2010
Division / Office	Division of Anesthesia, Analgesia and Rheumatology Products
Reviewer Name(s)	Robert A. Levin, M.D.
Review Completion Date	03 March 2010
Established Name	Buprenorphine Transdermal System
(Proposed) Trade Name	BuTrans™
Therapeutic Class	Opioid
Applicant	Purdue Pharma L.P.
Formulation(s)	BuTrans 5 mcg/h (45 by 45 mm matrix patch) BuTrans 10 mcg/h (45 by 68 mm matrix patch) BuTrans 20 mcg/h (72 by 72 mm matrix patch)
Dosing Regimen	Opioid-naïve patients start with

	BuTrans 5 mcg/h For conversion from other opioids to BuTrans start with BuTrans 10 mcg/h Titration should not be before 3 days of wear to a maximium dose of 20 mcg/h
Indication(s)	For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time
Intended Population(s)	Adult patients who required extended term analgesia

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an **Approval** action for the subject of the current application, BuTrans™ [buprenorphine transdermal system (BTDS)] for the indication for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Including data from the initial NDA submission, this application contains sufficient data from 35 clinical studies. The current complete response to the Not Approvable Letter includes two adequate and well-controlled Phase 3 studies (BUP3024 and BUP3015) that support a finding of efficacy for the above indication.

This NDA was originally submitted November 3, 2000. A 62-item Not Approvable Letter was issued August 31, 2001. The applicant believes that it has adequately addressed these deficiencies either based on recommendations in the Not Approvable Letter or based on changes in Division policy occurring after the Not Approvable Letter was issued. The majority of deficiencies were related to the nonclinical program. However, there were significant efficacy and safety deficiencies identified in the 2000-1 review cycle summarized below.

Deficiency #55 stated that the applicant had not provided substantial evidence of efficacy and results of additional adequate and well controlled studies of appropriate duration would be required. The applicant has successfully addressed this deficiency with two new pivotal studies in chronic low back pain that demonstrate a statistically significant reduction in pain at three months, measured on an 11-point numerical rating scale.

Deficiency #56 stated that the safety database and safety analyses were difficult to interpret and that safety data would need to be presented in a clear manner. The applicant has provided an appropriate integrated summary of safety that allows for meaningful interpretation of safety data. The overall safety profile of this new BTDS formulation of buprenorphine in general is similar to other opioids and patches but specific safety findings are summarized at the end of this section.

Deficiency #35 C requested a summary, from the clinical trials, of drug product complaints relating to the adhesiveness of the patches. The applicant reported that only one patch fell off in a subject who was perspiring while mowing his lawn and the patch would not stay on with taping. In study BUP3024 approximately 11% of subjects reported a problem with the patch adhesion, occurring more often with larger patches. In the Phase 1 studies assessing patch adhesiveness

there was buckling with larger patches, several smaller patches fell off and some patches required taping. Problems were more frequent toward the end of 7-day wear. The problem with patch adhesiveness can be adequately managed by taping the edges of the patch or (b) (4) as described in the proposed label.

Deficiency #52 required a reanalysis of the data from the hepatic impairment study by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment. This had been completed and reviewed by the clinical pharmacologist.

Deficiency #54 required data to address concerns from drug-drug interaction between CYP450 inhibitors and BTDS. This issue has been adequately addressed and reviewed by the clinical pharmacologist.

Deficiency #57 required that all safety measures include analyses in the ISS that focus on the relationship between BTDS dose and outcome. The applicant has included these analyses in the current submission.

Deficiency #58 required that the applicant include in the ISS analyses of electrocardiographic intervals. The applicant has analyzed the ECG data and in addition submitted a thorough QT study.

Deficiency #59 required information to justify a dose titration interval of three days. This deficiency was resolved prior to this submission when the FDA agreed that three days was an appropriate dose titration interval.

Deficiency #60 required a repeat abuse liability study to correct failures in the design of the first study. However, in the April 2, 2002 End-of-Review meeting with the applicant, the FDA agreed that an additional human abuse liability study would not be needed if buprenorhpine was placed in Schedule III. Since buprenorphine was reclassified to Schedule III from Schedule V an abuse liability study is no longer required. This deficiency also included the request to characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs. During the April 2, 2002 meeting, the Division indicated that the buccal absorption data provided was appropriate to address the concerns but a right of reference to access this data was needed.

Deficiency #61 was concerned with the potential for significant diversion of buprenorphine due to the large residual amount of buprenorphine remaining in the patch after use. The FDA requested that this risk be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the residual

buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix. In the April 2, 2002 End-of-Review Meeting, the Agency indicated that the current formulation could be approved (if all other issues were resolved) because there are no set standards for residual drugs in the patch. Given this statement by the FDA, this deficiency is no longer an approvable issue. The amount of residual buprenorphine following patch use is further discussed in the risk benefit assessment.

Deficiency #62 required that the patch have adequate adhesion characteristics since lack of adequate adhesion may affect the efficacy and diversion potential of this product. As discussed in response to Deficiency #35 use of tape to secure the patch is acceptable for those subjects where the patch becomes loose. There is no indication of patches suddenly falling off.

For a summary of potential safety issues the reader is referred to Section 1.2.

1.2 Risk Benefit Assessment

Benefit
Efficacy was demonstrated in two adequate and well-controlled (i.e., randomized, double-blind, placebo- or active-controlled) chronic back pain studies (BUP3024 and BUP 3015). There was statistically significant less pain at three months in subjects with chronic pain receiving BTDS compared to control. Efficacy was also supported by secondary endpoints.

Risk
The 6,042 subjects treated with BTDS and duration of exposure (183 subjects for ≥ 1 year) were adequate to assess the use of BTDS for the management of chronic pain. There was a greater incidence of deaths in the BTDS treatment group (0.2%) compared to placebo (0.09%) but when corrected for patient years the rates were similar (approximately 12.2 versus 9.4 deaths per 1,000 subject-years for BTDS and placebo respectively). There were 10 cardiac related deaths in the BTDS group and none in the placebo group but there were over six times more subjects in the BTDS than placebo group. For many deaths there was insufficient information to determine an exact etiology. There were medical comorbidities in all the cardiac deaths that could explain the death but BTDS-treatment could not be completely excluded as a possible contributing factor for several deaths. However, given the minimal QTcI prolongation in clinical trials (<10 msec), the known safety profile of buprenorphine, and the patient population studied (elderly with multiple comorbidities), there does not appear to be an increased risk for cardiac deaths. The non-cardiac deaths were unrelated to BTDs with the possible exception of drowning in a subject abusing cocaine.

The following safety issues were identified:

Respiratory Depression

There were three nonfatal SAEs and two deaths coded as respiratory depression. Two of the SAEs were unlikely to be related to BTDS. The third nonfatal SAE of respiratory depression may have been related to the use of a heating pad and concomitant use of a benzodiazepine. There were confounding medical issues in the two deaths making it impossible to determine an exact cause but there was no strong evidence to suggest that BTDS played a contributory role. One adverse event of respiratory depression not considered an SAE was of concern due to the severity of the respiratory depression that occurred in an opioid naïve subject treated with BTDS 20 who also received promethazine for nausea.

There is no evidence of severe respiratory depression in the BTDS development program when the product was used as recommended. As with all opioids respiratory depression is a concern. The proposed label adequately addresses the respiratory issues discussed above. There is sufficient warning in the label against using a heating pad and concomitant CNS depressants. Opioid naïve subjects are to start treatment with BTDS 5 and titrate no sooner than every three days.

In the original NDA review there was concern about respiratory depression in the immediate postoperative period. The additional studies submitted for this review do not study BTDS in the postoperative period; therefore the recommendation remains that postoperative subjects not be treated with BTDS.

Overdose

There were no cases of intentional overdose reported. There was one case of respiratory depression, also coded as overdose occurring in a subject who was using a heating pad and concomitant benzodiazepines. No cases of overdose were reported during the development program when the product was used as recommended. However, as with any opioid there is a risk of overdose. In fact the large amount of residual buprenorphine remaining after use may increase the risk of overdose if the patch is abused.

Drug Abuse

Eleven subjects were suspected of drug abuse. Of these 11 subjects, it was observed that 3 abused cannabis, 2 abused cocaine, 3 abused OxyIR, 2 abused Vicodin, and 1 abused Percocet/Soma. One subject who drowned tested positive for cocaine. As with all opioids the potential for abuse with a fatal outcome exists but there was no evidence from the development program the Butrans is more likely to be abused.

Withdrawal

There were 17 subjects reported to have drug withdrawal syndrome including: 15 of 6042 (0.25%) BTDS-treated subjects and 2 of 1085 (0.18%) placebo-treated subjects. One subject was hospitalized for "Drug withdrawal syndrome" nine days after discontinuing treatment with BTDS 20 following a 5-month exposure. It is well known that opioids can lead to withdrawal symptoms when discontinued abruptly and BTDS is no exception. The label adequately addresses the issue of potential withdrawal:

> When the patient no longer requires therapy with BuTrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

Residual buprenorphine: The amount of residual buprenorphine remaining (b) (4) in the patch after use poses a significant safety risk as well as abuse risk. In the development program there was no evidence of tampering with the patch to remove residual opioid. However, subjects with a history of drug abuse were excluded from the chronic pain studies. The applicant has reduced the potential for inadvertent exposure to children by providing two methods for ensuring safe disposal of used patches: fold-and-flush disposal method and occlusive-type disposal system when the primary fold-and-flush method is not possible. It is unclear how effective the occlusive-type disposal system will be in preventing children from accessing the drug since with enough effort the system can be defeated.

I believe that the original requirement for patch modification was appropriate but that the risk can still be adequately managed with a proper Risk Evaluation and Mitigation Strategy (REMS). The applicant has theoretically reduced the potential for inadvertent exposure to children by providing two methods for ensuring safe disposal of used patches: fold-and-flush disposal method and occlusive-type disposal system when the primary fold-and-flush method is not possible.

Need for Risk Management: A Risk Evaluation and Mitigation Strategies (REMS) program will be necessary to address the issues of residual buprenorphine in the patch after use in addition to the typical problems of abuse encountered with opioid use.

Pancreatitis
Four SAEs due to pancreatitis were identified but no definite conclusions could be made regarding the role of BTDS in these individual cases. However, it is known that opioids can increase sphincter of Oddi pressure which has been implicated as a cause of pancreatitis. Given a theoretical basis for opioids causing pancreatitis and the increased incidence of pancreatitis observed in

BTDS-treated subjects compared to placebo, it appears reasonable to conclude that there may be an association between BTDS and pancreatitis. The proposed label with the standard opioid warning appears adequate to address this risk:

> Buprenorphine may cause spasm of the sphincter of Oddi. Use with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase.

QT Interval Prolongation/Cardiac

In the thorough QT study a supratherapeutic dose of BTDS (40 mcg/h) prolonged QTcI by 9.2 ms (90% CI:5.2-13.3), an effect similar to that of 400 mg of moxifloxacin used in the same study. The therapeutic dose of BTDS 10 had no clinically meaningful effect on QTcI. The BTDS 20 dose was not studied but the exposure with the supratherapuetic dose would be twice that of the BTDS 20 dose. The final consult from the Division of Cardio-Renal Products is pending but their preliminary findings note that QTc outliers, QTc duration or QTc increases over baseline data showed a modest unbalance between placebo and BTDS arms, in particular at the highest dose studed (BTDS 20). In none of the groups analyzed mean changes from baseline in QTc were over 5.7 ms. The highest effect was seen in the BTDS 20 arm. There was a low incidence rate of AEs and SAEs related to E14 ICH Guidance even at the highest dose tested. Syncope was the AE and SAE with higher rate (0.1-0.3%) that was not necessarily linked to QT prolongation. The cardiology reviewer performed an MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration including PR, QRS and QT events and arrhythmias. No signals for Torsades and QT prolongation were detected. I reviewed the two cases of ventricular tachycardia and determined that they were unrelated to BTDS. There were six cases of SAEs involving seizures and syncope: 2 cases were unrelated to BTDS and for 4 cases there was insufficient information to make a determination but there was no convincing evidence that BTDS contributed to the event.

Although the risk of a proarrhythmic effect is low based on the QT data the label appropriately informs prescribers to consider these observations when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide) should consider the risk of adding BuTrans treatment.

Serious Adverse Events of the Skin

Five subjects (<0.1%) of the 6042 BTDS-treated subjects developed serious adverse events of the skin. One subject developed erytherma multiforme unrelated to BTDS. Four subjects developed either a rash or skin ulcers/necrosis. BTDS was probably the cause for only one of these subjects who developed a generalized rash requiring hospitalization. BTDS was not the cause for two subjects with ulcers/necrosis and unlikely the cause of one subject with a rash starting after two days on nambutone. There were frequent local skin irritations but this would be expected with use of a patch.

Laboratory Findings

Potentially elevated LFTs: Review of the shift tables from normal to high for LFTs suggested a possible weak signal for elevated LFTs. The applicant reports that no subjects were discontinued form the study due to elevated LFTs and conducted an analysis of adverse events coded to liver related signs and symptoms and found the rates were similar during the double-blind period of the controlled chronic pain studies (Group A). The incidence of all AEs under this subSMQ for BTDS-treated subjects was 0.6%, placebo-treated subjects 0.4%, and OxyIR-treated subjects 1.1%. There was one case meeting the definition of Hy's law that was due to acute cholecystitis. The issue is adequately addressed with the information in the proposed label:

> Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected.

Hematologic Laboratory Changes: Subjects treated with BTDS appear to have slightly lower hemoglobin, WBC and ANC values. This effect also appears to be present with other opioids but may be greater with BTDS on ANC. These changes are not felt to be clinically relevant.

Risk Benefit Analysis

The most serious risks of respiratory depression, addiction, overdose identified with BTDS are known to occur with other opioids. There is no evidence that they

occur more frequently with BTDS. The risk due to QT prolongation can be appropriately managed by excluding subjects at increased risk for QT related cardiac events.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As with other extended-release opioids, a risk evaluation and mitigation strategies (REMS) program will be necessary to ensure that the benefits of the product mitigate the risks of overdose, abuse, misuse, and addiction.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant will have to fulfill the requirements of the Pediatric Research Equity Act. This product was brought to the Pediatric Review Committee (PeRC) on 17-Feb-2010. Purdue proposed conducting (b) (4) studies: (b) (4)

The Division recommended that this product be studied in pediatric patients age 7 years to 16 years; the Division does not believe that the number of pediatric patients below the age of 7 is sufficient to study for this indication. Also, consistent with the conclusions of the December 3, 2009 Pediatric Analgesic Clinical Trials Workshop convened by the Division, demonstration of efficacy for patients age 7 to 16 is not necessary; efficacy for this opioid can be extrapolated from studies in adults. The Division will require PK and safety data for this product. PeRC agreed with the Division's recommendations as outlined above.

2 Introduction and Regulatory Background

BuTrans™ [buprenorphine transdermal system (BTDS)] is a transdermal formulation of buprenorphine, a Scehdule III controlled substance. The product is intended to provide continuous systemic delivery of buprenorphine over a period of 7 days in patients with moderate to severe pain requiring continuous, around-the-clock opioid treatment for an extended period of time. This NDA was originally submitted November 3, 2000. A Not Approvable Letter was issued August 31, 2001 as a result of 62 deficiencies. Study BUP3025 was conducted under a Special Protocol Agreement.

2.1 Product Information

Trade Name (established name): BuTrans™ [buprenorphine transdermal system (BTDS)]

Indication

Approved Indications

Buprenorphine is approved in a sublingual formulation for the treatment of opioid dependence and an IV/IM formulation for the treatment of moderate to severe pain.

Proposed Indication

"Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time"

Dose Regimen

Approved Dosing Regimen for Treatment of Opioid Dependence

The recommended dose is buprenorphine HCL sublingual tablets as a single daily dose in the range of 12 to 16 mg/day. Buprenorphine HCL sublingual tablets contain no naloxone and is preferred for use during induction. Following induction buprenorphine and naloxone HCL sublingual tablets, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The safety and effectiveness of buprenorphine HCL sublingual tablets in patients below the age of 16 have not been established.

Approved Dosing Regimen for Buprenorphine Hydrochloride Injection

Adults: the usual dosage for persons 13 years of age and over is 0.3 mg buprenorphine (1 ml) given by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6-hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage. In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half.

Children: Buprenex has been used in children 2-12 years of age at doses between 2-6 micrograms/kg of body weight given every 4-6 hours. There is insufficient experience to recommend a dose in infants below the age of two years, single doses greater than 6 micrograms/kg of body weight, or the use of a repeat or second dose at 30-60 minutes (such as is used in adults). Since there is some evidence that not all children clear buprenorphine faster than adults, fixed interval or "round-the-clock" dosing should not be undertaken until the proper inter-dose interval has been established by clinical observation of the child.

Proposed Dosing Regimen for BTDS

Opioid-Naïve Patients: Initiate treatment with BuTrans 5mcg/h. The dose can be titrated to the next higher level after 72 hours. The maximum BuTrans dose studied in analgesic trials was 20 mcg/h.

Conversion from Other Opioids to BuTrans: For patients on less than 30 mg of oral morphine equivalent the recommended BuTrans starting dose is 5 mcg/h. For subjects on 30-80 mg of oral morphine equivalent the recommended starting dose is 10 mcg/h. BuTrans may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. The minimum titration interval is 3 days since steady state is obtained by the third day. The maximum BuTrans dose studied in analgesic trials was 20 mcg/h.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2.1 summarizes the currently available treatments for the management of chronic pain.

Table 2.2.1: Available Treatments for Chronic Pain

Product	Route of Administration	Advantages	Disadvantages
NSAIDs	**Oral**	• **Anti-inflammatory activity** • **No respiratory depression** • **No effect on gastric emptying**	• **Increased bleeding due to platlet inhibition** • **GI damage** • **Renal Impairment** • **Poor bone or wound healing** • **Not as effective for severe pain**
Acetaminophen	**Oral**	• **No respiratory depression** • **No effect on gastric emptying** • **No effect on platelet aggregation**	• **No anti-inflammatory activity** • **Possible hepatic impairment from overdose** • **Not as effective for severe pain**
Opioids	**Oral** **Transdermal** **Intramuscular** **Subcutaneous** **Intravenous** **Sublingual** **Patient Controlled Analgesia (PCA)** **Epidural or intrathecal**	• **Effective for severe pain** • **With epidural or intrathecal use the opioid dose can be reduced.**	• **Hypotension** • **Respiratoy depression** • **Nausea and vomiting** • **Delayed gastric emptying and small bowel transit time** • **With epidural/ intrathecal use:** **- Epidural hematoma or Abscess** **- Nerve injury**
Local Anesthetics (Regional and local analgesia)	**Wound infiltration**	• **Postoperative pain** • **Not effective for chronic pain**	
	Nerve and plexus blocks	• **Effective for severe pain in a peripheral nerve of nerve root distribution**	• **Nerve injury**
	Epidural or Intrathecal	• **Effective for severe pain**	• **Epidural hematoma/ abscess** • **Nerve injury**

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine is an opioid analgesic with partial μ-agonist and κ-antagonist activity. Buprenorphine was initially approved as an injectable formulation, Buprenex, (NDA 018401) on December 29, 1981 for the treatment of moderate to severe pain.

Subutex (NDA 20-732) is a sublingual tablet formulation of buprenorphine and Suboxone (NDA 20-733) is a sublingual tablet formulation of buprenorphine and naloxone. Subutex and Suboxone were approved for the treatment of opioid dependence on October 8, 2002. Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services of their intent to prescribe this product for the treatment of opioid dependence. Subutex has been marketed in Europe since 1995. The recommended target dose of Suboxone is 16 mg/day. On October 7, 2002, the DEA rescheduled buprenorphine from Schedule V to Schedule III.

2.4 Important Safety Issues With Consideration to Related Drugs

Approved opioids including buprenorphine are all associated with potentially serious safety issues of respiratory depression, addiction and abuse.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2.5.1 displays highlights of the regulatory activity that occurred during the clinical development program for BTDS.

Table 2.5.1: Regulatory Interactions between the FDA and the Applicant

Date Meeting	Topics
April 1996 IND 50,273 opened	• IND for buprenorphine transdermal system o Date of Submission: April 4, 1996 o Date of Receipt: April 5, 1996
November 18, 1998 Pre-NDA Meeting	• (b) (4) [redacted] study BP96-0104 in post-operative pain was deemed irrelevant with regard to the claim of moderate to severe pain • Because studies BP96-0101 (osteoarthritis) and BP96-0102 (low back pain) did not meet their primary statistical endpoints, the Agency asked the Sponsor for an additional efficacy study.
November 3, 2000 NDA 21-306 submitted	• NDA submitted under 505 (b)(1) • Proposed indication: management of patients with pain requiring continuous opioid analgesia

August 31, 2001 Not Approvable Letter	• 62 deficiencies were identified • Most of the deficiencies were related to chemistry or pharmacology/toxicology • Clinical deficiencies (full list in Table 2.5.2) included efficacy and safety issues: o Failed to provide substantial evidence of efficacy - Study BP96-6004 demonstrated efficacy over the first 45 to 60 days but not throughout the entire 84 days - Study BP99-0203 did not provide any evidence of effectiveness o Presentation of safety data in the ISS precluded any meaningful interpretation of the safety data
November 6, 2001 End-of-Review Meeting	• The purpose of the meeting was to discuss the clinical issues from the August 31, 2001, not approvable letter • The Division stated that an in vivo drug-drug interaction study between CYP450 inhibitors and BTDS was acceptable • The Division stated that additional adequate and well-controlled studies would be required
April 2, 2002 End-of-Review Meeting	• The purpose of this second End-of-Review meeting was to discuss abuse liability issues from the Not Approvable letter • It was agreed that an additional human abuse liability study would not be needed if buprenorphine was placed in Schedule III • The Division indicated that the buccal absorption data referenced in the pre-meeting package would be adequate assuming right of reference • The Agency expressed concern over the amount of buprenorphine remaining (b) (4) in the patch after use o The amount of residual buprenorphine presents a significant safety risk as well as abuse risk o The Agency stated that the Sponsor should improve the patch to minimize the risk of abuse o The Agency indicated that the current formulation could be approved (if all other issues were resolved) because there are no set standards for residual drugs in the patch o The Agency reiterated that the formulation issue

	cannot prevent the product from being marketed and reminded the Sponsor of the risk if they ignore the possibilities for the potential for diversion/abuse of BTDS.
March 20, 2007 Teleconference	The Division made the following comments to the Applicant: • Demonstration of analgesic efficacy in two appropriately designed studies, both in enriched populations, would be considered adequate. In the setting of a study with an enriched population, the study design and results including the number of patients unable to successfully titrate to a tolerable dose will be important information to describe in the label. • A treatment intended for chronic use should be effective for the duration of the trial. Thus, an analysis that evaluates efficacy at the end of the study is most appropriate. Your analysis comparing mean pain using the proposed repeated measures analysis is acceptable. However, you must also conduct an analysis comparing the treatment groups based on an estimate at week 12. Both analyses must demonstrate efficacy. • Adequacy of the safety database is not expected to be an issue, given the number and duration of patient exposures.
May 25, 2007 Special Protocol Agreement	• Special protocol agreement granted to Study BUP3024 o This is one of the pivotal studies in the current submission

September 15, 2008 Pre-NDA Meeting	The Division made the following comments to the Applicant: • The full November 2000 NDA submission does not need to be included in the eCTD format of the Complete Response. However, all parts of the original NDA submission referenced in the Complete Response should be provided in eCTD format. • You must submit a pediatric plan including proposed studies and requests for deferrals and/or waivers (with justifications) as part of the complete response. • In the primary pool for safety analysis, including the "Non-enriched titration-to-effect studies pool" and "Enriched fixed duration studies pool," present adverse events by treatment group (i.e. placebo or active comparator and BTDS dose received). Perform separate analyses for the controlled double-blind and open label phases. • Present exposure and disposition data by BTDS dose and include placebo and active comparator treatment groups. • Include placebo and active comparators in the dose-response safety analysis. Present open-label and double-blind data analyses separately. • Section 5.3.6 of the NDA ("Reports of postmarketing experience") must contain a written summary of the post-marketing experience with BTDS since initial time of marketing. The PSUR is not adequate to meet this NDA requirement because it discusses the safety experience over the previous 6 months since the last PSUR, and because it is comprised predominantly of line listings and/or summary tabulations. • Deficiency 60 of the NA letter addressed the need for a study to evaluate the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, which is frequently misused with other drugs of abuse. As agreed in the February 2002 End-of-Review meeting, this issue has been completely addressed, dependent on your receiving right of reference regarding access to the buccal absorption data discussed in the November 6, 2001 meeting. Evidence of right of reference to these data should be provided. • Deficiency 60 of the NA letter also addressed the

	need for a human abuse potential study with BTDS. As agreed in the February 2002 End-of-Review meeting, the rescheduling of buprenorphine from Schedule V to Schedule III of the Controlled Substances Act (CSA) in October 2002 obviated the need for a human abuse potential study with BTDS. • Deficiency 61 of the NA letter addressed the potential for significant diversion of buprenorphine from BTDS and the need to redesign the patch or modify the BTDS matrix to limit residual buprenorphine in an individual BTDS upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the BTDS matrix. No information was provided in the briefing document regarding this issue. Thus, the response to this issue is incomplete. • A REMS proposal should be submitted with the upcoming NDA resubmission. This document should be complete and all educational materials should be included. • The "fold and flush" disposal method is recommended for use with other opioid patches (such as the fentanyl patch) and may be appropriate for BTDS. However, the Agency is in the process of reviewing all drug labels with disposal directions to assure that the recommended methods are still appropriate. Since no details were provided regarding the complete methods proposed for disposal of BTDS, the adequacy of these methods will be a review issue when the NDA is re-submitted.
9/25/2009 NDA submission	• NDA submitted under 505 (b)(1) • Submission contains: o 35 completed clinical trials o 2 pivotal efficacy studies (BUP3024 and BUP3015)

Table 2.5.2 summarizes the clinical deficiencies noted in the not approvable letter of August 31, 2001

Table 2.5.2: Summary of Clinical Deficiencies	
Item	**Description**
35 c	• Provide a summary, from the clinical trials, of drug product complaints relating to the adhesiveness of the patches.
52	• Your analyses of the hepatic impairment study were based on pooled data that do not allow for a reasonable understanding of the correlation between the clinical stage of disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic impairment into separate subgroups for mild and moderate hepatic impairment.
54	• You have not adequately addressed concerns pertaining to potential drug-drug interactions between CYP450 inhibitors and BTDS. Provide data to adequately address these concerns either from available literature or from in vivo drug-drug interaction studies.
55	• You have not provided substantial evidence that the drug will have its intended clinical effect o In Study BP99-0203, when patients who were discontinued due to a drug-related adverse event were re-classified as treatment failures, the difference between Norspan and placebo was no longer clinically or statistically significant. o While Study BP96-0604 met its protocol-specified primary endpoint, further review of the data calls into question the clinical relevance of the findings. The relatively favorable efficacy results in Norspan patients who dropped out (relative to placebo patients who dropped out) was a factor in the statistical demonstration of a superior effect of Norspan over placebo. Further review of the data indicates that both an endpoint analysis (i.e., an analysis using the last recorded observation on each randomized patient) and a completers' analysis (i.e., an analysis using the last observation only on patients who completed the protocol) indicate no statistically significant difference between Norspan and placebo. Using only observed data (i.e., no LOCF), there is no clinically meaningful difference in pain reduction after day 60 between placebo- and Norspan-treated patients. Additionally, the magnitude of effect of the between-group difference in mean change from baseline for Pain on the Average and Pain Right Now is of questionable clinical significance. o These findings from Studies BP99-0203 and BP96-0604, coupled with the negative findings from Studies BP96-0101 and BP96-0102, fail to demonstrate the effectiveness of the product o Submit the results of additional adequate and well-controlled studies of appropriate duration and in relevant target populations to provide evidence of the effectiveness of the product and the durability of the treatment effect.

56	• The extent of errors and inconsistencies in the safety database and in the safety analyses, especially the clinical laboratory data, preclude meaningful interpretation of the safety data. a. Submit safety data in clinical study reports and in an Integrated Summary of Safety that are accurate and presented in a clear manner. b. Adverse events were not coded consistently. Code all adverse events in the safety database in a consistent manner across all studies. c. Intercurrent diseases and conditions that were reported in some of the studies appear to be adverse events. Include in the analysis of adverse events an analysis of intercurrent diseases and conditions.
57	• The safety analyses did not analyze the effect of BTDS dose on safety outcomes. For all safety measures, include analyses in the ISS that focus on the relationship between BTDS dose at the time of a safety measure and the outcome of the safety measure.
58	• The electrocardiogram data do not analyze electrocardiographic intervals. Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT, QTc, etc) in view of reports of cardiotoxicity associated with other opioids.
59	• A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period, patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Address this issue, both in regard to the completed studies, and in the design of future studies. • The FDA agreed that 3 days is an appropriate titration interval
60	• Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation. a. Characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs b. The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Failure to use a standard comparator, such as morphine, and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. Repeat this study taking into consideration these design issues. o In the April 2, 2002 End-of-Review Meeting, it was agreed that an additional human abuse liability study would not be needed if buprenorphine was placed in Schedule III
61	• The potential for significant diversion of buprenorphine from Norspan is unacceptable for a controlled substance. This risk should be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the

	residual buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix. o In the April 2, 2002 End-of-Review Meeting, the Agency indicated that the current formulation could be approved (if all other issues were resolved) because there are no set standards for residual drugs in the patch
62	• Adequate adhesion characteristics of the patch should be ensured. This deficiency may affect the efficacy and diversion potential of this product.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted in Electronic Common Technical Document (eCTD) format. The submission was reasonably well-organized and paginated to allow for an acceptable review.

3.2 Compliance with Good Clinical Practices

Pivotal studies BUP 3024 and BUP3015 were conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki, 1964. Prior to initiating the studies each subject gave informed consent before any study-specific procedures were performed.

The Division of Scientific Investigation (DSI) inspected two sites for each pivotal study. For Study BUP 3024, the Division selected sites #1175A and #1210A based on the number of subjects enrolled and randomized at these two sites. For Study BUP 3015, the Division selected site #524A based on the highest enrollment and number of randomized subjects and site #513A based on the second highest number of subjects randomized.

The DSI inspection of the four clinical investigator sites for the two protocols verified the primary endpoint data. There were two isolated instances of unreported adverse events but these were considered isolated occurrences and unlikely to significantly impact the integrity of primary efficacy and safety data overall. The data submitted by the inspected entities were considered reliable in support of the NDA.

3.3 Financial Disclosures

Purdue submitted FDA Form 3454 certifying that the clinical investigators who supervised eleven clinical studies in support of this application since the original NDA submission dated November 3, 2000:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)]

Dr. Dal Pan, in his review of the initial NDA submission reported that the applicant submitted certification on the financial interest and arrangements for studies that were ongoing on or began after February 2, 1999 with the exception of Study BP96-0103 since this was an open-label safety study and as such did not require financial disclosure from the investigators. All investigators who responded reported no financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A detailed discussion of the chemistry issues by Dr. Xavier Ysern, the chemistry reviewer, is contained in the CMC section.

From a chemistry, manufacturing and controls (CMC) perspective, Dr. Ysern recommends an Approval action pending: (1) satisfactory response to the DMF holders to the deficiencies listed under DMFs (b) (4) and (b) (4), and (2) satisfactory justification by the applicant to support the amount of residual drug substance in BTDS after use. This issue regarding the residual amount of buprenorhpine is a concern of the Transdermal Working Group (TWG) within ONDQA and does not reflect any other specific concern regarding the chemistry, controls or manufacturing of the patch aside from the residual amount of buprenorphine. This issue is discussed in further detail in Section 1.2 Risk Benefit Assessment.

4.2 Clinical Microbiology

Not applicable for a dermal patch.

4.3 Preclinical Pharmacology/Toxicology

A detailed discussion of the Pharmacology/Toxicology issues is contained in the review by Dr. Gary Bond, the pharmacology reviewer.

The following information was obtained from the FDA pharmacologist, Dr. Gary Bond. The applicant was required to demonstrate safety for the dermal route of administration for BTDS. The applicant conducted a local tolerance study submitted in the original NDA that demonstrated no dermal concerns other than anticipated irritation. A complete (505)(b)(1) nonclinical dataset using the dermal route of exposure was submitted as well as a genotoxicity test battery and carcinogencity skin painting studies. In addition the potential monomeric components of the patch adhesive were not considered to be of carcinogenic concern given the low concentrations and /or lack of carcinogenicity. All submitted nonclinical data is consistent with agreements for submission and approval for NDA.

4.4 Clinical Pharmacology

A detailed discussion of the clinical pharmacology issues is contained in the review by Dr.Shettal Agarwal, the pharmacology reviewer.

There are no outstanding pharmacology issues impacting on the decision whether to approve this product. Results of the drug-drug interaction and hepatic impairment studies are discussed in Section 4.4.3 Pharmacokinetics.

4.4.1 Mechanism of Action

Buprenorphine is an opioid analgesic with partial mu agonist and κ antagonist activity. It produces typical opioid agonist effects such as analgesia, sedation, nausea and dizziness. Buprenorphine can also act as an antagonist and precipitate withdrawal symptoms. The precise mechanism of the analgesic action is unknown but appears related to opioid receptors identified throughout the brain and spinal cord.

4.4.2 Pharmacodynamics

Central Nervous System Effects
Buprenorphine binds to and dissociates from the mu-opioid receptor slowly. This could account for its longer duration of action than morphine, the unpredictability

of its reversal by opioid antagonists, and its low level of manifest physical dependence.

Since kappa-receptor agonist activity is related to psychotomimetic and dysphoric effects, buprenorphine is expected to produce fewer psychotomimetic and dysphoric effects than drugs with kappa-agonist activities (eg, pentazocine).

Cardiovascular Effects
Buprenorphine may cause a reduction in blood pressure in a manner similar to other opioids.

Cardiac Electrophysiology
The therapeutic dose of BuTrans 10 mcg/h had no effect on QTcI, however, a supratherapeutic dose of BuTrans 40 mcg/h (given as two 20 mcg/h patches) prolonged QTcI by an effect comparable to that of 400 mg of moxifloxacin.

Respiratory Effects
Respiratory depression may occur. Buprenorphine-induced respiratory depression may have slower onset and longer duration than that induced by morphine. Respiratory depression may be severe in individuals with compromised respiratory function or those concomitantly receiving benzodiazepines or other CNS/respiratory depressant drugs.

Endocrine Effects
Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Gastrointestinal Effects
Like other opioids, buprenorphine may cause nausea, vomiting, and constipation. Use of opioids may also result in an increase in biliary tract pressure as a result of spasm of the Sphincter of Oddi.

Other Effects
Buprenorphine causes dose-related miosis and produces urinary retention in some patients.

In-vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether buprenorphine, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

4.4.3 Pharmacokinetics

Each BuTran system provides a steady delivery of buprenorphine to 7 days. Steady state was achieved during the first application by Day 3. BuTrans 5, 10, and 20 mcg/h provide dose-proportional total buprenorphine exposures (AUC) following 7-day applications (Table 4.4.3.1). Dose proportionality across BuTrans 5, 10, and 20 mcg/h is also supported by buprenorphine plasma concentration data following repeated seven-day BuTrans application for 60 days. Plasma buprenorphine concentrations after titration showed no increase or unexpected accumulation over the 60-day period. After removal of BuTrans, mean buprenorphine concentrations decrease approximately 50% within 10–24 hours, with an apparent terminal half-life of approximately 26 hours.

Table 4.4.3.1: Pharmacokinetic Metrics of BuTrans in Healthy Subjects (Single 7-day Application) Mean (%CV)

Dose (mcg/h)	AUCinf (pg·h/mL)	Average Concentration* (pg/mL)	Cmax (pg/mL)
BuTrans 5	12087 (37)	71.95 (37)	176 (67)
BuTrans 10	27035 (29)	160.92 (29)	191 (34)
BuTrans 20	54294 (36)	323.18 (36)	471 (49)

*Steady-state average concentration projected form single-dose AUCinf.

Absorption
Transdermal delivery studies showed that buprenorphine is permeable across the human skin. In clinical pharmacology studies, the median time for BuTrans 10 mcg/h to deliver quantifiable buprenorphine concentrations (≥25 pg/mL) was approximately 17 hours. The absolute bioavailability of BuTrans relative to IV administration, following a 7-day application, is approximately 15% for all treatments (BuTrans 5, 10, and 20 mcg/h).

Distribution
Buprenorphine is approximately 96% bound to plasma proteins, mainly to alpha- and beta-globulin.

Studies of IV buprenorphine have shown a large volume of distribution (approximately 430 L), implying extensive distribution of buprenorphine.

Following IV administration, buprenorphine and its metabolites are secreted into bile and excreted in urine. CSF buprenorphine concentrations appear to be approximately 15-25% of concurrent plasma concentrations.

Metabolism
Buprenorphine metabolism in the skin following BuTrans application is negligible. Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. Buprenorphine and its metabolites are also eliminated in the feces.

Buprenorphine primarily undergoes N-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3-*O*-glucuronide. Norbuprenorphine, the major metabolite, is also glucuronidated (mainly UGT1A3) prior to elimination.

Norbuprenorphine is the only known active metabolite of buprenorphine. It has been shown to be a respiratory depressant in rats, but only at concentrations at least 50-fold greater than those observed following application to humans of BuTrans 20 mcg/h.

Since metabolism and excretion of buprenorphine occur mainly via hepatic elimination, reductions in hepatic blood flow induced by some general anesthetics (eg, halothane) and other drugs may result in a decreased rate of hepatic elimination of the drug, resulting in increased plasma concentrations.

Elimination
Following intramuscular administration of 2 mcg/kg dose of buprenorphine, approximately 70% of the dose was excreted in feces within 7 days. Approximately 27% was excreted in urine. The total clearance of buprenorphine is approximately 55 L/h in postoperative patients.

Drug Interactions
Effect of CYP3A4 substrates/inhibitors on buprenorphine
In a drug-drug interaction study, BuTrans 10 mcg/h (single-dose x 7 days) was co-administered with 200 mg ketoconazole, a strong CYP3A4 inhibitor or ketoconazole placebo twice daily for 11 days and the pharmacokinetics of buprenorphine and its metabolites were evaluated. Plasma buprenorphine concentrations did not accumulate during co-medication with ketoconazole 200 mg twice daily. Based on the results from this study, metabolism during therapy with BuTrans is not expected to be affected by co-administration of azole drugs such as ketoconazole.

Antiretroviral agents have also been evaluated for CYP3A4 mediated interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) do not appear to have clinically significant interactions with buprenorphine. However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and

atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine (Cmax and AUC values doubled) when buprenorphine was administered via the sublingual route. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It is important to note that atazanavir inhibits both CYP3A4 and UGT1A1 metabolizing enzymes that are important for buprenorphine metabolism to either norbuprenorphine (which is further glucuronidated) or buprenorphine-3-glucuronide, therefore its possible that co-administration with atazanavir leads to significant metabolic inhibition of buprenorphine as compared to ketoconazole which only inhibits CYP3A4 at the concentration at which it was administered in the DDI study.

Effect of CYP3A4 inducers on buprenorphine
The interaction between buprenorphine and CYP3A4 inducers has not been studied.

Effect of buprenorphine on CYPs
In-vitro studies conducted using recombinant human cytochrome P450 isoforms to determine effect of buprenorphine on CYP enzymes showed that buprenorphine is a weak inhibitor of CYP 1A2 (IC_{50} > 200 µM), CYP2A6 (IC_{50} > 100 µM), CYP3A4 (IC_{50} ≤25 µM); and a highly potent inhibitor of CYP2D6 with an IC_{50} of 0.05 µM. However, relatively low plasma concentrations of buprenorphine in clinical studies are not expected to raise significant drug-drug interaction concerns if the drug product is taken at the recommended doses.

Application Site
A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by BuTrans 10 mcg/h is similar when applied to the upper outer arm, upper chest, upper back, or the side of the chest.

The reapplication of BuTrans 10 mcg/h after various rest periods to the same application site in healthy subjects showed that the minimal rest period needed to avoid variability in drug absorption is 3 weeks (21 days)

External Heat
In a study of healthy subjects, application of a heating pad directly on the BuTrans 10 mcg/h system caused a transient, 26 - 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, applying heating pads directly to the BuTrans system during system wear is not recommended.

Endotoxin Challenge
In a crossover study of healthy subjects receiving endotoxin or placebo challenge during BuTrans 10 mcg/h wear, the AUC and Cmax were similar despite a physiologic response to endotoxin. The safety profile and BuTrans performance is unlikely to be significantly affected during intercurrent mild or moderate febrile illness. However, it must be realized that fever may increase the permeability of the skin, leading to increased buprenorphine concentrations during BuTrans treatment.

Flux Determination
Flux was determined in 2 studies by 3 methods of analysis each yielding similar results. Buprenorphine flux for the 7-day application period was established to be 5, 10, and 20 mcg/h for the 7-day application period, for the BuTrans patches containing 5, 10, and 20 mg of buprenorphine, respectively.

Specific Populations:

Gender:
In a pooled data analysis utilizing data from several studies that administered BuTrans 10 mcg/h to healthy subjects, no differences in buprenorphine Cmax and AUC or body-weight normalized Cmax and AUC were observed between males and females treated with BuTrans

Geriatric:
Following a single application of BuTrans 10 mcg/h to 12 healthy young adults (mean age 32 years) and 12 healthy elderly subjects (mean age 72 years), the pharmacokinetic profile of BuTrans was similar in healthy elderly and healthy young adult subjects, though the elderly subjects showed a trend toward higher plasma concentrations immediately after BuTrans removal. Both groups eliminated buprenorphine at similar rates after system removal *[see DOSAGE AND ADMINISTRATION (2.4) and USE IN SPECIFIC POPULATIONS (8.5)]*.

In a study of healthy young subjects, healthy elderly subjects, and elderly subjects treated with thiazide diuretics, BuTrans at a fixed dose-escalation schedule (BuTrans 5 mcg/h for 3 days, followed by BuTrans 10 mcg/h for 3 days and BuTrans 20 mcg/h for 7 days) produced similar mean plasma concentration vs. time profiles for each of the three subject groups. There were no significant differences between groups in buprenorphine Cmax or AUC

Pediatrics
BuTrans has not been studied in children and is not recommended for pediatric use.

Renal Impairment
No studies in patients with renal impairment have been performed with BuTrans.

It was found that plasma buprenorphine concentrations were similar in patients with normal renal function and in patients with impaired renal function or renal failure. In a separate investigation of the effect of intermittent hemodialysis on buprenorphine plasma concentrations in chronic pain patients with end-stage renal disease who were treated with a transdermal buprenorphine product (marketed outside the US) up to 70 mcg/h, no significant differences in buprenorphine plasma concentrations before or after hemodialysis were found.

No notable relationship was observed between estimated creatinine clearance rates and steady-state buprenorphine concentrations among patients during BuTrans therapy.

Hepatic Impairment:
The pharmacokinetics of buprenorphine following an IV infusion of 0.3 mg of buprenorphine was compared in 8 patients with mild impairment (Child-Pugh A), 4 patients with moderate impairment (Child-Pugh B) and 12 subjects with normal hepatic function. Buprenorphine and norbuprenorphine exposure did not increase in the mild and moderate hepatic impairment patients.

For patients with mild hepatic impairment, the mean Cmax value for buprenorphine was 54% and for norbuprenorphine was 73% of that for the healthy and for patients with moderate hepatic impairment, the Cmax value for buprenorphine was only 39% and for norbuprenorphine was only 59% of that for the healthy. However, extent of exposure over time (AUCt) for buprenorphine or norbuprenorphine did not change significantly with severity in hepatic impairment. BuTrans has not been evaluated in patients with severe (Child-Pugh C) hepatic impairment.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Purdue has submitted safety data from 35 completed clinical trials: 18 pharmacology studies (Table 5.1.1) and 17 pain studies (15 in chronic pain and 2 in acute pain) (Table 5.1.2).

Table 5.1.1: Phase 1 Studies		
Study Study Dates	**Description**	**Randomized/ Dosed/ Completed**
BP95-0901 4-22-96 to 7-7-96	PK/PD study in healthy subjects. Single and multiple doses of BTDS 20 and 0.3 mg IV administered in randomized, 3-way crossover study	28/27/23
BP97-0303 5-13-98 to 12-19-98	Open-label, 3-group, parallel study in young healthy, elderly subjects and elderly hypertensive subjects treated with thiazide diuretic to evaluate PK and orthostatic changes with BTDS 5, 10 and 20	NA/36/34
BP99-0204 May 23, 1999 to June 27, 1999	Open-label study to determine PK following the application of BTDS 5 to healthy subjects and the effects on plasma concentrations of local heating in the first 3 hours after removal of the 3rd BTDS 5	NA/28/27
BUP1002 Nov 19, 2000 to March 18, 2001	Open-label study in healthy subjects to determine the minimum application site rest period that ensured that reapplication of BTDS 10 to the same deltoid region would not result in increased absorption	70/70/64 (Not including subjects receiving only naltrexone)
BUP1011 July 2, 2004 to Dec 16, 2004	Randomized, double-blind, placebo-and positive-controlled parallel group study to evaluate the effect of BTDS 10 and 40 on QT intervals in healthy subjects	132/131/126
BC88-0705 Oct 1988	Single-dose, double-blind, crossover, paired-comparison study in healthy subjects of the irritancy potential of buprenorphine hydrochloride 0.3 mg/mL	10/10/10
BP96-0304 Sep 10, 1996 to Oct 14, 1996	Single-dose, open-label, randomized, 3-treatment, crossover study in healthy subjects to assess the bioequivalence of two BTDS 5 patches versus a single BTDS 10 and the dose proportionality of BTDS 10 and BTDS 20	28/28/24
BP96-0501 Jan 17, 1997 to March 17, 1997	Single-dose, open-label, randomized, 4-treatment crossover study in healthy subjects to assess the bioequivalence of BTDS 10 applied to 3 test application sites (upper outer arm, upper chest, upper back) using application to the midaxillary line as the reference treatment	24/24/22
BP96-0702 Jun 9, 1997 to Jun 20, 1997	Single-dose study in healthy elderly and young subjects to compare the PK/PDof a single BTDS 10 worn for 7 days	NA/24/24

BP96-0803 Oct 28, 1996 to Nov 4, 1996	Single-dose, open-label study in healthy adults to evaluate the PK/PD of BTDS 10 applied over a 7-day period and to assess duration of wear for 3 BTDS sizes	NA/24/24
BP96-1102 Jan 6, 1998 to March 7, 1998	Single-dose, single-blind, randomized crossover PK study to assess the effect of elevated body temperature (endotoxin induced) on BTDS 10 bioavailability	22/22/20
BP97-0112 March 25, 1998 to May 14, 1998	Single-dose, open-label, parallel group study to assess the effect of hepatic impairment on the PK of buprenorphine injectable 0.3 mg. Enrollment included 12 subjects with hepatic impairment (8 with mild and 4 with moderate impairment) and 12 healthy subjects.	NA/24/24
BP97-0501 May 20, 1998 to July 13, 1998	Single-dose, randomized, crossover study to determine the PK and absolute bioavailability of BTDS 5, 10 and 20 in healthy subjects	36/36/32
BP97-1001 April 23, 1998 to May 14, 1998	Single-dose, third-party blind, double-dummy study to evaluate the effects of BTDS 10 plus midazolam 1mg and of fentanyl transdermal patch plus midazolam on respiratory depression and vital signs in healthy young subjects.	36/36/36
BP98-0201 April 1, 1998 to May 8, 1998	Open-label, randomized, single-dose PK study in healthy subjects to evaluate the apparent absorption and disposition kinetics of buprenorphine after 1, 2, 3, 4, 5, 6, and 7 days of wear of BTDS 10	84/84/83
BP98-0202 April 30, 1998 to June 6, 1998	Third-party blind, double-dummy single-dose study to evaluate the effect of BTDS 10 plus Prochlorperazine and of Fentanyl Transdermal plus Prochlorperazine on respiratory depression and vital signs in young healthy volunteers	36/36/36
BP98-1202 Dec 22, 1999 to Jan 8, 2001	Abuse potential study in non-opioid dependent volunteers with a recent history of opioid abuse. Double-blind, double-dummy, randomized 3-way crossover (placebo, BTDS 20 x 2 and active control, 0.3mg IM buprenorphine) study preceded by a single-blind, double-dummy, single-dose safety evaluation and practice session.	9/9/9
BP98-1204 Sep 21, 1999 to Nov 15, 1999	Single-dose, open-label, randomized, 2-way crossover, repeated-dose study to assess PK/PD during the application of external heat on BTDS 10 in healthy subjects	20/20/19

BUP1009 Oct 21, 2002 to June 20, 2003	Randomized, double-blind, placebo-controlled, 2-way crossover study to assess PK of BTDS 10 with or without Ketoconazole.	20/20/15

Table 5.1.2: Phase 2 and 3 Studies		
Chronic Pain Studies		
Study Study Dates	**Description**	**Randomized/ Dosed/ Completed**
BUP3014 Jan, 7, 2004 to March 9, 2005	Randomized, double-blind, active-controlled, open-label run-in study to evaluate BTDS 20 versus BTDS 5 in subjects on opioids with moderate to severe OA pain of the hip, knee or spine. The study was terminated early for administrative reasons.	345 screened 96/96/71
BUP3015 (Pivotal Study) Feb 25, 2004 to Sep 23, 2005	Randomized, double-blind, double-dummy, active comparator, open label run-in study to compare BTDS 20 or Oxy IR capsules (40 mg/day) to BTDS 5 in subjects on opioids with moderate to severe chronic low back pain. This study was terminated early for administrative reasons.	2066 screened 662/660/143
BUP3019 April 2, 2004 to July 18, 2005 Failed study	Randomized, double-blind, active-control, open label run-in study to compare BTDS 20 or Oxy IR with BTDS 5 in subjects on opioids with moderate to severe OA of the hip, knee or spine.	1254 enrolled 418/418/216
BUP3024 (Pivotal Study) June 27, 2007 to July 24, 2008	Randomized, double-blind, placebo-control, open-label run-in study to evaluate BTDS 10 and BTDS 20 compared to placebo in opioid naïve subjects with chronic low back pain.	1466 screened 1027 run-in 541/539/369
BUP3011 Dec 12, 2003 to March 2, 2005	Randomized, double-blind, placebo controlled, open-label run-in study to evaluate BTDS 10 or 20 compared to placebo in subjects with moderate to severe OA pain of the hip, knee or spine. Enrollment was terminated early for administrative reasons and no formal efficacy analysis was conducted due to the reduced statistical power.	324 screened 107/107/92
BUP3012 April 25, 2003 to June 1, 2004	Randomized, double-blind, placebo-controlled, open-label run-in study to evaluate BTDS 5, 10 or 20 versus placebo in subjects with moderate to severe OA pain of the hip or knee.	327/327/310

BUP 3201 March 19, 2001 to July 22, 2001	An open-label run-in followed by a randomized, double-blind, placebo-controlled, parallel group study to show the effect of BTDS – 5, 10 and 20 on subjects with chronic non-malignant pain syndromes on prior opioid therapy.	638 screened 588 run-in 267/267/255
BP96-0604 Dec 10, 1997 to May 8, 1998	Randomized, double-blind, placebo- and active-controlled, parallel group study to evaluate the effect of BTDS 5, 10 or 20 and Oxy/APAP 5 mg/325 mg compared to placebo in subjects with chronic back pain.	134/134/67
BP98-1201 April 21, 1999 to Oct 11, 1999	Randomized, double-blind, active-controlled, parallel group study to evaluate the effect of BTDS – 5, 10 and 20 compared to hydrocodone/acetaminophen in subjects with chronic back pain.	270/270/139
BP99-0203 June 4, 1999 to Oct 2, 1999	Randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of BTDS 5, 10 or 20 in subjects with OA pain of the hip or knee	315/315/155
BUP3002 Dec 20, 2000 to Nov 2, 2001	Randomized, double-blind, placebo-controlled, pilot study to evaluate the effect of BTDS 5, 10 or 20 in elderly residents of supervised living environments.	107/107/89
BP96-0101 Nov 6, 1996 to Nov 6, 1997	Randomized, double-blind, parallel-group, placebo- and active-controlled study of BTDS 5, 10 or 20 compared to oxycodone/APAP and placebo in subjects with chronic pain due to osteoarthritis	270/270/126
BP96-0102 April 9, 1997 to Jan 6, 1998	Randomized, double-blind, placebo- and active-controlled, parallel-group study with BTDS 5, 10 or 20 compared to oxycodone/APAP or placebo in patients with chronic low back pain.	249/249/136
BUP3018 June 26, 2003 to July 21, 2004	Randomized, double-blind study to evaluate the dose conversion from Vicodin to a starting dose of BTDS 10 or 20 in subjects with osteoarthritis pain of the hip or knee	203/203/167
Uncontrolled Open-Label Extension Studies		
Study Study Dates	**Description**	**Dosed/ Completed**
BP96-0103 Jan 27, 1997 to March 29, 1999	Open-label safety study of BTDS 5, 10 and 20 in subjects from clinical studies BP96-0101, BP96-0102, and BP96-0604. The mean duration of treatment was 234 days (minimum, 1 day; maximum, 609 days)	384/127

Extension to BUP3002 March 9, 2001 to May 23, 2002	28 week duration	69/40
Extension to BUP3011 April 5, 2004 to March 2, 2005	52 week duration	39/10
Extension to BUP3012 May 28, 2003 to July 2, 2004	24 week duration	290/202
Extension to BUP3014 May 13, 2004 to March 9, 2005	52 week duration	55/7
Extension to BUP3015 June 17, 2004 to Sep 23, 2005	52 week duration	354/15
Extension to BUP3019 April 2, 2004 to Aug 5, 2005	52 week duration	196/0
Extension to BUP3201 April 16, 2001 to Feb 27, 2002	28 week duration	
Studies in Acute Pain		
BP96-0104 Oct 31, 1996 to Nov 10, 1997	Single-dose, randomized, double-blind, placebo-controlled, parallel-group study to evaluate BTDS 5, 10 or 20 in subjects following orthopedic surgery	110/92
BUP2003 Nov 2, 2006 to April 20, 2007	Randomized, double-blind, placebo-controlled, parallel-group pilot study to evaluate the analgesic efficacy of BTDS 10, 20 and 30 on postoperative pain following total knee arthroplasty. This trial was terminated early due to administrative reasons.	10/7

5.2 Review Strategy

Efficacy

Studies BUP3024 and BUP3015 were reviewed to support the efficacy of BuTrans for the relief of moderate to severe pain in patients requiring continuous,

around-the-clock opioid treatment for an extended period of time. Both studies were considered pivotal studies for the following reasons:

- Well-controlled (i.e., randomized, double-blind, placebo- or active-controlled)
- Included a significant number of patients
- Provided for dosing up to three months

Safety
Purdue's integrated safety analyses included safety data from 35 studies completed between July 1996 and March 2009 was reviewed and discussed in Section 7 on Safety.

5.3 Discussion of Individual Studies/Clinical Trials

To support efficacy, the applicant submitted two Phase 3 trials (BUP3015 and BUP3024) in addition to the studies previously submitted in the original NDA. A review of the two new controlled efficacy studies follows.

5.3.1 BUP3024

Study BUP3024 was conducted under a Special Protocol Agreement. The following summary of the design of BUP3024 was derived from the revised protocol incorporating amendment #1 (May 22, 2007). This amendment was enacted prior to screening the first subject on June 27, 2007.

Title: "A Multicenter, Randomized, Double-blind, Placebo-controlled Study With an Open-label Run-in to Assess the Efficacy, Tolerability, and Safety of BTDS 10 or BTDS 20 Compared to Placebo in Opioid-naïve Subjects With Moderate to Severe, Chronic Low Back Pain"

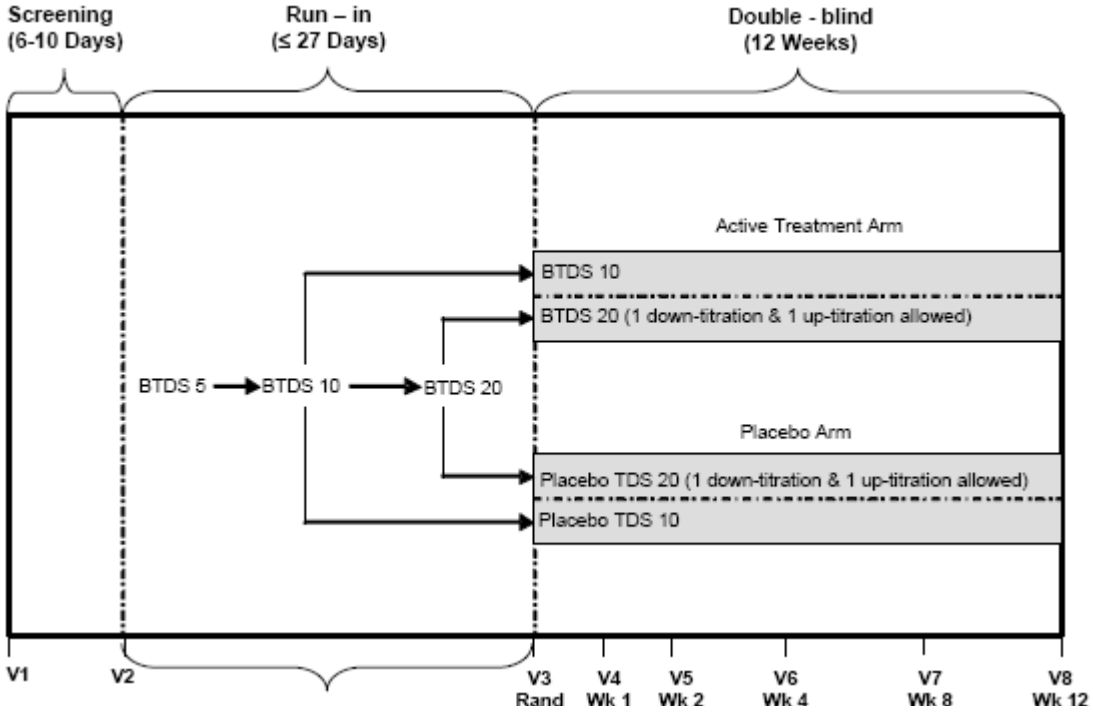
Dates Conducted: The first subject was screened June 27, 2007 and the last subject completed the study July 24, 2008.

Objectives: The primary objective of the study was to evaluate the analgesic efficacy and safety of Buprenorphine Transdermal System (BTDS) in subjects with moderate to severe chronic low back pain.

Overall Design: This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study of BTDS 10 and BTDS 20 in the treatment of opioid naïve subjects with moderate to severe chronic low back pain. The study design was to have included a prerandomization phase (screening and run-in periods) and double-blind phase. Subjects meeting screening criteria during the prerandomization phase were to have entered into the open-label run-in period to receive BTDS 5 for three days. Subjects not able to tolerate BTDS 5 were to have

been discontinued form the study. Subjects tolerating BTDS 5 were to have had their dose increased to BTDS 10 for an additional 10 days. Subjects who both tolerated and responded to BTDS 10 were to have been randomized to BTDS 10 or matching placebo while subjects who did not tolerate BTDS 10 were to have been discontinued from the study. Responsiveness to BTDS was to have been defined by the following two criteria: 1) a ≥ 2-point reduction in "average pain over the last 24 hours" on 3 consecutive days prior to randomization compared to screening and 2) "average pain over the last 24 hours" of ≤ 4 on 3 consecutive days immediately prior to randomization. Subjects who tolerated BTDS 10 but did not show efficacy, were to have had their dose increased to BTDS 20 for an additional 10 days. Subjects on BTDS 20 who both tolerated and responded to therapy were randomized to BTDS 20 or placebo. Subjects who did not tolerate and/or respond to BTDS 20 were to have been discontinued form the study. Subjects in the double-blind phase were to have been treated for 12 weeks. Only subjects randomized to the BTDS 20 group were to have been allowed one down-titration and one up-titration back to BTDS 20.

Figure 5.3.1.2: Overall Study Design BUP3024



Reference: Figure 1. Overall Study Design, pg 33 Clinical Study Report BUP3024

Inclusion Criteria:

Patients were to have met the following criteria:

1. Males and females ≥ 18 years of age with moderate to severe chronic low back pain (lasting several hours daily) for at least 3 months prior to Screening
2. Back pain may be related to non-malignant conditions such as: intervertebral disc disease, spinal stenosis, spondylolysis, spondylolisthesis, osteoarthritis
3. Chronic low back pain treated within the 14 days prior to Screening with non-opioid therapy only, or with therapy including opioids at a dose of < 5 mg oxycodone (or equivalent) per day
4. Average pain over the past 14 days ≥ 5 (on an 11-point numerical pain scale) evaluated at Screening while taking their incoming non-opioid analgesic medications
5. 'average pain over the last 24 hours' ≥ 5 for 2 consecutive days during the Screening Period (excluding the day when subjects stopped all analgesic medications)
6. Adjunct therapy for back pain, such as physical therapy, biofeedback therapy, acupuncture therapy or herbal remedies, such treatment should be either stopped at Screening or remain unchanged during the entire study
7. Subjects deemed by the Investigator to be appropriate candidates for the protocol-specified, around-the-clock opioid therapeutic regimen
8. Females less than one year post-menopausal or who have not had surgical sterilization must have a negative serum pregnancy test, be non-lactating, and willing to use adequate contraception throughout the study
9. 2 ECGs at the initial screening visit with each showing a QTcB value of < 480 msec. *Amendment 2 added: In addition, each tracing must show a QTcF value of < 480 msec in order for subjects to continue in the study.*
10. Serum potassium level within the normal range
11. Willing and able to be compliant with the protocol, and read, understand, and sign the written informed consent

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Females who are pregnant or lactating
2. Radicular symptoms, acute spinal cord compression, acute compression fracture, seronegative spondyloarthropathy, acute nerve root compression, cauda equina compression, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), diabetic amyotrophy, meningitis, discitis, or back pain due to secondary infection, tumor or postherpetic

neuralgia. *Amendment 2 added: gout, pseudogout, psoriatic arthritis, active Lyme Disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, ischial tuberosity bursitis or neuropathic pain conditions.*

3. History of regular opioid use (i.e., daily) at a dose of ≥ 5 mg oxycodone (or equivalent) per day over the three months prior to Screening
4. Subjects who cannot stop their analgesic medications and other medications used for chronic pain
5. Unable to stop local regional pain treatments during the study (nerve/plexus blocks, neurosurgical procedures, or Botulinum toxin injections). The subject must not have had a nerve/plexus block within 4 weeks of screening or a Botulinum toxin injection in the low back within 3 months of screening
6. Surgical procedures directed towards the source of back pain within 6 months of screening or planned during the study conduct period
7. Use of any investigational medication within 30 days
8. History of seizure (history of pediatric febrile seizures allowed)
9. Current uncontrolled depression or other uncontrolled psychiatric disorder (subjects with controlled depression or other psychiatric disorder must be on a stable medication for ≥ 1 month to participate in the study)
10. History of alcohol or other substance abuse or addiction
11. Clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia
12. History of Long QT Syndrome or an immediate family member with this condition
13. Receiving Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide)
14. Unstable respiratory disease
15. Evidence of impaired liver function (AST or ALT ≥ 3 times ULN or bilirubin ≥ 1.3 mg/dl)
16. Evidence of impaired kidney function (serum creatinine > 2.5 mg/dl)
17. Biliary tract disease, hypothyroidism, adrenal cortical insufficiency, or any other medical condition that in the Investigator's opinion is inadequately treated and precludes entry into the study
18. History of malignancy within past 2 years, with exception of basal cell carcinoma that has been successfully treated
19. Allergic to both acetaminophen and ibuprofen
20. Allergic to buprenorphine or a history of allergies to other opioids
21. Allergies or other contraindications to transdermal delivery systems or patch adhesives
22. Dermatological disorder at any relevant patch application site that precludes proper placement and/or rotation of patch

23. Treatment with direct external heat sources such as heat lamps, electric blankets, saunas, or heating pads
24. Receiving monoamine oxidase inhibitors (MAOIs) or who have been taking MAOIs within two weeks of screening
25. Participated previously in a Buprenorphine Transdermal System (BTDS) study
26. Ongoing Workman's Compensation claim and/or litigation related to their pain
27. In the opinion of the investigator unsuitable to participate in the study

Study Medication

BTDS 5, 10 and 20 mcg/h patches were to have been applied every seven days.

During the Pre-randomization Phase all subjects were to have applied a BTDS 5 patch for three days. A BTDS 10 patch was to have been applied for at least 10 days to all subjects who tolerated the BTDS 5 patch. Subjects who both tolerated and responded to BTDS 10 patch were to have been randomized in a one to one ratio to BTDS 10 or matching placebo while subjects who did not tolerate BTDS 10 were to have been discontinued from the study. Subjects tolerating but not responding to BTDS 10 were to have had their dose up-titrated to BTDS 20 for at least 10 days. Subjects on BTDS 20 who both tolerated and responded to therapy were to have been randomized in a one to one ratio to BTDS 20 or placebo.

Concomitant Therapy

Rescue Analgesia

For the first six days post-randomization, subjects were to have been permitted to take oxycodone IR 5 mg twice daily following which they were to have been instructed to discontinue the oxycodone. For the remainder of the study, subjects were to have been permitted to take Sponsor-provided acetaminophen 500 mg every six hours as needed. If acetaminophen were contraindicated, the subject was to have been permitted to take ibuprofen 200 mg every six hours. Subjects were to have been instructed to refrain from taking any supplemental analgesic medication for 30 hours prior to the Weeks 2, 4, 8 and 12 visits.

Concomitant Therapy and Restrictions

Opioids: With the exception of the first 6-day period after randomization, opioid analgesics other than BTDS were to have been prohibited throughout the study.

NSAIDs, aspirin, acetaminophen: Concomitant use of NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen was to have been permitted during the Double-blind Phase provided that the total daily doses did not exceed 2 grams for acetaminophen or 800 mg for ibuprofen. Medications such as aspirin and other non-steroidal anti-inflammatory drugs were to have been permitted only for conditions other than chronic pain (e.g., headache, fever, and cardiovascular

disease prophylaxis). If treatment with such drugs occurred the dose, frequency, and reason for ingestion was to have been recorded.

Muscle relaxants were to have been permitted for treatment of muscle spasms.

Antidepressants and anticonvulsants: antidepressants and anticonvulsants were to have been allowed if they were not used for chronic pain and the dose was stable for at least 1 month prior to the start of the study and the dose was expected to remain stable.

Corticosteroid injections: Intra-articular corticosteroid injections administered to the low back or intramuscular steroid injections were not to have been allowed for a period of 6 weeks prior to screening or during the course of the study.

Oral corticosteroids were to have been allowed if stable for at least 6 weeks prior to the screening visit.

Glucosamine and/or chondroitin sulfate were to have been allowed if the dose was stable for at least 2 months prior to study entry and the same dose was to be used for the duration of the study.

Ancillary therapy: Transcutaneous electrical nerve stimulation (TENS), biofeedback, physical therapy, and relaxation therapy initiated at least 14 days prior to study entry were to have been allowed at the same intensity and frequency.

Study Procedures:

A schedule of assessments is contained in Table 5.3.1.1

Table 5.3.1.1: Schedule of Assessments in Study BUP3024

Phase Period	Pre-Randomization							Double-blind						
	Scrn	Run-in												
		Dose-titration												
Duration	6-10 days	≤ 27 days						84 days						
Study Visit	V1	V2	Day 3 Phone Call[e]	V2A BTDS 10 Eval [a]	V3			V4 Wk 1	V5 Wk 2	V6 Wk 4	V7 Wk 8	V8 [b] Wk 12	Unscheduled Visits	
					BTDS 20 Eval[e,h]	Run-in fail	Rand						Dose Adj Visit	Study Drug D/C Visit [d]
ICF	X													
Incl./Excl. Criteria	X													
Pain History	X													
Medical Hx	X													
ECG[c]	X					X	X			X		X		X
Serum Preg. Test	X					X						X		X
Phys. Exam[e]	X					X						X		X
Lab Evaluations	X					X	X					X		X
Vital Signs	X	X				X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Begin Run-in		X												
Con-meds & therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone Contact	X [f]		X[e]					X[g]	X[g]	X[g]	X[g]	X[g]		
Evaluate BTDS[e]			X	X	X									
SOWS[i]								Daily						
Oswestry		X					X	X	X	X	X	X		X
BPI-SF		X					X	X	X	X	X	X		X
MOS Sleep Scale		X					X	X	X	X	X	X		X
SF-36		X					X	X	X	X	X	X		X
PGIC												X		X
Diary	Daily	Daily	Daily	Daily	Daily		Daily	Daily	Daily	Daily	Daily	Daily		
'Average Pain over the last 14 Days'	X													
'Average Pain over the Last 24 Hrs'[j]	X	X	X	X	X			X	X	X	X	X		X
Review of Subject Diary		X	X	X	X			X	X	X	X	X	X	X
Dispense/collect Study Med & review for MHIs		X		X	X		X	X	X	X	X	X	X	X
Randomization							X							
Study compl.or D/C												X		
DB Study Drug D/C														X

[a] = If after 10 days, the subject responded to and tolerated BTDS10, he/she will proceed to V3 Randomization on the same day. If the subject did not tolerate BTDS 10, he/she will proceed to V3 Run-in Failure on the same day. If the subject tolerated BTDS 10 but did not respond to treatment, he/she will receive BTDS 20 for another 10 days.

[b] = "Visit 8/end of study" evaluations should be performed for subjects that (a) complete all 84 days of the Double-blind Phase or (b) discontinue study-drug prior to completing 84 days and choose NOT to continue to complete all remaining clinic visits and procedures. The "Visit 8/End of Study" procedures should be completed as soon as possible after discontinuing study-drug. Importantly, the subject should record his/her "average pain over the last 24 hours" score on his/her diary at the time of discontinuation of study-drug.

[c] = 2 readings a minimum of 10 minutes apart

[d] = "Study Drug Discontinuation" procedures should be performed for subjects that discontinue study-drug for any reason prior to completing all 84 days of the Double-blind Phase and choose to continue to complete all remaining clinic visits and procedures. The "Study Drug Discontinuation" procedures should be completed as soon as possible after discontinuing study-drug. Importantly, the subject should record his/her "average pain over last 24 hours" score on his/her diary at the time of discontinuation of study-drug.

[e] = Procedures must be performed by a MD or DO.

[f] = Once all Inclusion/Exclusion criteria (with exception of the daily pain scores) are met, the Investigator or site staff will call the subject and instruct him/her to stop all incoming analgesic medications and other medications used for chronic pain. Starting 2 days after the subject discontinued all pain medications used for chronic pain, the Investigator or the site staff will contact to the subject daily to assess the subject's pain scores for qualification to enter the Run-in Period.

[g] = The site personnel will contact the subject two days before the scheduled visits to remind him/her NOT to take any supplemental analgesic medications during the 30 hour period prior to the clinic visit

[h] = Applicable only to subjects who received BTDS 20 for 10-12 days.

[i] = SOWS will be conducted daily on Post-randomization Days 1 through 7.

[j] = During the Pre-Randomization Phase, 'average pain over the last 24 hours' scores will be recorded daily in the diary at around 8pm. During the Double-blind Phase, 'average pain over the last 24 hours' scores will be recorded at the study visits.

Reference: Table 1. Schedule of Visits and Procedures from Amendment 1 of Protocol BUP3024, pg 27

Screening Period (Days -10 to -1)
Subjects were to have signed an informed consent form at Visit 1 prior to undergoing any study-specific procedures. Subjects were to have recorded their average low back pain over the past 14 days on medication. Subjects meeting preliminary eligibility criteria were to have the following tests:

- 2 ECGs 10 minutes apart: Subjects with one or more QTcB ≥ 480 msec (*Amendment 2 added: one or more QTcF ≥ 480 msec*) were to have been discontinued. All electronic ECG data was to have been transmitted to (b) (4) for cardiologist interpretation. A copy of these and all subsequent ECGs were to have been saved in the subject's file
- Blood, urine and pregnancy testing

If and when subjects met all eligibility criteria (with exception of the daily pain scores), the Investigator or site staff were to have immediately contacted the subjects by telephone and instructed them to discontinue all analgesic medications and other medications used for chronic pain. Subjects were then to have started recording their daily 'average pain over the last 24 hours' scores in the diary at approximately 8pm every evening. Starting 2 days after all pain medications were to have been stopped, the Investigator or site staff were to have contacted subjects daily by telephone to assess their pain scores. Subjects were to have been instructed to stop recording pain scores and return to the clinic for Visit 2 as soon as possible after reporting two consecutive days of 'average pain over the last 24 hours' scores ≥ 5 (excluding the day pain medications were stopped). Eligible subjects were to have been enrolled in the Open-label Run-in Period.

Open-label Run-in Period (Day 1 up to Day 27)
To be eligible, to enter the Open-label Run-in Period subjects were to have an average pain rating over the last 24 hours ≥5 for 2 consecutive days during the Screening Period.
The following treatments were to have been administered in the Run-in Period:

- BTDS 5 patch applied to all subjects at the first visit and worn for up to 3 days;
- BTDS 10 patch administered to all subjects who tolerate the BTDS 5 patch and worn for at least 10 days;
- BTDS 20 patch applied for at least 10 days to all subjects who tolerate the BTDS 10 patch but do not meet protocol-specified responsiveness criteria.

Subjects were to have been trained in application of BTDS 5 patch and reminded to record the average pain over the last 24 hours at 8:00pm every evening and

patch removal/application information in their diary. Subjects were to have been provided three BTDS 10 patches (2 patches for the 10-day treatment and 1 extra). Subjects were to have worn BTDS 5 for three days. At three days subjects were to have been contacted by the staff and those subjects not able to tolerate BTDS 5 were to have been discontinued from the study and considered Run-in Failure. Subjects able to tolerate BTDS 5 were to have been instructed to remove the BTDS 5 patch and apply a BTDS 10 patch to a different location for an additional 10 days. Subjects who responded and tolerated BTDS 10 were to have been randomized to BTDS 10 or matching TDS placebo. Subjects who do not tolerate BTDS 10 were to have been discontinued from the study. Subjects who tolerate BTDS 10 but do not adequately respond were to have their dose increased to BTDS 20 for an additional 10 days.

Responsiveness to BTDS was defined as:

- ≥2 point reduction from Screening in "average pain over the last 24 hours" scores on the 3 consecutive days immediately prior to randomization, and;
- "average pain over the last 24 hours" score of ≤4 for his/her low back pain on the 3 consecutive days immediately prior to randomization.

For all subjects who received BTDS 10 treatment unused study medication was to have been collected. Subjects who both tolerate and respond to BTDS 20 were to have entered the Double-blind Phase and be randomized to either BTDS 20 or matching TDS placebo. Subjects who do not tolerate or respond to BTDS 20 were to have been discontinued from the study. Subjects were not to have used supplemental analgesic medications.

Double-blind Randomized Period(12 weeks)

To be eligible for randomization the following procedures were to have been met at
Visit 3:

- 2 ECGs a minimum of 10 minutes apart with QTcB of <480 msec on both ECGs
    - If QTcB interval is ≥ 480 msec on one or more ECG the data must be transmitted to the cardiologists at (b) (4) for a rapid review. If the subject is not willing to wait they will be discontinued from the study.
    - If the results show that one or more QTcF values are ≥ 500 msec the subject must be discontinued due to the reason of Adverse Event recorded as "QTcF prolonged (≥ 500 msec)."
    - If the rapid review results show the QTcF value(s) are <500 msec and if the subject did not wait for the rapid review results, the reason for discontinuation must be recorded as "Administrative: subject unwilling to wait for rapid review results" and if the subject did wait at the site, he/she will continue in the study.

- *Amendment 2 added the following ECG guidelines for QTcF: If, after the subject has been randomized, the report shows one of the following results, the subject must be evaluated per the parameters below to determine if he/she qualifies to continue in the study:*
  1) If the results from the (b) (4) *review show that one or more QTcF values are ≥ 500 msec, the subject must be discontinued due to the reason of Adverse Event. In such cases, an adverse event should be recorded on the AE CRF page as "QTcF prolonged (≥ 500 msec)."*
  2) *If the results from the* (b) (4) *review show that one or more QTcF value(s) are between 480 and 499 msec, inclusive, then* (b) (4) *will calculate the change in the average QTcF value from baseline to Visit 3. If the change in the average QTcF value from baseline is > 60 msec, the subject must be discontinued due to the reason of Adverse Event. The adverse event should be recorded on the AE CRF page as "QTcF prolonged (QTcF ≥ 480 and ≤ 499 msec and ΔQTcF > 60 msec)."*
  3) If the results from the (b) (4) *review show that the QTcF values are between 480 and 499 msec, inclusive, with a change in average QTcF value from baseline to Visit 3 ≤ 60 msec, the investigator will immediately contact the Sponsor Medical Monitor (or designee) to discuss the subject's medical history, concomitant medications and evaluate whether, in their medical judgment, there is any risk to the subject's health if he/she continues in the study. If the subject is discontinued, an adverse event should be recorded on the AE CRF page as "QTcF prolonged (QTcF ≥ 480 and ≤ 499 msec, ΔQTcF ≤ 60 msec, unfavorable risk benefit)."*
- *Amendment 2 added the following ECG guidelines for QTcB: If one or more QTcB intervals generated at the site are ≥ 480 msec, the electronic ECG data must be transmitted immediately to* (b) (4) *for a rapid review. The subject should wait for the review results at the site (approximately 2-4 hours).*
  1) If the results from the (b) (4) *rapid review show that one or more QTcF values are ≥ 500 msec, the subject must be discontinued due to the reason of Adverse Event regardless of the subject's willingness to wait for the results. In such cases, an adverse event should be recorded on the AE CRF page as "QTcF prolonged (≥ 500 msec)."*
  2) *If the results from the* (b) (4) *rapid review show that one or more QTcF value(s) are between 480 and 499 msec, inclusive,*

then (b) (4) *will calculate the change in the average QTcF value from baseline to Visit 3. If the change in the average QTcF value from baseline is > 60 msec, the subject must be discontinued due to the reason of Adverse Event regardless of the subject's willingness to wait for the results. In such cases, an adverse event should be recorded on the AE CRF page as "QTcF prolonged (QTcF ≥ 480 and ≤ 499 msec and ΔQTcF > 60 msec)."*

3) *If the results from the* (b) (4) *rapid review show that the QTcF values are between 480 and 499 msec, inclusive, with a change in average QTcF value from baseline to Visit 3 ≤ 60 msec, and:*

a. If the subject did not wait for the rapid review results, he/she must be discontinued from the study. The reason for discontinuation must be recorded as "Administrative: subject unwilling to wait for rapid review results."

b. If the subject did wait at the site for the rapid review results, the investigator will immediately contact the Sponsor Medical Monitor (or designee), while the subject is on site, to discuss the subject's medical history, concomitant medications and evaluate whether, in their medical judgment, there is any risk to the subject's health if he/she continues in the study. If the subject continues in the study, the remaining Visit 3 study procedures, as described below, will be followed. If the subject is discontinued, an adverse event should be recorded on the AE CRF page as "QTcF prolonged (QTcF ≥ 480 and ≤ 499 msec, ΔQTcF ≤ 60 msec, unfavorable risk benefit)."

4) If the results from the (b) (4) *rapid review show that the QTcF values are < 480 msec, and:*

a. If the subject did not wait for the rapid review results, he/she must be discontinued from the study. The reason for discontinuation must be recorded as "Administrative: subject unwilling to wait for rapid review results."

b. If the subject did wait at the site for the rapid review results, he/she will
continue in the study.

For study visits during the maintenance phase of the study, the same ECG algorithm described for the randomization phase applied (Amendment 2)

Figure 5.3.1.1 summarizes the above actions based on the results of the ECG rapid review changes from Amendment 2.

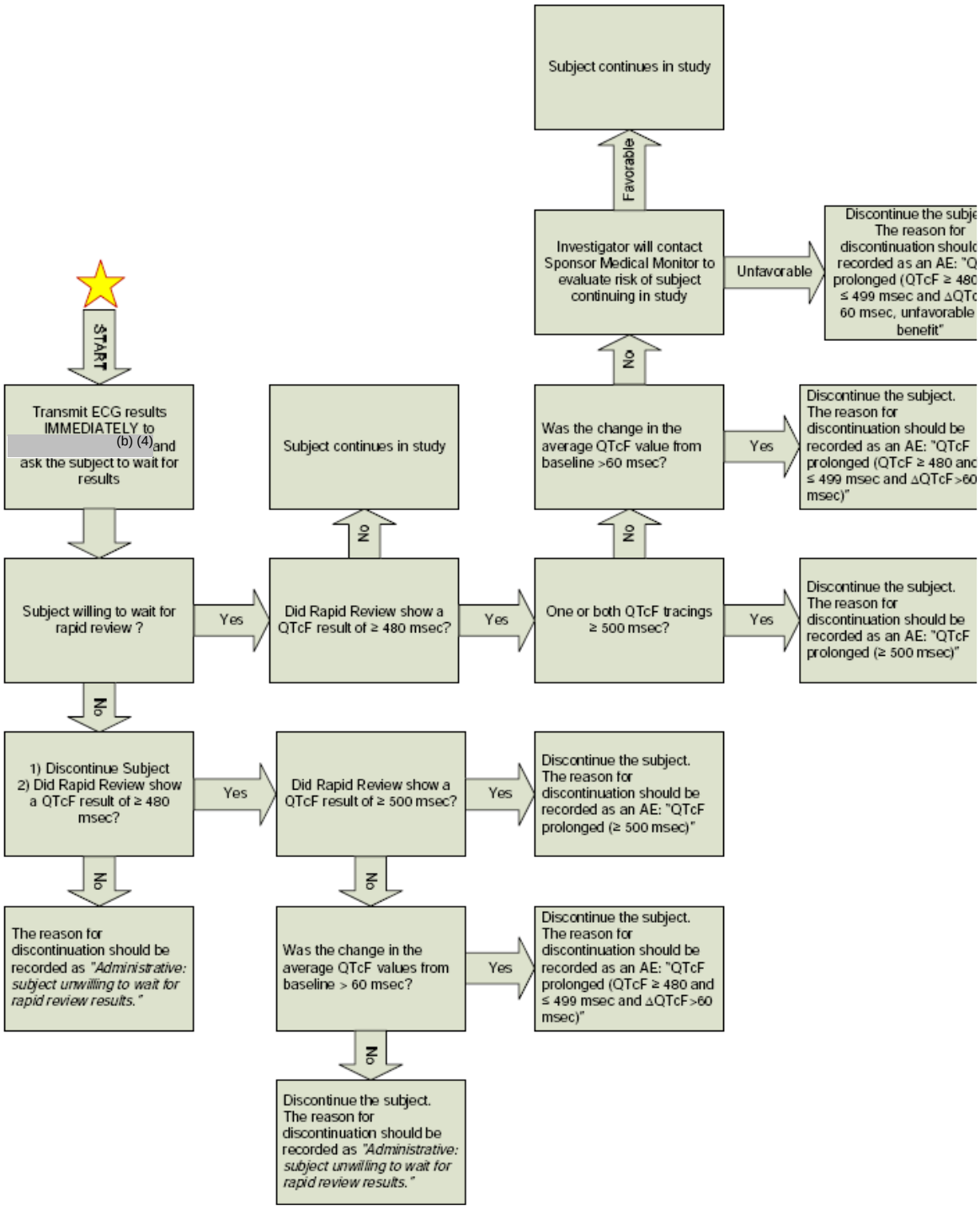
- Responsive criteria
- Tolerated BTDS treatment
- Not using non-study analgesic medications

- Completed the diary appropriately

Subjects who were eligible for randomization were to have had the following procedures/evaluations:

- Vital signs
- Draw blood for lab evaluations
- Collect urine for lab evaluations
- Record responses to the following questionnaires: Oswestry Disability Index, Brief Pain Inventory (BPI) Short Form, Medical Outcomes Study (MOS) Sleep Scale, and SF-36

Figure 5.3.1.1: Decision Points Based on Results of ECG Rapid Review



Reference: Figure 4: Evaluation of Rapid Review Results from (b) (4) Protocol BUP3024 Amendment 2

Randomization was to have been stratified so that subjects who tolerated and responded to BTDS 10 were to have been randomized in a 1:1 ratio to BTDS 10 or matching TDS placebo, and subjects who tolerated and responded to BTDS 20 were to have been randomized to BTDS 20 or matching TDS placebo. For the first 6 days post-randomization, subjects were to have been provided immediate-release oxycodone 5 mg twice daily as supplemental analgesia. For the remainder of the study supplemental analgesia was to have been acetaminophen or ibuprofen. Subjects were to have refrained from taking supplemental analgesic medication for 30 hours prior to each visit and were to have received a reminder call two days prior to each scheduled Double-blind Phase clinic visit. At each visit, the subjects were to have assessed their pain during the prior 24 hours. Subjects were to have been allowed a ± 2-day window for each scheduled visit.

The following procedures were to have been performed at each visit:

- Verify that subject has abstained from using supplemental analgesic during the 30 hours prior to this visit. If the subject did not comply with this requirement, every attempt should be made to reschedule this visit within 1 day if this is a Week 1 visit, or within 3 days if this is a Week 2, 4, or 8 visit
- Collect all used/unused study medication
- Record all concomitant medications
- Record all adverse events
- Have the subject record his/her 'average pain over the last 24 hours' score
- Review the subject's diary including SOWS (Visit 4 only), patch application/removal information (date/time/site of application), and supplemental analgesic use (time/date/amount of analgesics taken for low back pain)
- Obtain vital signs
- For Visit 6 only, 2 ECGs 10 minutes apart were to have been obtained. *Amendment 2 changed the discontinuation parameters for QTcB and QTcF to be consistent with the randomization eligibility paramters.*
- Dispense Double-blind study medication and remind the subject that each patch should be worn for 7 days
- Dispense supplemental analgesic medication (APAP or ibuprofen)
- Have the subject record his/her responses to the following questionnaires: Oswestry Disability Index, Brief Pain Inventory (BPI) Short Form, Medical Outcomes Study (MOS) Sleep Scale, and SF-36
- Instruct the subject to record his/her responses to the following information in the diary:
    - Date/time/amount of supplemental analgesic medication taken for low back pain

- ‘Pain right now’ score immediately prior to the time of ingestion of supplemental analgesic for low back pain
- Patch removal/application information (date/time/site of application)

Dose Adjustment: Dose titration was to have been allowed for subjects randomized to BTDS 20 or matching TDS placebo consisting of one down-titration and if needed one up-titration back to BTDS 20. No dose titration was to have been permitted for subjects randomized to BTDS 10 or matching placebo.

Visit 8 (Double-blind Week 12) End of Study: The following procedures were to have been completed at this visit:

- Verify that the subject has abstained from using supplemental analgesic during the 30 hours prior to this visit
- Collect all used/unused study medication
- Record all concomitant medications and non-drug therapies
- Record all adverse events
- Have the subject record his/her “average pain over the last 24 hours”
- Perform physical exam and obtain vital signs
- Lab evaluations and pregnancy testing
- Obtain Urine
- Obtain two ECGs a minimum of 10 minutes apart
- Have subject record: Oswestry Disability Index, Brief Pain Inventory Short Form, medical Outcomes Study (MOS) Sleep Scale, SF-36, and Patient’s Global Impression of Change (PGIC)

Efficacy Assessments/Endpoints

The following efficacy assessments were to have been performed:

Primary Efficacy Assessment/Endpoint

- Average pain over the last 24 hours assessed at weeks 1, 2, 4, 8 and 12 of the Double-blind Phase. The primary efficacy endpoint was to have been ‘average pain over the last 24 hours’ at Week 12

Secondary Efficacy Assessments/Endpoints

- Daily number of tablets of non-opioid supplemental analgesic medications during weeks 2 through 12 of the Double-blind Phase (daily number of tablets of sponsor-supplied acetaminophen or ibuprofen was to have been recorded in the subjects’ diaries)
- Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale

- consists of 12 individual items: 4 sleep disturbance, 2 sleep adequacy, 1 quantity of and optimal sleep, 3 somnolence, 1 snoring, 1 shortness of breath

Other Efficacy Assessments

- Responder Analysis 1: Using the "average pain over the last 24 hours" a response to treatment will be calculated based on the subject achieving various levels of percent reduction in pain severity from Screening mean to Week 12. Subjects who discontinue study drug prior to Week 12 will be assigned a 0 reduction in pain.
- Responder Analysis 2: Missing Week 12 "average pain in the last 24 hours" scores will be estimated using the following hybrid imputation approach: BOCF method of imputation for discontinuations due to adverse events and LOCF imputation for other discontinuation reasons
- Patient Global Impression of Change (PGIC)
- Oswestry Disability Index (ODI)
- Brief Pain Inventory Short Form (BPI-SF)
- Medical Outcomes Study 36-item Short-Form (SF-36)
- Time to discontinuation due to lack of therapeutic effect

Safety Assessments

The following pre-specified safety assessments were to have been performed:

- Vital signs: Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, and weight were to have been obtained at the following visits: Visit 1 (Screening), Visit 2 (start of Run-in), Visit 3 (start of Double-blind), Visits 4-8 (week 1-12 of Double-blind) and at the Dose adjustment Visit or early study drug discontinuation if any. Blood pressure and pulse were to have been measured after the subject had been sitting for 3 minutes

- ECG: Two 12-lead ECGs a minimum of 10 minutes apart were to have been performed at the following visits: Screening, Visit 3 (start of Double-blind), Visit 6 (week 4 of the Double-blind), Visit 8 (week 12 of the Double-blind) and at any visit that subjects discontinue study-drug

- Modified Subjective Opiate Withdrawal Scale (SOWS): The SOWS was to have been collected daily for the first seven days of the Post-randomization Phase.

- Laboratory Tests:
  Laboratory tests were to have been obtained at the following visits: Visit 1 (Screening), Visit 3, Visit 8 and if the subject discontinued study-drug early.

Hematology: RBC, hemoglobin, hematocrit, platelets, and WBC with differential

Serum Chemistry: Sodium, potassium, chloride, calcium, bicarbonate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, BUN, creatinine, glucose, albumin, cholesterol, triglycerides, phosphorus, lactate, dehydrogenase (LDH), total protein, globulin, *Amendment 2 added uric acid*

Urinalysis: pH, protein, glucose, ketone, occult blood, RBC, WBC, epithelial cells, bacteria, casts, crystals, specific gravity

- Serum pregnancy test: Pregnancy testing was to have been conducted at Screening, Visit 3, Visit 8, or at any visit that subjects discontinued study drug

- Adverse Events: Adverse events were to have been recorded through the 7 days following the last dose of study drug or until the last study visit, whichever was later. Subjects with adverse events that were ongoing were to have been followed until resolution or for 30 days after the subject's last study drug dose, whichever comes first. All serious adverse events were to have been followed until the event resolves, or stabilizes.

Statistical Methods:

Subject Populations

- *Enrolled Population:* Subjects who provided informed consent
- *Safety population:* Subjects who received study drug and had at least one safety assessment during the Open-label run-in period. Safety assessments include adverse events, laboratory measurements, ECG and vital signs.
- *Randomized Safety Population:* Subjects who were randomized, received at least one dose of the double-blind study medication, and had at least one safety assessment during the Double-blind Phase.
- *Full Analysis Population:* Subjects who were randomized and received at least one dose of Double-blind study medication
- *Per Protocol Population:* Subset of the Full Analysis Population of subjects who were not considered major protocol violators. The criteria for defining the per protocol set were to have been fully defined in the statistical analysis plan prior to unblinding the study.

Statistical Analysis

Efficacy: The primary efficacy analysis of 'average pain over the last 24 hours' was to have used a mixed effects general linear model with repeated measures. Missing scores were to have been imputed by the following hybrid BOCF and LOCF method:

- The subject's screening mean pain will be carried forward (BOCF) for discontinuations due to adverse events
- The subject's last non-missing score prior to discontinuation of double-blind study medication will be carried forward (LOCF) for other discontinuation reasons.

To assess the sensitivity of the primary efficacy analysis to the choice of missing data imputation and analysis method, additional analyses were to have been conducted on the choice of primary outcome and imputation method.

- Choice of primary outcome: 'average pain over the last 24 hours score' will be assessed comparing the group means at Weeks 4, 8 and 12 using the hybrid imputation method and the same mixed effects general linear model as in the primary analysis.
- Choice of imputation method: The week 12 analysis of 'average pain over the last 24 hours' scores will be performed with various imputation methods for missing data:
    - BOCF (baseline observation carried forward) imputation: Missing data at scheduled study visits subsequent to the discontinuation of study medication will be imputed using the screening mean value
    - LOCF (last observation carried forward) imputation: Missing data at scheduled study visits subsequent to the discontinuation of study medication will be imputed suing the subject's most recent non-missing assessment data prior to study medication discontinuation.
    - Retained dropout ITT: Data collected subsequent to the discontinuation of study medication and prior to discontinuation from study will be treated as observed data (retained dropout ITT analysis). Missing data due to premature discontinuation of study will not be imputed. Only observed data will be used in this sensitivity analysis.

The secondary efficacy variables were to have been the mean daily number of tablets of nonopioid supplemental analgesic medications and the sleep disturbance subscale of the MOS-Sleep Scale. In order to control Type I error rate at the 5% level, a gate-keeping strategy was to have been employed. First, the primary efficacy analysis was to be performed at the 5% level. If this test failed to show significance, then no hypothesis tests for the secondary efficacy variables were to have been performed. If the test was significant, then comparison between BTDS and Placebo for the two secondary variables were to have been performed.

Safety Analyses
Evaluation of safety was to have been performed for all subjects in the safety population and the randomized safety populations. Safety data was to have included AEs, clinical laboratory results, vital signs, ECGs, physical examinations and SOWS.

AEs were coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA), version 10. Verbatim description and the MedDRA system organ class (SOC), preferred term, and lower level term for all AEs were to have been contained in the subject data listings.

Protocol Amendments:

Original Protocol April 11, 2007
No subjects were enrolled under this protocol.

Amendment #1, May 22, 2007
The preceding protocol review was based on Protocol Amendment 1. The first subject was screened under this amended protocol. Amendment 1 added detailed instructions on the management of subjects whose QT interval was prolonged and corrected typographical errors.

Amendment #2, October 24, 2007
Amendment 2 further clarified decisions based on subjects who had QTcB or QTcF prolongation (specific ECG parameters are included in italics in the protocol review above).
Additional diagnoses were added to the exclusion criteria: gout, pseudogout, psoriatic arthritis, active Lyme Disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, ischial tuberosity bursitis, or neuropathic pain conditions. Uric acid was added to the clinical laboratory tests

Amendment 03, March 5, 2008
The following key changes were made to the protocol in this amendment:

- The lower limit of Alert Laboratory Range for sodium was increased from <125 mmol/L to <130 mmol/L.

Study Results

Enrollment/Randomization
A total of 1466 subjects were screened in 86 centers in the USA, including 19 subjects who were rescreened and counted twice. 1027 subjects qualified for

entry into the run-in period (3 subjects were not dosed resulting in 1024 subjects in the safety population). A total of 541 subjects were randomized, 257 to the BTDS group and 284 to the placebo group. There was no safety data during the double-blind phase for two subjects (one each in the placebo and BTDS treatment groups), resulting in a randomized safety population of 539 subjects.

Subject Disposition

Run-in phase
Of the 1024 subjects entered into the Run-in phase, 541 (53%) completed this phase and 483 (47%) discontinued. The two most frequent reasons for study drug discontinuation during the Run-in period were adverse event (23%) and loss of therapeutic effect (14%). Three subjects (0.3%) discontinued study drug due to "confirmed or suspected diversion." The reasons for drug discontinuation are summarized in Table 5.3.1.2. A total of 37% (382/1024) of subjects discontinued study drug during the Run-in phase either due to an adverse event or lack of therapeutic effect.

Double-blind Phase
A total of 34% (86/256) of subjects in the BTDS treatment group and 30% (84/283) of subjects in the placebo treatment group prematurely discontinued study drug. The main reasons for discontinuing study drug in the two treatment groups, summarized in Table 5.3.1.2, were different with more than twice as many subjects in the BTDS group than the placebo group discontinuing due to an adverse event, 16% (40/256) and 7% (20/283), respectively. More subjects in the placebo group than BTDS group discontinued due to lack of therapeutic effect, 13% (36/283) and 9% (22/256), respectively. The higher incidence of discontinuations in the BTDS group due to adverse events and in the placebo group due to lack of therapeutic effect would be expected.

Table 5.3.1.2: Subject Disposition and Reasons for Discontinuation

Category	Prerandomization Phase	Double-blind Phase[a] N = 539	
	Run-in Period[b] (n = 1024[c])	BTDS (n = 256)	Placebo (n = 283)
Completed period/phase on study drug, n (%)	541 (53)	170 (66)	199 (70)
Discontinued study drug – all cases,[d] n (%)	483 (47)	86 (34)	84 (30)
Drug discontinuation reason			
Adverse event	239 (23)	40 (16)	20 (7)
Subject's choice	37 (4)	10 (4)	11 (4)
Lost to follow-up	21 (2)	8 (3)	11 (4)
Lack of therapeutic effect	143 (14)	22 (9)	36 (13)
Confirmed or suspected diversion	3 (< 1)	0	0
Administrative	40 (4)	6 (2)	6 (2)
Discontinued study drug and study simultaneously, n (%)		70 (27)	71 (25)
Drug discontinuation reason			
Adverse event		32 (13)	18 (6)
Subject's choice		10 (4)	11 (4)
Lost to follow-up		8 (3)	11 (4)
Lack of therapeutic effect		15 (6)	25 (9)
Confirmed or suspected diversion		0	0
Administrative		5 (2)	6 (2)

[a] There were 2 subjects who were randomized but did not have safety data during the double-blind treatment and thus were not included in the randomized safety population: subject 0043020 (randomized to placebo), discontinued due to subject's choice and subject 0018008 (randomized to BTDS), lost to follow-up
[b] does not include screen failures.
[c] Does not include subjects 0039009, 0019038, and 0067001 who entered the run-in period, but were not dosed and were therefore excluded from the safety population.
[d] Subjects could discontinue double-blind study drug but elect to complete all visits and assessments.
Reference: Table 5. Subject Disposition and Reasons for Discontinuation: Safety and Randomized Safety Population, Clinical Study Report BUP3024, pg 101

Protocol Violations
Protocol deviations as categorized by the applicant included: exclusionary medical history, violation of pain score criteria either prior to entering the run-in period or the double-blind phase, supplemental medication deviations, and other. The FDA statistician noted that of the 541 subjects in the full analysis set, 148 subjects (27%) had at least one protocol deviation, major or minor. The proportion of deviations was balanced across treatment groups. Further, 98 subjects (18%) had at least one major protocol deviation, as deemed by the applicant. These were also balanced across treatment groups (Table 5.3.1.2).

Table 5.3.1.2: Major Protocol Deviations for BUP3024

	Treatment Group			
	Placebo (N=284)		BTDS (N=257)	
Deviation Category	**n(%)**	**R**	**n(%)**	**R**
Any Major Protocol Deviation	54(19.0)	83	44(17.1)	79
Medical History Inclusion/Exclusion Criteria Not Met	1(0.4)	1	1(0.4)	1
Incoming Opioid Dose > 5mg Oxycodone/Day	0	0	1(0.4)	1
Other Inclusion/Exclusion Criteria Not Met	0	0	1(0.4)	1
Subject Did Not Meet Run-In Criteria for Pain	6(2.1)	6	3(1.2)	3
Subject Did Not Meet Randomization Criteria for Pain	13(4.6)	27	12(4.7)	34
Randomization Kit Error	0	0	1(0.4)	1
Subject Took Prohibited Non-Opioid Medication	1(0.4)	1	0	0
Subject took Prohibited Opioid Medication	3(1.1)	3	1(0.4)	1
Supplemental Analgesic Taken Within 30 Hours Prior to Visit	35(12.3)	45	29(11.3)	37

N = number of subjects in full analysis population
n = number of subjects with at least one deviation
% = n/N
R = total number of deviations

Reference: Sponsor provided table from March 1, 2010 submission

Demographics
The demographic characteristics of the subjects randomized to BTDS were similar to those subjects randomized to placebo with respect to age, sex, race, weight and underlying diagnosis (Table 5.3.1.3). The pain scores during the screening Phase and prerandomization were also similar between the BTDS and placebo groups.

Table 5.3.1.3: Demographics and Baseline Characteristics in Randomized Population for BUP3024			
Parameter		**BTDS** N=256	**Placebo** N=283
Age	Mean (SD)	48.9 (12.5) years	50.1 (13.3) years
	Range	18-80 years	19-84 years
Gender	Male, n (%)	123 (48%)	120 (42%)
	Female, n (%)	133 (52%)	163 (58%)
Race	White, n (%)	183(71.0%)	196(69%)
	Black, n (%)	58 (23%)	62 (22%)
	Asian	12 (5%)	20 (7%)
	All other, n (%)	3 (1%)	5 (2%)
Ethnicity	Hispanic or Latino	39 (15%)	33 (12%)
	Not Hispanic	217 (85%)	250 (88%)
Weight (kg)	Mean (SD)	88.8 (21.9) kg	89.7 (22.67) kg
	Range	43-173	41-186
Diagnoses associated with back pain	Intervertebral disc	114 (45%)	109 (39%)
	Spinal Stenosis	8 (3%)	10 (4%)
	Spondylolysis	5 (2%)	3 (1%)
	Spoondylolisthesis	2 (<1%)	7 (2%)
	Osteoarthritis	89 (35%)	115 (41%)
	Other nonmalignant cause	38 (15%)	39 (14%)
Time since back pain diagnosis (years)	Mean (SD)	8.6 (8.01) years	9.5 (9.68) years
	Median	5.9 years	5.9 years
Average pain over the 14 days prior to screening	Mean (SD)	6.9 (1.21)	6.8 (1.26)
	Median	7.0	7.0
Screening mean pain scores (prior to entering run-in period)	Mean (SD)	7.2 (1.26)	7.2 (1.22)
	Median	7.0	7.0
Prerandomization pain scores	n	257	284
	Mean (SD)	2.57 (1.283)	2.56 (1.207)
Double-blind Week 12 pain scores	N	257	283
	Mean (SD)	3.83 (2.738)	4.38 (2.690)
Reference: Adapted from Table 7. Summary of Demographic and Baseline Characteristics: Randomized Safety Population, Clinical Study Report page 107 and Table 9. Summary of the "Average Pain Over the Last 24 Hours" Scores at Screening, Prerandomization, and Week 12 of the Double-blind Phase, Clinical Study Report page 109			

Efficacy Results

Primary Endpoint

The primary efficacy endpoint "average pain over the last 24 hours" at week 12 compared to baseline was statistically superior for BTDS compared to placebo (Table 5.1.3.4). Using a "hybrid" imputation method (BOCF for subjects who discontinued study medication due to an adverse event and LOCF otherwise)

agreed to under a Special Protocol Agreement, the primary efficacy analysis resulted in week 12 adjusted LS means (SE) of 3.81 (0.166) for the BTDS group and 4.39 (0.152) for the placebo group. BTDS was statistically superior (P=.0104) compared to placebo by a difference of 0.58 on an 11-point numerical rating scale. However, the confidence interval was fairly wide, showing that the effect could be between .14 and 1.02. The FDA statistician was able to verify the applicant's findings.

Table 5.1.3.4: Pain Scores at Screening, Prerandomization, and Week 12 of the Double-blind Phase – Hybrid Imputation, Full Analysis Population

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)	

Cross-references: Table 14.2.1.1; Appendices 16.2.6.1, 16.2.6.2, 16.2.6.4, and 16.1.9.2.1.
LS = least squares, SE = standard error

[a] Screening mean pain was the mean of the diary "average pain over the last 24 hours" scores during the 2 consecutive days in the screening period that qualified the subject to enter the run-in period.
[b] Prerandomization mean pain was the mean of the diary "average pain over the last 24 hours" scores during the days of the run-in period that qualified the subject for randomization to double-blind treatment.
[c] Statistics are based on a mixed effect general linear model with subject as a random component, treatment and time as fixed components, and the screening mean pain and prerandomization mean pain as fixed covariates.
[d] Does not include 1 subject who completed the study but the site did not collect the pain score.

Note: Number of subjects with data varies between visits because missing pain scores were only imputed for subjects who discontinued double-blind treatment early. Intermittent missing pain scores were not imputed.
Note: Based on the selection algorithm in the SAP, an unstructured covariance matrix was used.
Note: Pain scale is 11 points (0 = no pain to 10 = pain as bad as you can imagine).

Reference: Table 9. Summary of the "Average Pain Over the Last 24 Hours" Scores at Screening, Prerandomization, and Week 12 of the Double-blind Phase – Hybrid Imputation Using Adjudicated Reasons for Study Drug Discontinuation: Full Analysis Population, pg 109 of Clinical Study Report BUP3024

The applicant conducted a number of sensitivity analyses (Table 5.1.3.5). Statistical significance was not demonstrated with BOCF imputation but the results trended in the right direction, difference -0.34, P=.1502. Other sensitivity analyses demonstrated statistical significance. The FDA statistician, Jonathan Norton, confirmed the findings of the different sensitivity analyses submitted by the applicant and also noted that the statistical analysis plan for the Special Protocol Agreement did not require that the applicant demonstrate statistical significance with all of the sensitivity analyses.

More subjects had SOWs scores greater than 23 during the first week of the double-blind phase in the placebo group compared to BTDS group, 10 subjects (8%) and 2 subjects (<1%) respectively. This may have been related to opioid withdrawal symptoms but SOWs items are nonspecific and the relatively modest number of subjects involved is unlikely to substantially affect the efficacy results.

Table 5.1.3.5. Sensitivity Analyses of the Primary Efficacy Variable

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

Reference: Table10. Sensitivity Analyses of the Primary Efficacy Variable, pg 110 of Clinical Study Report

Secondary Endpoints

Results of the analysis of the two secondary efficacy variables, sleep disturbance and use of supplemental analgesics, tested using a stepwise gate-keeping approach to control the overall Type I error-rate at 5% are shown in Table 5.1.3.5. Using the sleep disturbance subscale of the MOS-Sleep Scale there was a statistical difference between BTDS and placebo. The applicant's analysis of sleep disturbance is based on weeks 4, 8 and 12. The FDA statistician reanalyzed sleep disturbance at Week 12 to be more consistent with current Division policy and determined that the effect of BTDS is still significant (p=.035) with a similar point estimate (-3.78). No statistically significant difference was noted in the mean daily number of tablets of nonopioid supplemental analgesic used during weeks 2 to 12 of the double-blind phase but the placebo group trended toward using more supplemental analgesia.

Table 5.1.3.5. Summary of Secondary Efficacy Results

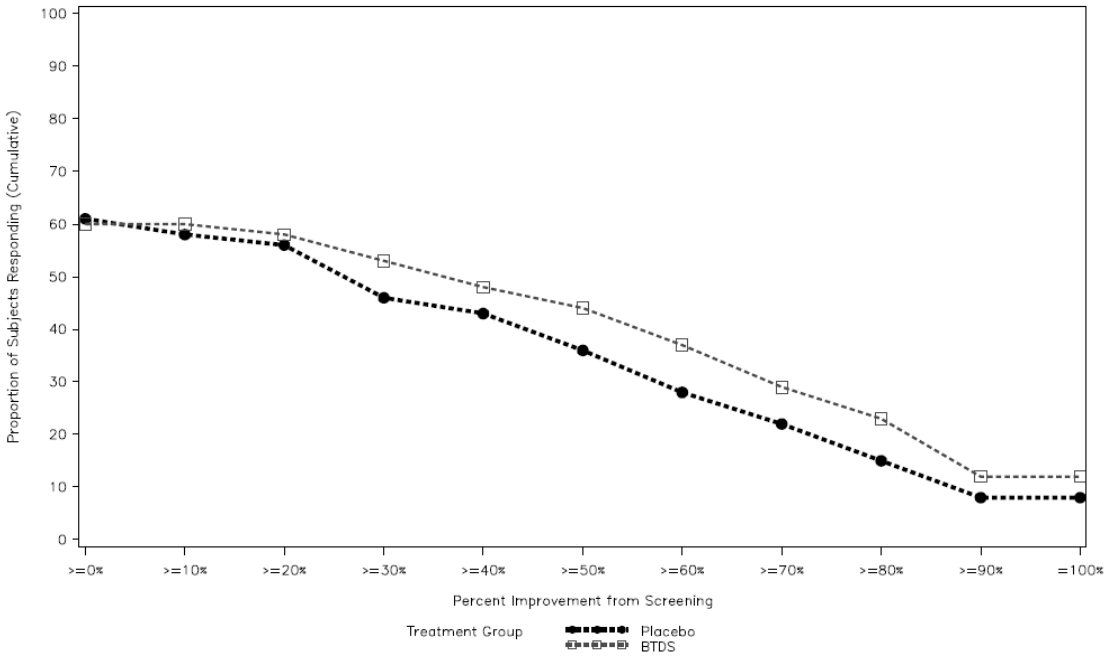
Treatments/Measurements	Treatment Difference (95% CI)	*P* Value	α-Level	Decision
Sleep disturbance subscale of the MOS-Sleep Scale at weeks 4, 8, and 12	−4.40 (−7.55, −1.25)	.0062	.025	Significant
Mean daily number of tablets of nonopioid supplemental analgesic during weeks 2 to 12 of double-blind treatment	−0.124 (−0.296, 0.048)	.1586	.05	NS

Reference: Table11. Application of a Gate-keeping Method to Assess Statistical Significance of Multiple Endpoints: BTDS vs Placebo: Full Analysis Population, pg 111 of Clinical Study Report

Responder Analysis

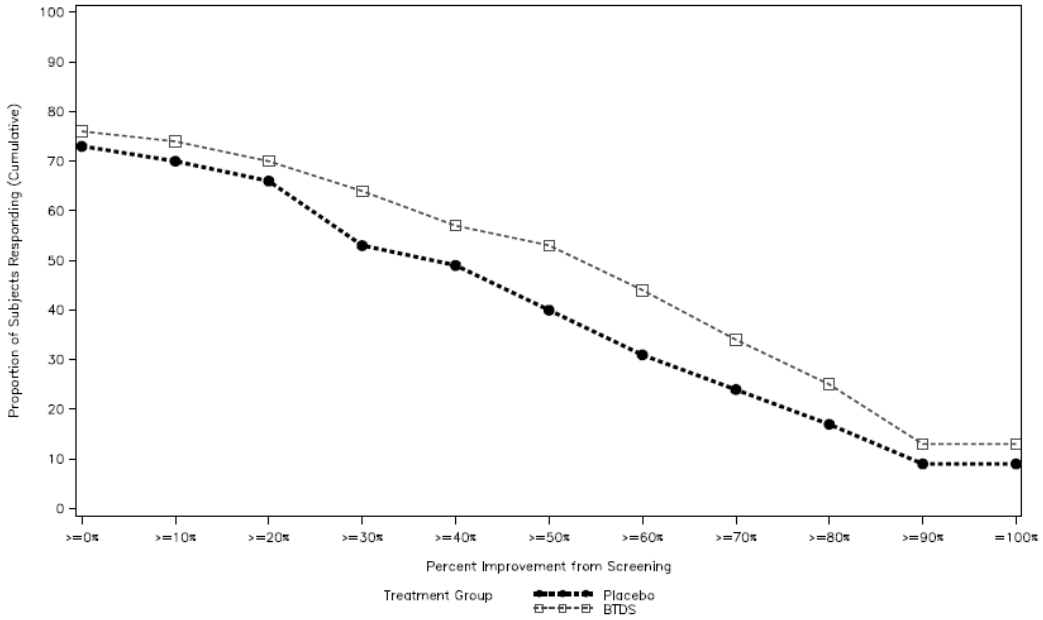
The applicant performed two versions of the responder analysis. In responder analysis 1, subjects who discontinued before week 12 were regarded as nonresponders (Figure 5.1.3.1.2). The plot demonstrates that subjects receiving BTDS reported a greater percent reduction in pain severity than placebo subjects but the difference was small. Subjects reporting a greater than or equal to 30% reduction in pain form baseline was 53% in the BTDS group versus 46% in the placebo group for responder analysis 1. The FDA statistician noted that the proportion of responders in the two treatment arms at the 30% cut point were not significantly different at the conventional .05 level (chi-square test, p=.10). The benefit was more noticeable when a hybrid imputation was used for dropouts in responder analysis 2. In responder analysis 2 the number of subjects reporting a greater than or equal to 30% reduction in pain from baseline was 64% for the BTDS group versus 53% for the placebo group (Figure 5.1.3.1.3).

Figure 5.1.3.1.2: Plot for Responder Analysis 1
Discontinuations Prior to Week 12 Regarded as Non-responders



Reference: Figure 14.2.11.9. Plot for Responder Analysis 1-discontinuations Prior to Week 12 Regarded as Non-responders, Double-blind Period, Full Analysis Population, pg 283 of Clinical Study Report

Figure 5.1.3.1.3: Plot for Responder Analysis 2
Hybrid Imputation Used for Dropouts Prior to Week 12



Reference: Figure 14.2.11.10. Plot for Responder Analysis 2-Hybrid Imputation, Double-blind Period, Full Analysis Population, pg 284 of Clinical Study Report

5.3.2 BUP3015

The following summary of the design of BUP3015 was derived from the original protocol dated October 15, 2003.

Title: "A multicenter, randomized, double-blind, active comparator study to determine the efficacy and safety of BTDS 20 or OxyIR® versus BTDS 5 in subjects with moderate to severe low back pain"

Dates conducted:
The study was conducted from February 25, 2004 to September 23, 2005. The applicant reports that enrollment was terminated early for administrative reasons unrelated to safety or efficacy.

Objectives:
The primary objective of the study was to evaluate the analgesic efficacy and safety of Buprenorphine Transdermal System (BTDS) in subjects with moderate to severe chronic low back pain who required opioid analgesics for pain control.

Overall Design:
This was a Phase 3, randomized, double-blind, double-dummy, active comparator, parallel-group, multicenter study comparing BTDS 20 or OxyIR® (oxycodone HCl immediate-release) capsules to BTDS 5 in opioid experienced subjects with moderate to severe chronic low back pain. It is important to note that OxyIR is an unapproved, marketed product and is not valid for comparison.

The study design was to have included a prerandomization phase (screening and run-in periods), double-blind phase and extension phase. Subjects demonstrating benefit and tolerability with BTDS 20 during the run-in period were to have been randomized in the 12-week double-blind phase to receive BTDS 20, BTDS 5, or oxycodone (two 5-mg capsules every 6 hours for a daily dose of 40 mg) and matching placebos. Following completion of the double-blind phase there was to have been an open-label extension phase during which subjects could receive BTDS 5, 10 or 20 for up to six months. *The extension phase was increased to 52 weeks (Amendment 2)*

Rationale for BTDS 5 and Oxy IR Treatment Groups
BTDS 5: The applicant reports that an active control design was employed to decrease the likelihood of withdrawal and increase the chances of maintaining subjects in the study for 12 weeks.

OxyIR: The applicant picked OxyIR as the active comparator because it is an opioid known to be effective for the treatment of low back pain and would serve as a good measure of trial sensitivity.

Inclusion Criteria:

Patients were to have met the following criteria:

- Males or females age 18 years or older (females must have a negative serum pregnancy test, be non-lactating, and willing to use adequate and reliable contraception throughout the study)
- Clinical diagnosis of low back pain for 3 months or longer as confirmed by radiographic evidence with or without radiation to the lower extremities of the following: conditions related to intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis or other, similar non-malignant condition
- *Subjects must rate their average low back pain on their preexisting therapy for the 14 days prior to enrollment (Visit 1) as none or mild using the following 5-point scale: 0=none, 1=mild, 2=moderate, 3=moderately-severe, and 4=severe. (Amendment 1 deleted this inclusion criteria)*
- Subjects must be willing to discontinue their current opioid analgesic regimen.
- Subjects must be willing to adjust the dose of their non-opioid analgesic regimen.
- Subjects must be compliant with routine medical care and able to read, understand, and sign the written informed consent.
- Subjects must be taking between 30-80 mg of oral morphine sulfate or equivalent/day, at least 4 days a week, for at least the 30 days prior to Visit 1.
- *Baseline ECGs at visit 1 with a mean QTcF of < 480 msec (mean of 4 tracings) and all individual QTcF determinations < 500 msec (Amendment 4)*
- *Serum potassium concentration within normal range (Amendment 4)*

Exclusion Criteria:

Patients were to have been excluded if any of the following applied:

- Subjects taking more than 80 mg per day of oral morphine sulfate or equivalent within 30 days of screening.
- Subjects who have a history of chronic condition(s), in addition to low back pain, requiring frequent analgesic therapy (e.g., headaches, osteoarthritis, fibromyalgia, gout, rheumatoid arthritis, diabetic neuropathy).
- Subjects scheduled for surgery of the disease site (e.g., disk repair surgery), or any other major surgery during the study.

- Subjects who are truly allergic to buprenorphine or oxycodone or who had a history of allergies to other opioids. This does not include patients who experienced common opioid side effects (e.g., nausea, constipation, etc).
- Subjects who received initiation or an increase in the dose of oral corticosteroids within 6 weeks prior to entering the study.
- Patients who had intra-articular or intramuscular steroid injections within 6 weeks of entering the study.
- Subjects with QTc > 500 msec recorded at Visit 1 or 3. *Amendment 2 also added or QT > 500 msec. Amendment 4 deleted this entire exclusion criteria and replaced it with stricter inclusion criteria*
- Subjects with clinically unstable respiratory disease, cardiac disease, dysfunction of the biliary tract, hypothyroidism, adrenal cortical insufficiency, or renal stricture, or any other medical condition, that, in the investigator's opinion, precludes entry into this study.
- Subjects with evidence of impaired liver function upon entry into the study (values ≥ 3 times the upper limit of normal for aspartate transaminase (AST) or alanine transaminase (ALT), or bilirubin ≥ 1.3 mg/dl), or, in the investigator's opinion, liver function impairment to the extent that the subject should not participate in this study.
- Subjects with evidence of impaired kidney function, serum creatinine > 2 mg/dl.
- Subjects with a current or past (within 5 years) history of substance or alcohol abuse, or subjects who have demonstrated addictive or substance abuse behaviors.
- Subjects who have depression or other psychiatric disorder such that participation in the study may, pose an unacceptable risk to the subject.
- Subjects with a dermatological disorder at any relevant patch application site that precludes proper placement and/or rotation of patch placement.
- Subjects receiving buprenorphine, methadone, or levo-alpha acetyl methadol (LAMM) for pain control or treatment of addiction.
- Subjects receiving hypnotics or other central nervous system (CNS) depressants that may pose a risk of additional CNS depression.
- Subjects receiving monoamine oxidase inhibitors (MAOIs) or who have been taking MAOIs within two weeks of entering the study.
- Subjects who have allergies or other contraindications to transdermal delivery systems or patch adhesives.
- Subjects with uncontrolled seizures or convulsive disorder.
- Subjects who participated in a clinical research study involving a new chemical entity within 30 days of study entry.
- Subjects who participated previously in a BTDS study.
- Subjects with a requirement for treatment with direct external heat sources.

- Subjects who cannot cut the hair at the patch site for proper patch placement.
- Subjects with an ongoing workman's compensation claim and/or litigation.
- Subjects who are unsuitable for any other reason to receive study medication, in the opinion of the investigator.
- *Subjects currently using fentanyl (Duragesic) for pain control or Methadone (Amendment 2)*
- *Subjects with congenital Long QT Syndrome or a family member with this condition (Amendment 4)*
- *Subjects receiving Class 1A antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide)(Amendment 4)*
- *Subjects receiving Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide)(Amendment 4)*
- *Clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active or symptomatic myocardial ischemia (Amendment 4)*

Study Medication

- BTDS 10 mg patch was to have been applied to all subjects at the first visit of the Run-in Period and worn for up to 7 days.
- BTDS 20 mg patch was to have been applied to all subjects meeting titration criteria during the Run-in Period. This strength patch will be worn for 7 -11 days but no individual patch was to be worn for more than 7 days.
- During the Double-blind Phase the treatment arms were to have been as follows:
    - BTDS 20 mg patch or matching placebo worn for 7 days. At each visit, subjects were to have been dispensed the number of 7 day patches needed until their next scheduled study visit.
    - BTDS 5 mg patch or matching placebo worn for 7 days. At each visit subjects were to have been given the number of 7 day patches needed until their next scheduled study visit.
    - OxyIR or matching placebo was to have been supplied to the subjects at the first visit of the double-blind phase to be taken by the subjects (10mg [two 5 mg capsules]) every 6 hours.

Concomitant Therapy

Rescue Analgesia
During the double-blind phase, subjects were to have been permitted to take supplemental analgesic medication in the form of ibuprofen (200 mg) or

acetaminophen (500 mg) up to every 4 hours for their low back pain. Ibuprofen was to have been the preferred medication, unless the subject was unable to take ibuprofen, in that case, acetaminophen was to have been allowed. In subjects whose pain was not managed with either ibuprofen or acetaminophen alone, a combination of the two medications was to have been allowed. On each occasion that supplemental analgesic medication was ingested for low back pain, subjects were to have recorded their 'pain right now', prior to taking the supplemental analgesic medication.

Concomitant Therapy and Restrictions

Opioid Analgesics: Following the Screening Period, opioid analgesics other than BTDS were to have been prohibited throughout the study.

NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen: The use of these medications was to have been allowed only at one-half the baseline dose or minimum therapeutic dose. Acetaminophen and ibuprofen use was to have been permitted provided that the total daily dose (sponsor provided plus other source) does not exceed 4 grams and 3200mg, respectively. Analgesics (including aspirin) indicated for other conditions (e.g., headache, fever, cardiovascular disease prophylaxis) were to have been permitted. If treatment with such drugs occurred, the medication (dose, frequency and reason for ingestion) were to have been recorded in the subjects' diary.

Adjuvant Analgesics: Adjuvant analgesics such as antidepressants (e.g., amitriptyline,
desipramine, nortriptyline, selective serotonin re-uptake inhibitors) and anticonvulsants (e.g., gabapentin, lamotrigine) prescribed for chronic pain were to have been allowed if the dose was stable for at least 1 month and expected to remain stable or the duration of the study.

Corticosteroid injections: Intra-articular corticosteroid injections administered to the lower back *or intramuscular steroid injections (Amendment 3)* were not to have been allowed for a period of 6 weeks prior to screening or during the course of the core study.

Oral Corticosteroids were to have been allowed if stable for at least 6 weeks prior to the screening visit.

Glucosamine and/or chondroitin sulfate were to have been allowed if the dose was
stable for at least 2 months prior to the study entry and is continued at the same dose for the duration of the study.

Ancillary Therapy: Ongoing transcutaneous electrical nerve stimulation (TENS), biofeedback, physical therapy, and relaxation therapy initiated at least 14 days prior to study entry were to have been allowed at the same intensity and frequency. Subjects receiving treatment with direct external heat sources such as heat lamps, electric blankets, saunas, heating pads, or who use heated water beds were to have been excluded.

Study Procedures:

A schedule of assessments from the original protocol is contained in Table 5.3.2.1.

Table 5.3.2.1: Original Protocol Schedule of Visits and Procedures for Study BUP3015

Phase	Pre-Randomization					Double-Blind				
Period	Screening			Run-in						
	Prospective Assessment	Opioid Taper								
Duration	7 days	≤7 days		14 days		84 days				
Study Visit	V1	V2	V3	V4	V5[a]	V6	V7	V8	V9	V10[b]
Written Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Pain History	X									
Medical History and current medical conditions	X									
Electrocardiograms	X[c]		X[c]					X[d]		X[d]
Pregnancy Test	X									X
Physical Examination	X									X
Laboratory Evaluations	X				X[f]					X
Vital Signs	X	X	X	X	X[f]	X	X	X	X	X
Adverse Events		X	X	X	X[f]	X	X	X	X	X
Discontinue current opioid medications		X								
Begin Run-in medication			X							
Concomitant medications and therapy	X	X	X	X	X[f]	X	X	X	X	X
SOWS[h]		daily								
Oswestry Disability Index[e]		X			X			X	X	X
BPI-SF[e]		X			X			X	X	X
MOS Sleep Scale[e]		X			X			X	X	X
Healthcare Utilization Questionnaire[e]		X						X	X	X
WPAI[e]		X						X	X	X
POMS-SF		X			X			X	X	X
SF-36[e]		X			X			X	X	X
PGIC										X
Paper Diary Completion[g] - Pain right now at bedtime - Pain right now with supplemental analgesic use - Supplemental analgesic use - Nighttime awakenings	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily	Daily
'Average Pain over Last 24 Hours'						X	X	X	X	X
'Worst Pain over Last 24 Hours'						X	X	X	X	X
Dispense/collect Subject Diary	X	X	X	X	X[f]	X	X	X	X	X
Opioid Taper time of onset			X							
Dispense/collect Study Medication[k]			X	X	X[f]	X	X	X	X	X
Randomization					X					
Complete abuse/diversion questionnaire										X
Study drug discontinuation[j]						X	X	X	X	
Study completion/discontinuation					X[f]					X

[a] = Visit 5, final run-in period visit; may occur any time a subject meets randomization criteria, or is discontinued from study-drug during Run-in Period.
[b] = Visit 10 evaluations will be performed when the subject discontinues study drug and when the subject completes the study or discontinues the study early.
[c] = 2 readings 10 minutes apart.
[d] = 4 readings 10 minutes apart.
[e] = The Oswestry Disability Index, BPI-SF, MOS Sleep Scale, Healthcare Utilization Questionnaire, WPAI, and SF-36 will be collected via phone interview by a call center at Visit 2, Visit 5, and Visits 8, 9 and 10. Except at Visit 5 the Healthcare Utilization Questionnaire and WPAI will not be collected.
[f] = Filled out for those who complete run-in period or at time of early discontinuation.
[g] = Questions shown are those asked during the Double-Blind Phase; different questions are asked during the Prerandomization Phase
[h] = SOWS will be conducted daily starting at Visit 2 and ending at Visit 3, but not including Visit 3.
i = These are the only procedures to be performed for subjects who enter the run-in period but do not continue into the Double-blind Phase.
j = Completed only if subject discontinues study drug during the Double-blind Phase and continues in the study. Study drug discontinuation may occur at or between visits.
k = Study medication will also be dispensed 2 weeks after Visit 8 and Visit 9 during the Double-Blind Phase.

FINAL
15, October 2003

Reference: Table1. Schedule of Visits and Procedures, pg 24 Original Protocol BUP3015

Numerous changes were made to the protocol by the applicant in the 5 amendments submitted to the original protocol. The key amendments are described in the review of the original protocol and included in the Table below of the Schedule of Visits from the final protocol.

Table 5.3.2.2: Schedule of Visits and Procedures for Study BUP3015 Based on the Final Protocol

Phase	Prerandomization								Double-blind					
Period	Screening				Run-in				Maintenance					
	Prospective Assessment	Opioid Taper												
Duration	7 Days	≤ 7 Days			≤ 21 Days				≤ 84 Days					
Study Visit	V1	V2	V3		V4	V4.1	V5 [a]		V6	V7	V8	V9	V10 [b]	Unscheduled Visit [f]
			Taper fail	Run-in			Run-in Fail	Rand.					D/C study	D/C study drug
Informed consent	X													
Inclusion/Exclusion criteria	X													
Pain history	X													
Medical history	X													
X-Ray [e]	X													
ECG [c]	X					X	X [d]				X		X	X
Serum pregnancy test	X						X						x	X
Physical exam	X						X						X	X
Lab evaluations	X						X	X					X	X
Vital signs	X	X		X	X		X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Begin run-in				X										
Concomitant medications & therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SOWS [g]		daily												
ODI [i]		X						X			X	X	X	X
BPI-SF [i]		X						X			X	X	X	X
MOS Sleep Scale [i]		X						X			X	X	X	X
HUQ [i]		X						X			X	X	X	X
WPAI [i]		X						X			X	X	X	X
POMS-SF		X						X			X	X	X	X
SF-36 [i]		X						X			X	X	X	X
PGIC													X	X
Diary (Protocol, Appendix A)	daily	daily		daily	daily	daily		daily	daily	daily	daily	daily	daily	daily
"Average pain over last 24 hours"									X	X	X	X	X	X
"Worst pain over last 24 hours"									X	X	X	X	X	X
Dispense/Collect subject diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
(continued)														
Opioid taper time of onset			X	X										
Dispense/Collect study drug [h]				X	X	X	X	X	X	X	X	X	X	
Randomization								X						
Abuse/Diversion							X						X	
Study completed/d/c													X	
DB study drug discontinuation (on-study/off-drug)														X

[a] Visit 5, final run-in period visit; occurred any time a subject met randomization criteria, or was discontinued from study drug during run-in period.

[b] "Visit 10/end of study" evaluations were performed for subjects who (a) completed all 84 days of the double-blind (DB) phase or (b) discontinued study drug prior to completing 84 days and chose NOT to continue to complete all remaining clinic visits and procedures. The "visit 10/end of study" procedures were completed as soon as possible after discontinuing study drug. Importantly, the subject recorded his/her average pain and worst pain over last 24 hours scores on his/her paper diary at the time of discontinuation of study drug.

[c] Four readings a minimum of 10 minutes apart.

[d] Four ECGs were not required if the subject had 4 ECGs performed in accordance with visit 4.1 procedures.

[e] X-ray was taken at visit 1 only if necessary (if not done within past 2 years).

[f] "Unscheduled visit" procedures were performed for subjects who discontinued study drug for any reason prior to completing all 84 days of the double-blind phase and chose to complete all remaining clinic visits and procedures. The "unscheduled visit" procedures were completed as soon as possible after discontinuing study drug. Importantly, the subject recorded his/her average pain and worst pain over last 24 hours scores on his/her paper diary at the time of discontinuation of study drug.

[g] SOWS were conducted daily starting at visit 2 and collected until subjects met criteria to enter the run-in period.

[h] Study drug was dispensed 2 weeks after visit 8 and visit 9 during the double-blind phase.

[i] Questionnaires, The Oswestry Disability Index (ODI), Brief Pain Inventory-SF (BPI-SF), Medical Outcomes Sleep Scale (MOS), Low Back Pain Health Utilization Questionnaire (HUQ), Work Productivity and Activity Impairment Questionnaire (WPAI), SF-36 Health Survey (SF-36) and Profile of Mood States-Short Form (POMS-SF) were collected via phone interview by a call center.

Reference: Table1. Schedule of Visits and Procedures, pg 46 CSR BUP3015

Screening Period (Visit 1)
Subjects were to have signed an informed consent form at Visit 1 prior to undergoing the following evaluations:

- Confirmation that subjects were taking a stable dose between 30-80 mg of oral MSO4 or equivalent per day, at least 4 days per week, for at least 30 days
- *Confirm subjects were receiving an adequate analgesic regimen by rating their average pain over the prior 14 days for their low back pain as none or mild where 0=none, 1=mild, 2=moderate, 3=moderately-severe, and 4=severe (Amendment 1 deleted this inclusion criteria)*
- Physical examination, medication history and current medical conditions, and concomitant medication and therapy
- ECG evaluation (2 readings, a minimum of 10 minutes apart) *Amendment 4 changed this to 4 ECGs a minimum of 10 minutes apart*
- X-ray (if not done in past 2 years)
- Vital signs
- Serum pregnancy test (if applicable)
- Laboratory evaluations
- Dispense subject diary
- Return for Visit 2 in 7 days

Opioid Taper (Visit 2)
After review of evaluations done at Visit 1, subjects who no longer met study criteria were to have been discontinued. Subjects continuing to meet the inclusion/exclusion criteria were to have received the following instructions/evaluations:

- Review diary for completeness
- Confirm that between 30-80 mg of oral MSO4 or equivalent was taken on at least 4 of previous 7 days.
- Complete Oswestry Disability Index, Healthcare Utilization Questionnaire, Brief Pain Inventory-Short Form (BPI-SF), SF-36, WPAI, Medical Outcomes Study (MOS) Sleep Scale and Profile of Mood States (POMS) Short Form
- Complete SOWS starting at Visit 2 and daily between Visits 2 and 3
- Instruct subject to reduce dose of chronic nonopioid pain medication to one-half of his/her baseline dose or minimum therapeutic dose for the remainder of the study
- Instruct subject to discontinue all intermittent pain medications
- Begin opioid taper. The opioid tapering regimen was to have been based on recommendations published by the American Pain Society, in its 1999 Guidelines as follows:

Weaning a patient from chronically used opioids may proceed as follows: one-half of the previous daily dose may be given in divided doses every 6 hours for the first 2 days and reduced by 25% every 2 days. This schedule is continued until a total daily dose of 30mg/day of oral morphine is reached. After 2 days at this minimum dose, the analgesic may be discontinued.

Tapering regimens of some commonly prescribed opioids:

American Pain Society Opioid Tapering Algorithm					
	Equianalgesic dose of 80mg of oral morphine (mg)	**Day 1 & 2** (May be given in divided doses) (mg/day)	**Day 3 & 4** (25% reduction of Day 1 & 2 dose and equianalgesic dose of 30mg/day oral morphine) (mg/day)	**Day 5 & 6*** (mg/day)	**Day 7**** (25% reduction of Day 5 & 6 dose) (mg/day)
Hydrocodone	40	20	15	15	10
Morphine	80	40	30	30	20
Propoxyphene	600	300	225	225	150
Levorphanol	5	2.5	2	2	1.5
Hydromorphone	10	5	4	4	3
Codeine	250	125	90	90	60
Oxycodone	40	20	15	15	10
Meperidine	400	200	150	150	100

[1]American Pain Society. (1999). Principles of analgesic use in the treatment of acute pain and cancer pain (Fourth edition). Glenview, IL: American Pain Society.
*Day 5 and 6 are the same dose as Day 3 and 4. They are added for dosing convenience and the assurance of slow tapering and hence, the avoidance of withdrawal upon opioid discontinuation.
**Day 7 is the 25% reduction of dose of Day 5 and 6. It is added for dosing convenience and the assurance of slow tapering and hence, the avoidance of withdrawal upon opioid discontinuation.

Reviewer's Note: The above opioid tapering regimen uses a rather rapid taper at the end which may result in symptoms of withdrawal in some patients. However, this taper occurs prior to randomization and therefore would not be expected to affect the efficacy results. The applicant included in Amendment 1 a provision for discontinuing subjects from the study with SOWS > 23.

- *The site was to have called the subject on day 3 of the opioid taper to determine eligibility (Amendment 1).*
- *Subjects with SOWS > 23 during the opioid taper segment were to have been discontinued from the study. (Amendment 1)*
- *For subjects entering the study with poor pain control (i.e. Average pain over prior 14 days score of "moderate" or greater) and meeting the other eligibility criteria, the investigator was to have had the option to enroll the subject in the Run-in Period without tapering (Amendment 1).*

- If at any time over the 7-day period the subject reports an 'average pain over the last 24 hours' score for their low back pain of ≥ 5 on 2 consecutive days, with a SOWS score of ≤ 23 recorded they will be considered eligible to enter the open-label run-in period.

Opioid Taper Completed, Start of Run-in Period (Visit 3)
Visit 3 was to have been scheduled to occur upon completion of the opioid taper and up to 7 days after Visit 2. The Run-in Period was to have lasted 14 days and was to have identified subjects whose pain was controlled with and who tolerate BTDS 20. At Visit 3, the following information was to have been collected:

- Concomitant medication and non-drug therapy
- Adverse events
- Review diary and confirm that completion of the diary was appropriate and legible, and
- The subject recorded an 'average pain over the last 24 hours' score for their lower back pain on 2 consecutive days out of the last 7days of ≥ 5 (defined as inadequate analgesia), with associated SOWS score on those days of ≤ 23
- The subject tapered their opioid as instructed
- The subject had reduced their nonopioid analgesic dose to one-half the baseline dose or minimum therapeutic dose (whichever is higher)
- Subjects who do not meet the above criteria during or after the 7-day opioid taper has concluded must be discontinued from the study.
- Subjects who do meet the above criteria will proceed immediately to the run-in period.

Subjects who met the run-in criteria were to have the following:
- Vital signs
- ECG evaluation (2 readings, a minimum of 10 minutes apart)
- Apply a BTDS 10 patch
- Dispense new diary
- Dispense supplemental analgesic medication:
    - Ibuprofen 200 mg tablets or
    - Acetaminophen 500 mg tablets
- Instruct subjects to discontinue all opioid medications
- Schedule subject to return for Visit 4 seven days later

Dose Titration
- Subjects were to have started treatment on BTDS 10
- After three days (72 hours) the investigator was to have contacted the subject, and, if the subject tolerated the BTDS 10 patch, the subject was to apply the BTDS 20 patch to a different site. If the subject did not

tolerate the BTDS 10 patch well enough to increase to BTDS 20, the subject was not to have been up-titrated.

Run-in Period (Visit 4)
Subjects on BTDS 20 were to have been continued for another week, and subjects on BTDS 10 who were able to tolerate BTDS 10 were to have been titrated-up to BTDS 20. Subjects not able to tolerated BTDS 10 after seven days were to have been discontinued

ECG Visit (Visit 4.1)
This visit was added in Amendment 4. The Visit was to have occurred seven days after Visit 4 for the collection of 4 ECGs while on BTDS 20. The subject was supposed to return in seven days for Visit 5.

Start of Double-blind Period (Visit 5)
Subjects were to have been eligible to enter the 12 week double-blind phase if all of the following criteria were met:

- The subject tolerated BTDS 20
- The subject reported an 'average pain over the last 24 hours' score for their lower back pain of ≤4 on 6 of 7 days
- The subject ingested supplemental analgesic medication of ≤800 mg/day ibuprofen (200 mg), or ≤2000 mg/day acetaminophen (500 mg) for their low back pain on 6 of 7 days
- The subject did not use nonstudy opioid analgesic medication for low back pain
- *All 4 ECGs at Visit 4.1 required QTcF determinations <500 msec (Amendment 4)*

Eligible subjects were to have been randomized in a 1:1:1 ratio to BTDS 20, BTDS 5 or OxyIR (10 mg every 6 hours). To maintain the study blind, a double-dummy technique was to have been used. For subjects on chronic stable nonopioid analgesics, their nonopioid analgesic was to have been allowed at one-half their baseline dose or at the lowest available dose. Subjects were not to have been permitted to down-titrate study drug during the double-blind phase.

Reviewers Note: Subjects randomized to BTDS 5 during the double-blind period were switched from BTDS 20 to BTDS 5 without any opioid taper. No SOWS scores were collected at this time to assess for possible opioid withdrawal. However, the likelihood of opioid withdrawal was minimized since opioids were not completely discontinued and rescue with Oxycodone IR 5 mg bid was allowed for the first six days.

During the double-blind phase the following was to have been completed:

- Pain diary each day, including pain assessments, number of nighttime awakenings due to pain and supplemental analgesic medication use
    - Daily pain assessments 'pain right now' scores for low back pain once each evening, in addition to each time a dose of supplemental analgesic medication taken and the amount of each supplemental analgesic dose
    - Subjects instructed not to take sponsor-provided supplemental analgesic medication for 48 hours prior to each remaining study visit (Visits 6, 7, 8, 9, and 10). Subjects will be called 72 hours prior to each visit to remind them

Visits 6, 7, 8, 9 (Double-blind Weeks 1, 2, 4, and 8)
Weekly telephone interviews were to have been conducted with each subject to go over the diary and supplemental analgesic medication use. Once monthly, information was to have been collected via phone interview for the following measures: Oswestry Disability Index, BPI-SF, MOS Sleep Scale, Healthcare Utilization Questionnaire, WPAI, and SF-36. *The previously listed instruments were to have been administered by the call center and completed by them directly onto a CRF for Visits 8 and 9 only. The profile of Mood States (POMS) Short Form was to have been administered on site and completed by the subject directly onto a CRF during Visits 8 and 9 (Amendment 2).*

At the scheduled visits the following information was to have been collected:

- Adverse events
- Concomitant medication therapy
- Vital signs
- "Average pain over the last 24 hours" score
- "Worst pain over the last 24 hours" score
- Collect and review diary, dispense new diary
- Dispense double-blind study medication / collect unused study medication
- Dispense supplemental analgesic medication
- ECG evaluation (4 readings, a minimum of 10 minutes apart at Visit 8 only)
- Oswestry Disability Index (Visits 8 and 9, collected during phone interviews from call center)
- BPI-SF (Visits 8 and 9, collected during phone interviews from call center)
- MOS-Sleep Scale (Visits 8 and 9, collected during phone interviews from call center)
- POMS-SF (Visits 8 and 9 only)
- SF-36 (Visits 8 and 9, collected during phone interviews from call center)

- Healthcare Utilization Questionnaire (Visits 8 and 9, collected during phone interviews from call center)
- Work Productivity and Activity Impairment Instrument (WPAI) (Visits 8 and 9, collected during phone interviews from call center)
- If subject discontinues study medication but continues participation in the study, the Visit 10 procedures need to be conducted at the time of study medication discontinuation and again when the subject discontinues or completes the study.
- Subjects will return to the site two weeks after Visit 8 and Visit 9 to be resupplied with study medication and to return unused study medication.

Visit 10 (Double-blind Week 12) and/or end of study

The following evaluations/procedures were to have been completed:

- Physical examination
- Concomitant medication and nondrug therapy
- 'Average pain over the last 24 hours' score
- 'Worst pain over the last 24 hours' score
- Vital signs
- Adverse events
- Laboratory evaluations
- ECG evaluation (4 readings, a minimum of 10 minutes apart)
- Return study drug to site
- Oswestry Disability Index (collected during phone interviews from call center)
- BPI-SF (collected during phone interviews from call center)
- MOS-Sleep Scale (collected during phone interviews from call center)
- POMS -SF
- SF-36 (collected during phone interviews from call center)
- Patient Global Impression of Change (PGIC)
- Healthcare Utilization Questionnaire (collected during phone interviews from call center)
- WPAI (collected during phone interviews from call center)
- Complete the Abuse/Diversion Questionnaire (described in section on Safety Assessments)

Extension Phase

Subjects were to have been permitted to enter the extension phase within three days following completion of the double-blind phase. *Subjects who discontinue study medication due to lack of therapeutic effect in the double-blind Phase and complete all visits of the double-blind Phase off study–drug were to have been eligible to enroll into the Extension Phase (Amendment 2).* Subjects entering the extension phase were to have retained their original subject number and were to

have been started on BTDS 5 and titrated, if necessary, to a maximum of BTDS 20 with a minimum of 72 hours before up-titration to the next strength patch.

Efficacy Assessments

The following efficacy assessments were to have been performed:

Primary Efficacy Assessment/Endpoint

- Average pain over the last 24 hours assessed on an 11-point numerical rating scale. The primary efficacy endpoint was to have been average pain over the last 24 hours assessed at study visits during Weeks 4, 8, and 12.

Secondary Efficacy Assessments/Endpoints

- 'Average pain over the last 24 hours' score at Week 2
- 'Worst pain during the last 24 hours' score at Weeks 2, 4, 8, and 12
- Supplemental analgesic medication use. *This variable was changed to the daily number of tablets of supplemental analgesic medications during the double-blind Phase (Amendment 3).*
- Oswestry Disability Index at Weeks 4, 8, and 12
- Average number of nighttime awakenings during Weeks 2-4 and weeks 2-12
- Sleep Disturbance subscale in the Medical Outcome Study (MOS)-Sleep Scale at Weeks 4, 8, and 12.

Other Efficacy Assessments

- The mean (among days) of the scheduled daily diary 'pain right now' scores during weeks 2-4 and weeks 2-12
- The average (among days) of the number of daily pain right now scores (scheduled or presupplemental analgesic) greater than or equal to 5 during weeks 2-4 and weeks 2-12.
- The 3 monthly assessments of severity of pain and interference of pain scales of BPI-SF
- Sleep adequacy subscale, somnolence subscale, and sleep problems Index II of the MOS Sleep Scale during the double-blind Phase
- The 3 monthly assessments of the Profile of Mood States - Short Form
- Healthcare utilization variable frequencies and/or means
- WPAI measure of % work time missed
- SF-36 score for the 8 scales: role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health, the general health question, and 2 summary measures of physical health (aggregate of physical functioning, role-physical, bodily pain and general health

scales) and mental health aggregate of the vitality, social functioning, role-emotional and mental health scales)
- Patient Global Impression of Change (PGIC) rating score
- Percent compliance with study medications during double-blind phase

Safety Assessments

Multiple pre-specified safety assessments were to have been performed including the following:

- Vital signs: Systolic blood pressure, diastolic blood pressure, heart rate and weight were to have been obtained at the following visits: Visit 1 (Screening), Visit 2 (start of Opioid Taper), Visit 3 (Opioid Taper completed), Visit 4 (Run-in), and Visits 5-10 (Double-Blind). Blood pressure and pulse were to have been measured after the subject had been sitting for 3 minutes

- ECG: Electrocardiograms were to have been performed by study center staff and sent to research Technologies for additional analysis. A standard 12-lead ECG was to have been collected at Visits 1 and 3 (2 readings, a minimum of 10 minutes apart) and Visits 8 and 10 or at the end of study medication treatment (4 readings, a minimum of 10 minutes apart). The ECG tracing, with interpretation, was to have been filed with subject source documents.

- Modified Subjective Opiate Withdrawal Scale (SOWS): The SOWS was to have been conducted daily starting at Visit 2 (start of opioid taper) and ending at Visit 3 (start of Run-in) but no including Visit 3.

- Laboratory Tests: Laboratory tests were to have been obtained at the following visits: Visit 1 (Screening), Visit 5 (start of Double-blind), Visit 10 (end of Double-blind) and it the subject discontinued study-drug early.

Hematology: RBC, hemoglobin, hematocrit, platelets, and WBC with differential

Chemistry:
Electrolytes: Sodium, potassium, chloride, calcium, bicarbonate
Liver function Tests: Alkaline phosphatase, aspartate aminotransferase (AST),
alanine aminotransferase (ALT), total bilirubin, direct bilirubin
Renal Function: BUN, creatinine
Other: Fasting (deleted Amendment 2) glucose, albumin, cholesterol, triglycerides, phosphorus, lactate,
dehydrogenase (LDH), total protein, globulin

Urinalysis: pH, protein, glucose, ketone, occult blood, RBC, WBC, epithelial cells,
bacteria, casts, crystals, specific gravity

- Serum pregnancy test: Pregnancy testing was to have been conducted at Screening and final double-blind visit.

- Adverse Events: Adverse events were to have been recorded through the 7 days following the last dose of study drug. Subjects with adverse events that were ongoing were to have been followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

- Serious Adverse Events: All SAEs occurring up to 30 days following the subject's last study visit will be recorded on the Adverse Events CRF. Subjects with SAEs must be followed until the event resolves or the event or sequelae stabilize.

- Abuse or Diversion of Study Drug: The Abuse or Diversion of Study Drug assessment was to have been completed at the end of the study or upon early discontinuation. The questionnaire consisted of the following three questions:
  - Was there any indication of abuse of alcohol or illicit drugs by this subject at any time during the study?
  - Was there any indication of abuse of the study drug by this subject at any time during the study?
  - Was there any indication of diversion of this subject's study drug to someone other than the subject at any time during the study?

Statistical Methods

Subject Population
Full analysis: The full analysis population was to have consisted of subjects who were randomized, received at least one dose of double-blind study drug, and had at least one primary efficacy assessment during the double-blind phase. *The requirement for an efficacy assessment was eliminated in Amendment 3.*

Statistical Analysis
The statistical analysis plan changed significantly form the time of the original protocol to the final protocol. However, the applicant reports that there were no changes to the statistical analyses after the data were unblinded.

Statistical Analysis Original protocol
All efficacy analyses (primary, secondary and exploratory) were to have been performed on the full analysis population with LOCF imputation. The full analysis population was defined as subjects who are randomized, receive at least one dose of double-blind study drug, and have at least one primary efficacy assessment during the double-blind phase. The primary efficacy variable was to have been the pain on the average (during the last 24 hours) scores assessed at visits during Weeks 4, 8, and 12 and were to have been analyzed using repeated measures Analysis of Covariance (ANCOVA).

Statistical Analysis Amendment 2
This amendment added a sensitivity analysis of the primary efficacy variable using the full analysis population with the BOCF approach. The primary efficacy analysis was updated to include subject as a random effect and exclude center from the mixed effects linear model since there would be a large number of centers with few subjects.

Statistical Analysis Amendment 3
The imputation method was changed from LOCF to BOCF for the primary efficacy analysis. Three sensitivity analyses were added to reflect the change to the primary efficacy analysis. The requirement for the full analysis population to have an efficacy assessment was eliminated. Efficacy for this clinical trial was defined as statistical significance for the primary efficacy analysis of the comparison between BTDS 20 and BTDS 5 To address the issue of multiplicity (one primary efficacy analysis and three secondary efficacy analyses), a gatekeeping strategy was to have been employed. First, the primary efficacy analysis was to have been performed. The hypothesis for the primary analysis was to have been tested at the 5% error level. If this test failed to show significance (at 5% level), then no hypotheses tests for the secondary efficacy variables were to have been performed. If the test is significant (at 5% level), then the tests (the comparison between BTDS 20 and BTDS 5) for the secondary variables were to have been performed using Holm's method. Due to the change in the missing data imputation approach, sample size was adjusted accordingly. from 723 to 891 randomized subjects. Two responder analyses were added as exploratory analyses in accordance with FDA's recommendation.

Statistical Analysis Amendment 5
The primary efficacy analysis was changed to a linear mixed model using the available data; no imputation of missing data was to be done.

- The analysis of the primary and secondary variables will use Weeks 4, 8, and 12 as the three repeated measures but will be based on the mixed effect linear model fitted to available data on Weeks 1, 2, 4, 8 and 12.

To evaluate the sensitivity of the primary efficacy analysis, the following four sensitivity analyses, Retained Dropout ITT, BOCF, LOCF and Valid Pain Score Substitution will be performed:

- The first sensitivity analysis is a retained dropout ITT analysis. In this analysis the 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication (and prior to the completion or discontinuation from study) will be treated as observed scores (retained dropout ITT analysis). Missing data due to premature discontinuation of study will not be imputed. Only observed pain scores (either on or off study drug) will be used in this sensitivity analysis. The same repeated measures analysis as described for the primary efficacy analysis will be applied to the data.
- The second sensitivity analysis is an analysis with LOCF (last observation carried forward) imputation: In this imputation approach, any 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication in the Double-blind phase will be treated as missing. Missing 'average pain over the last 24 hours' scores at study visits in the Double-blind phase will be imputed by carrying forward the last nonmissing observation. The same repeated measures analysis as described for the primary efficacy analysis will be applied.
- The third sensitivity analysis is an analysis with BOCF (baseline observation carried forward) imputation: In this imputation approach, any 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication in the Double-blind phase will be treated as missing. Missing 'average pain over the last 24 hours' scores at scheduled study visits subsequent to the discontinuation of study medication in the Double-blind phase will be imputed using the baseline 'average pain in the last 24 hours' score. The baseline score is established as the screening mean pain.
- The fourth sensitivity analysis valid pain score substitution is designed to evaluate the effect of supplemental analgesic use in the 48 hours prior to visit at Weeks 4, 8 or 12 to the primary efficacy conclusion. Data collected after discontinuation of study medication will be treated as missing and will not be imputed.

Protocol Amendments:

Original Protocol, October 15, 2003
First patient enrolled February 25, 2004.

Amendment #1, May 13, 2004
The following key changes were made to the protocol in this amendment:

- The requirement for stable pain control in the inclusion criteria/exclusion criteria was removed.
- A phone call to subjects was required on day 3 of the opiod taper to determine if the subjects qualified for the run-in period.
- Subjects with SOWS > 23 during the opioid taper segment were discontinued from the study.

Amendment #2, October 18, 2004
The following key changes were made to the protocol in this amendment:

- The duration of the extension Phase was extended to 52 weeks.
- Subjects who discontinued double-blind study drug due to lack of efficacy and chose to complete all remaining scheduled visits were now eligible for enrollment into the extension phase.
- The primary efficacy analysis was updated to include subject as a random effect and exclude center from the mixed effects linear model. According the applicant, subject as a random effect was added based on FDA correspondence; center was removed from the model since there will be a large number of centers with few subjects per center (ICH E9). A sensitivity analysis of the primary efficacy variable using the full analysis BOCF approach was added.
- Subjects commonly requiring analgesic treatment for chronic conditions in addition to low back pain were excluded from study participation.
- Subjects with QTc or QT intervals > 500 msec recorded at Visit 1 or 3 were excluded from study participation
- Subjects receiving methadone for addiction were excluded from study participation
- Subjects receiving transdermal fentanyl for pain control upon entry into the study were excluded from study participation.

Amendment #3, February 25, 2005
The following key changes were made to the protocol in this amendment:

- The applicant reports that based on comments by the FDA the statistical methods for the efficacy analysis were changed as follows:
    - In the primary efficacy analysis the average pain scores subsequent to the discontinuation of study drug will be imputed using the BOCF approach instead of the LOCF approach.
    - Three sensitivity analyses were added to reflect the change to the primary efficacy analysis.

  - Three secondary efficacy variables and their analyses were planned and the primary and secondary error rate would be controlled through the gate-keeping strategy and Holm's method.
  - The full analysis population was changed to consist of all subjects who were randomized and received at least 1 dose of double-blind study drug, following the ITT principle and FDA's suggestion.
  - Due to the change in the missing data imputation approach to be used in the primary efficacy analysis (changed from LOCF to BOCF), sample size was adjusted accordingly. The number of subjects planned was increased from 723 to 891 randomized subjects.
  - Two responder analyses were added as exploratory analyses in accordance with FDA's recommendation.
- Instructions were added that required rescheduling of the double-blind visit at the clinic if it was discovered that a subject had ingested supplemental analgesic medication in the 48 hours prior to the visit.

Amendment #4, March 31, 2005
The following key changes were made to the protocol in this amendment:

- Additional ECG measurements were incorporated into the protocol following completion of Study BUP1011 designed to assess the effect of buprenorphine on QT interval. The results of the study demonstrated that BTDS twice the highest dose (2 x BTDS 20) prolonged the QT interval.
  - Seven days after Visit 4, the subject was to have returned to the site for Visit 4.1 for the collection of 4 ECGs (a minimum of 10 minutes apart). These ECGs would provide a safety assessment of the QT interval while on study treatment. After acquisition of ECGs at Visit 4.1 the subject was to have applied a new BTDS 20 and return for Visit 5 in 7 days.
  - The run-in period was increase to 21 days to accommodate Visit 4.1
  - To enter the double-blind Phase at Visit 5 all 4 ECGs at Visit 4.1 required QTcF determinations <500 msec
  - accordance with FDA's recommendation.
- Subjects with Long QT Syndrome, on Class 1A and Class III antiarrhythmic medications and with unstable cardiac disease were excluded.

Amendment #5, September 15, 2006
The following key changes were made to the protocol in this amendment:

- The primary efficacy analysis was changed to a linear mixed model using the available data; no imputation of missing data was to be done.

  - The analysis of the primary and secondary variables will use Weeks 4, 8, and 12 as the three repeated measures but will be based on the mixed effect linear model fitted to available data on Weeks 1, 2, 4, 8 and 12.

- To evaluate the sensitivity of the primary efficacy analysis, the following four sensitivity analyses, Retained Dropout ITT, BOCF, LOCF and Valid Pain Score Substitution will be performed:
  - The first sensitivity analysis is a retained dropout ITT analysis. In this analysis the 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication (and prior to the completion or discontinuation from study) will be treated as observed scores (retained dropout ITT analysis). Missing data due to premature discontinuation of study will not be imputed. Only observed pain scores (either on or off study drug) will be used in this sensitivity analysis. The same repeated measures analysis as described for the primary efficacy analysis will be applied to the data.
  - The second sensitivity analysis is an analysis with LOCF (last observation carried forward) imputation: In this imputation approach, any 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication in the Double-blind phase will be treated as missing. Missing 'average pain over the last 24 hours' scores at study visits in the Double-blind phase will be imputed by carrying forward the last nonmissing observation. The same repeated measures analysis as described for the primary efficacy analysis will be applied.
  - The third sensitivity analysis is an analysis with BOCF (baseline observation carried forward) imputation: In this imputation approach, any 'average pain over the last 24 hours' scores collected subsequent to the discontinuation of study medication in the Double-blind phase will be treated as missing. Missing 'average pain over the last 24 hours' scores at scheduled study visits subsequent to the discontinuation of study medication in the Double-blind phase will be imputed using the baseline 'average pain in the last 24 hours' score. The baseline score is established as the screening mean pain.
  - The fourth sensitivity analysis valid pain score substitution is designed to evaluate the effect of supplemental analgesic use in the 48 hours prior to visit at Weeks 4, 8 or 12 to the primary efficacy

conclusion. Data collected after discontinuation of study medication will be treated as missing and will not be imputed.

The applicant reports that there were no changes to the statistical analyses after the data were unblinded.

Study Results

Enrollment
A total of 2066 subjects were screened in 75 centers in the United States. Of the 1292 subjects that entered the opioid taper, 1160 entered the run-in period resulting in 662 subjects randomized into the double-blind phase. The Full Analysis Population was 660 subjects, since two randomized subjects did not receive study drug.

Subject Disposition
Opioid Taper Period
Of the 1292 subjects entered into the opioid taper approximately 90% (1160) were eligible for the Run-in Period.

Run-in Period
Of the 1160 subjects entered into the Run-in Period, 662 (57%) completed this phase and 498 (43%) discontinued. The two most frequent reasons for study discontinuation during the Run-in Period were 'Lack of therapeutic effect' (21%) and 'adverse event' (12%).

Double-blind Phase
There were 660 subjects in the Full Analysis Population, since two out of the 662 randomized subjects did not receive study drug. A total of 42% (93/221) of subjects in the BTDS 5 treatment group, 33% (73/219) of subjects in the BTDS 20 treatment group and 28% (61/220) of subjects in the OxyIR treatment group prematurely discontinued study drug. The main reasons for discontinuing study drug in the three treatment groups, summarized in Table 5.3.2.3 were adverse event and lack of therapeutic effect. The FDA statistician, Jonathan Norton, verified the contents of this table provided by the applicant. Discontinuations due to adverse events were twice as high in the BTDS 20 group compared to the BTDS 5 group, 13% (29/219) and 6% (14/221), respectively. More subjects in the BTDS 5 group than BTDS 20 group discontinued due to lack of therapeutic effect, 24% (52/221) and 11% (22/219), respectively. The higher incidence of discontinuations in the BTDS 20 group due to adverse events and in the BTDS 5 group due to lack of therapeutic effect is expected. Of note the OxyIR group appeared to have the best overall combined profile of efficacy and tolerability with the least number of discontinuations due to lack of therapeutic effect 7%

(16/220) and approximately the same number of discontinuations due to adverse event, 7% (16/220),

Table 5.3.2.3: Subject Disposition and Reasons for Discontinuation

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)

Reference: Table 5. Disposition and Reasons for Discontinuation: Safety Population, Clinical Study Report BUP3015, pg 77

Protocol Violations
The applicant reported 44 protocol deviations in the randomized patient population, involving 43 patients. The deviations were evenly balanced across the three treatment groups (Table 5.3.2.4). Most of the deviations fell into two main categories: screening deviations and use of prohibited opioids on the day of certain visits. The applicant conducted a sensitivity analysis excluding subjects who took opioid analgesia before a study visit, and the results for the primary comparison were virtually unchanged.

Table 5.3.2.4: Major Protocol Deviations BUP3015

	Treatment Group					
	BTDS 5 (N=221)		BTDS 20 (N=219)		Oxy IR (N=220)	
Deviation Category	**n(%)**	**R**	**n(%)**	**R**	**n(%)**	**R**
Any Major Protocol Deviation	13(5.9)	14	15(6.8)	15	15(6.8)	15
Opioid Requirement Not Met	0	0	0	0	1(0.5)	1
Other Inclusion Criteria Not Met	0	0	2(0.9)	2	1(0.5)	1
Run-in Pain Criteria Not Met	7(3.2)	7	9(4.1)	9	5(2.3)	5
Double-blind Pain Criteria Not Met	2(0.9)	2	0	0	1(0.5)	1
Opioids <30 Hrs Prior to Visit	5(2.3)	5	4(1.8)	4	3(1.4)	3
Compliance Deviation	0	0	0	0	4(1.8)	4

N = number of subjects in Full Analysis population
n = number of subjects with at least one deviation
% = n/N
R = total number of deviations

Reference: Sponsor provided table from March 1, 2010 submission

Demographics
The demographic characteristics of the subjects randomized to BTDS 5, BTDS 20 and OxyIR were similar with respect to age, gender, race, weight and underlying diagnoses. The average pain over the 14 days prior to screening appeared similar in the different treatment groups.

Table 5.3.2.4: Summary of Demographics and Baseline Characteristics in Randomized Safety Population for Study BUP3015

Parameter		BTDS 5 N=221	BTDS 20 N=219	OxyIR® N=220
Age (years)	Mean (SD)	50.2 (12.9)	50.4 (11.9)	49.5 (12.4)
	Range	24-82	22-84	21-89
Gender	Male, n (%)	120 (54%)	106 (48%)	120 (55%)
	Female, n (%)	101 (46%)	113 (52%)	100 (45%)
Race	White, n (%)	206 (93%)	193(88%)	201(91%)
	Black, n (%)	13 (6%)	21 (10%)	14 (6%)
	Asian	2 (1%)	0 (0%)	1 (<1%)
	All other, n (%)	0	5(2%)	4 (2%)
Weight (kg)	Mean (SD)	88.4 (22.6)	90.2 (21.4) kg	90.8 (20.5) kg
	Median	86.4	87.2	88.1
	Range	44-165	52-160	53-157
Diagnoses associated with back pain	Intervertebral disc	134 (61%)	128 (58%)	138 (63%)
	Nerve Root Entrapment	2 (1%)	6 (3%)	5 (2%)
	Spoondylolisthesis	17 (8%)	16 (7%)	14 (6%)
	Osteoarthritis	45 (20%)	47 (21%)	41 (19%)
	Nonmalignant Condition	7 (3%)	8 (4%)	4 (2%)
	Other	11 (5%)	12 (5%)	15 (7%)
Average pain over the 14 days prior to screening	None	1 (<1)	2 (1)	2 (1)
	Mild	100 (45)	96 (44)	98 (45)
	Moderate	56 (25)	59 (27)	60 (27)
	Moderately Severe	50 (23)	47 (21)	49 (22)
	Severe	8 (4)	10 (5)	7(3)

Reference: Adapted from Table 7. Summary of Demographic and Baseline Characteristics: Randomized Safety Population, Clinical Study Report page

Efficacy Results

Primary Endpoint:

The protocol-specified primary efficacy endpoint was the "average pain over the last 24 hours" score at weeks 4, 8, and 12. Table 5.3.2.5 presents the pain scores at screening and prerandomization and the applicant's analysis at weeks 4, 8, and 12. The applicant used no imputation for missing data. For the 39 subjects who discontinued study drug but remained in the study, the applicant did not impute missing pain scores but used the available observed pain scores. Mean pain scores at screening and prerandomization were similar for all groups. At weeks 4, 8 and 12 there was a statistically significant treatment difference of -0.67 in favor of BTDS 20 versus BTDS 5, P<.001 and a statistically significant treatment difference of -0.75 in favor OxyIR versus BTDS 5, P<.001. The FDA statistician confirmed the results of the applicant's analysis of the primary endpoint.

Table 5.3.2.5: Summary of the "Average Pain Over the Last 24 Hours" Score at Screening, Prerandomization, and Weeks 4, 8, and 12 of the Double-blind Phase

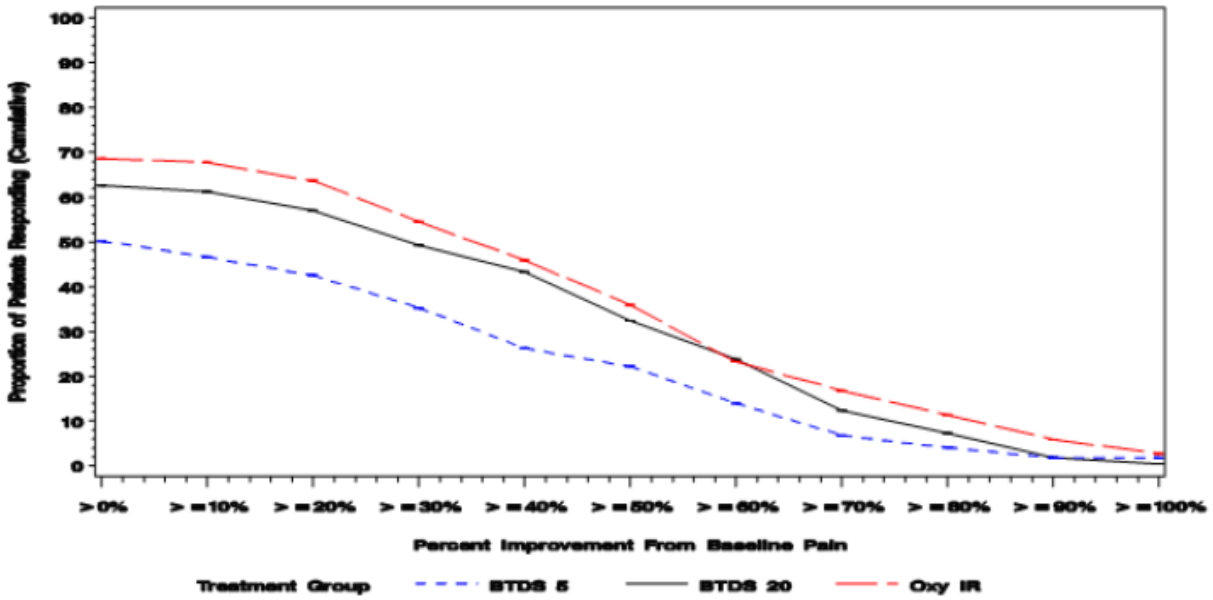
Visits/Weeks	BTDS 5 (N = 221)	BTDS 20 (N = 219)	OxyIR® (N = 220)
Screening[a]			
n	221	219	220
Mean (SE)	6.36 (0.075)	6.46 (0.084)	6.46 (0.079)
Median	6.0	6.5	6.0
Min, Max	4, 10	1, 10	3, 10
Prerandomization[b]			
n	221	219	219
Mean (SE)	2.84 (0.075)	2.91 (0.075)	2.74 (0.074)
Median	3.0	3.1	2.9
Min, Max	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)

Reference: Table 9. Summary of the "Average Pain Over the Last 24 Hours" Scores at Screening, Prerandomization, and Weeks 4, 8, and 12 of the Double-blind Phase: Full Analysis Population, Clinical Study Report page 86

The applicant's primary efficacy analysis of data from Weeks 4, 8 and 12 is not consistent with the Division's current standard for a chronic pain indication. The FDA statistician analyzed the data at Week 12 using a BOCF imputation method. This analysis also showed BTDS 20 to be statistically superior to BTDS 5 (p<.0001). The estimated treatment effect (difference in least-squares means) was .62, with a standard error of .19. This is similar to the treatment effect of .67 found using the Applicant's analysis. The BTDS5 treatment arm showed a (least-squares) mean pain at Week 12 of 4.96, and the mean pain for the BTDS20 arm was 4.33.

Responder Analysis
A responder was defined based on the percentage improvement from the screening mean to the means of the primary efficacy variable, "average pain over the last 24 hours" scores for weeks 4, 8, and 12. In Responder Analysis 1, the more conservative analysis, subjects who discontinued or had an increase in pain scores postrandomization were assigned a percentage improvement of zero (failure). Figure 5.1.3.1 is a graphic presentation of the results of Responder Analysis 1. For the BTDS5 treatment group 35% of subjects showed ≥30% improvement compared to 49% for BTDS 20. The analysis of the FDA statistician revealed slightly different results but the percent responding did not differ by more than 1% in any cell.

Figure 5.1.3.1: Plot for Responder Analysis 1
Discontinuations Prior to Week 12 Regarded as Non-responders



Reference: Figure 3. Percentage Change from Baseline in Average of Week 4, 8 and 12 "Average Pain over the Last 24 Hours" Scores (Responder Analysis 1): Full Analysis Population, BUP3015 Clinical Study Report, pg. 93

Secondary Efficacy Endpoints
Secondary efficacy variables consisted of the daily number of supplemental analgesic tablets used during the double-blind phase, the Oswestry Disability Index (ODI) score, and the Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale. To address the issue of multiplicity, a gate-keeping strategy and a stepwise approach to the analysis of the secondary efficacy results were used to evaluate statistical significance. The results of the analyses of the secondary efficacy endpoints are shown in Table 5.3.2.6. The FDA

statistician confirmed the findings for the MOS Sleep Scale and supplemental analgesia, but did not look at the ODI outcome.

Table 5.3.2.6: Summary of Secondary Efficacy Results

Treatments/Measurements	Treatment Difference (95% CI)	*P* Value	α-Level	Decision
BTDS 20 vs BTDS 5				
MOS Sleep Scale - Sleep Disturbance Subscale	−6.23 (−9.64, −2.82)	< .001	.0167	Significant
Supplemental analgesic medication	−0.5 (−0.90, −0.13)	.006	.025	Significant
ODI Score	−1.72 (−3.55, 0.11)	.065	.05	NS
OxyIR® vs BTDS 5				
ODI Score	−1.99 (−3.79, −0.18)	.031	.0167	NS
MOS Sleep Scale- Sleep Disturbance Subscale	−2.65 (−6.01, 0.70)	.121	.025	NS
Supplemental analgesic medication	−0.3 (−0.70, 0.09)	.158	.05	NS

Reference: Table 12. Application of a Gate-keeping Method to Assess Statistical Significance of Multiple Endpoints, Clinical Study Report page 90

Treatment with BTDS 20 resulted in statistically less sleep disturbance (-6.23, P<.001) and decreased use of supplemental analgesic medication (-0.5, P=.006) compared with BTDS 5. There was no statistically significant difference in the Oswestry Disability Index score between BTDS 20 and BTDS 5 treatment groups.

Number of Supplemental Analgesic Tablets
Supplemental analgesic use prior to randomization, measured during the last seven days of the run-in period, was similar for all groups. During the double-blind treatment, least squares mean doses were 3.8 tablets for the BTDS 5 treatment group, 3.3 tablets for the BTDS 20 treatment group, and 3.5 tablets for the OxyIR treatment group.

Oswestry Disability Index (ODI) Score
Mean ODI scores were similar across treatment groups at screening and prerandomization. There was no significant difference in scores between the treatment groups at weeks 4, 8 and 12.

Sleep Disturbance Subscale of MOS-Sleep Scale at Weeks 4, 8, and 12
Mean Sleep Disturbance Subscale scores were similar for all treatment groups at screening and prerandomization. Mean scores at week 12 for the three treatment groups were the following: 40.85 (BTDS 5), 33.65 (BTDS 20), and 41.60 (OxyIR). The applicant reported that the difference in scores was statistically significant and in favor of the BTDS 20 group compared to the BTDS 5 group.

Other Efficacy Endpoints

Patient Global Impression of Change (PGIC)

More subjects reported "very much improved" or "much improved" at the end of study in the BTDS 20 and OxyIR treatment groups compared to the BTDS 5 group. The percentage of subjects reporting "very much improved" or "much improved" was 33% in BTDS 5 group, 54% in BTDS 20 group and 56% in OxyIR group.

6 Review of Efficacy

Efficacy Summary

The applicant conducted two pivotal studies (BUP3024 and BUP3015) in support of the efficacy of Buprenorphine Transdermal System (BTDS) for the indication for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Study BUP3024, conducted under a Special Protocol Agreement, enrolled opioid-naïve subjects and Study BUP3015 enrolled opioid-experienced subjects with chronic low back pain. Both studies demonstrated a statistically significant difference in effect between BTDS and control treatment groups on the primary endpoint, average pain over the last 24 hours assessed on an 11-point numerical rating scale. In Study BUP3024 the primary endpoint was average pain over the last 24 hours at end of study (Week 12). In Study BUP3015 the primary endpoint was average pain over the last 24 hours at Weeks 4, 8 and 12, with the primary comparison between BTDS 5 and BTDS 20. The current standard of the Division for a chronic pain indication is to demonstrate evidence of efficacy at three months. The FDA statistician, Jonathan Norton, for study BUP3015 assessed efficacy at Week 12 and demonstrated statistical significance at this time point. The FDA statistician also confirmed the findings of efficacy at Week 12 for study BUP3024. Secondary outcome measures of less sleep disturbance in both pivotal studies and decreased use of supplemental analgesic medication in BUP3015 were supportive of the primary efficacy findings.

Key Issues

Two major issues impacting the interpretation of the efficacy findings were the use of observed pain scores in BUP3015 after subjects discontinued study drug but continued in the study and the potential unblinding of the treatment arm during the double-blind period of the opioid taper. For study BUP3015 the applicant did not impute missing pain scores for subjects who discontinued study drug and remained in the study. The use of observed pain scores after the subject discontinued from the study could result in a favorable score unrelated to study medication e.g. favorable score may have been the result of rescue medication. The FDA statistician confirmed that treating these subjects as

dropouts would still result in a statistical significant difference between treatments.
For Study BUP 3015, subjects randomized to BTDS 5 during the double-blind period were switched from BTDS 20 to BTDS 5 without any opioid taper. No SOWS scores were collected at this time to assess for possible opioid withdrawal. However, the likelihood of opioid withdrawal was minimized since opioids were not completely discontinued and in addition rescue with Oxycodone IR 5 mg bid was allowed for the first six days. For Study BUP3024 more subjects in the placebo group than BTDS group had SOWS scores greater than 23 during the first week of the double-blind phase, 10 subjects (8%) and 2 subjects (<1%) respectively. The SOWS items are nonspecific for opioid withdrawal but even if one assumes the worst case scenario that all the subjects with SOWS scores greater than 23 had symptoms of opioid withdrawal, the relatively modest number of subjects involved is unlikely to substantially affect the efficacy results.

6.1 Indication

Proposed Indication
Purdue's proposed indication is the following:

> BuTrans, a transdermal system providing systemic delivery of buprenorphine over a 7-day period, is indicated for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Approved Indication
Buprenorphine is approved as two separate formulations for two different indications:

- A sublingual formulation for the treatment of opioid dependence
- An IV/IM formulation for the treatment of moderate to severe pain

6.1.1 Methods

The applicant has submitted two new controlled efficacy studies to support a finding of efficacy for the indication of BuTrans for the management of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The two studies were adequate and well-controlled (i.e., randomized, double-blind, placebo- or active-controlled) studies in subjects with chronic low back pain. The primary efficacy measure, pain on an 11-point numerical rating scale meets the Division's standard for an acceptable primary efficacy measure. The pre-specified primary endpoint, average daily pain at week 12 was an acceptable primary efficacy endpoint for study BUP3024 which was conducted under a Special Protocol Assessment agreement. For

Study BUP3015 the primary endpoint, average pain over the last 24 hours at Weeks 4, 8 and 12, was not consistent with Division's current standard of a landmark analysis at three months for a chronic pain indication. The FDA statistician for study BUP3015 assessed efficacy at Week 12 and demonstrated statistical significance at this time point.

6.1.2 Demographics

Table 6.1.2.1 summarizes the overall demographic and baseline characteristics for all randomized subjects in controlled chronic pain studies (Group A) treated with BTDS, placebo or active comparator. The characteristics are similar for the different treatment groups except for in the BTDS group more subjects had previous opioid experience. The individual demographic characteristics for Study BUP3024 and Study BUP3015 are summarized in Section 5.

Table 6.1.2.1: Demographic and Baseline Characteristics of Randomized Subjects in Controlled, Chronic Pain Studies (Group A)

Variable	Placebo N=995	Oxy/APAP N=150	OxyIR N=353	HCD/APAP N=130	BTDS N=2130
Age, years [a]					
n	994	150	350	130	2129
Mean	58.3	58.3	52.7	52.7	55.6
Median	58	60.5	52	51	55
Std	13.91	15.75	12.32	13.45	13.54
(Min, Max)	(19, 95)	(19, 90)	(21, 89)	(28, 88)	(18, 98)
Age group, n (%)					
<65 years	658 (66.1)	88 (58.7)	294 (83.3)	102 (78.5)	1563 (73.4)
≥65 years	336 (33.8)	62 (41.3)	56 (15.9)	28 (21.5)	566 (26.6)
≥75 years	129 (13)	25 (16.7)	18 (5.1)	8 (6.2)	191 (9)
Sex, n (%)					
Male	369 (37.1)	60 (40)	159 (45)	62 (47.7)	820 (38.5)
Female	626 (62.9)	90 (60)	194 (55)	68 (52.3)	1310 (61.5)
Race, n (%)					
Black	95 (9.5)	6 (4)	36 (10.2)	7 (5.4)	236 (11.1)
White	843 (84.7)	138 (92)	310 (87.8)	121 (93.1)	1820 (85.4)
Other	57 (5.7)	6 (4)	7 (2.0)	2 (1.5)	74 (3.5)
Previous opioid experience, n (%)					
No	617 (62)	109 (72.7)	0	0	730 (34.3)
Yes	378 (38)	41 (27.3)	353 (100)	130 (100)	1400 (65.7)
Pain site/etiology, n (%) [a]					
Back pain	646 (64.9)	124 (82.7)	253 (71.7)	130 (100)	1440 (67.6)
Osteoarthritis	302 (30.4)	26 (17.3)	100 (28.3)	0	648 (30.4)
Other	47 (4.7)	0	0	0	41 (1.9)

Reference: Table 17. Demographic and Baseline Characteristics of Randomized Subjects in Controlled, Chronic Pain Studies (Group A), ISS page 90

The applicant analyzed nonrandomized vs randomized subjects in the in the enriched chronic pain studies (Group A2) to evaluate for any potential selection bias. A total of 2418 out of 4301 subjects from the open-label run-in period, were randomized to the double-blind period. Results of this analysis demonstrated no

significant difference between randomized and nonrandomized groups with respect to age, race, sex or previous opioid experience (Table 6.1.2.2).

Table 6.1.2.2: Demographic and Baseline Characteristics of Nonrandomized and Randomized Subjects in Enriched, Chronic Pain Studies (Group A2)

Variable	Randomized N=2418	Nonrandomized N=1883	Total N=4301
Age, years			
n [a]	2413	1880	4293
Mean	54.5	54.2	54.3
Median	55.0	54.0	54.0
Std	12.61	13.40	12.96
(Min, Max)	(18, 89)	(19, 85)	(18, 89)
Age group, n (%)			
<65 years	1880 (77.8)	1449 (77.0)	3329 (77.4)
≥65 years	533 (22.0)	431 (22.9)	964 (22.4)
≥75 years	134 (5.5)	144 (7.6)	278 (6.5)
Sex, n (%)			
Male	975 (40.3)	780 (41.4)	1755 (40.8)
Female	1443 (59.7)	1103 (58.6)	2546 (59.2)
Race, n (%)			
Black	290 (12.0)	202 (10.7)	492 (11.4)
White	2037 (84.2)	1615 (85.8)	3652 (84.9)
Other	91 (3.8)	66 (3.5)	157 (3.7)
Previous opioid experience, n (%)			
No	868 (35.9)	685 (36.4)	1553 (36.1)
Yes	1550 (64.1)	1198 (63.6)	2748 (63.9)
Pain site/ etiology, n (%)			
Back pain	1468 (60.7)	1273 (67.6)	2741 (63.7)
Osteoarthritis	912 (37.7)	561 (29.8)	1473 (34.2)
Other	38 (1.6)	49 (2.6)	87 (2.0)

Reference: Table 6.1.2.1 Demographic and Baseline Characteristics of Nonrandomized and Randomized Subjects in Enriched, Chronic Pain Studies (Group A2), ISS page 91

6.1.3 Subject Disposition

The integrated subject disposition for all subjects treated with BTDS, OxyIR, or placebo during the two pivotal studies (BUP3024 and BUP3015) is displayed in Table 6.1.3.1. The two most frequent reasons for study drug discontinuation during the run-in period of the pivotal studies were adverse event (18%) and lack of therapeutic effect (17%). While the discontinuation rate during the open-label run-in period was similar for both studies (~45%), the primary reasons for discontinuation differed. In Study 3015, conducted in opioid-experienced patients, a greater percentage of patients discontinued during run-in due to lack of efficacy (21%) than adverse event (12%). In Study 3024, conducted in opioid-naïve patients, the rate was 14% for lack of efficacy and 23% for adverse event.

The aggregate discontinuation findings are similar to the findings during the Run-in period for subjects in all chronic pain studies (Table 6.1.3.2). For the double-blind period the dropout rate due to adverse events was similar for the BTDS group in the pivotal studies (15%) and in all chronic pain studies (15%). However, discontinuations due to lack of therapeutic effect for the BTDS group was lower in the pivotal studies (10%) compared to all chronic pain studies (14%). The higher discontinuation rate due to lack of therapeutic effect in all chronic pain studies may be partly due to the fact that not all of the studies were enriched with subjects who had demonstrated benefit from BTDS during the run-in period. The overall completion rate for the BTDS group during the double-blind period in the pivotal studies (67%) was higher than in all chronic pain studies (62%). The higher completion rate in the pivotal studies would be expected since the enrichment design decreases postrandomization discontinuation rates.

Table 6.1.3.1: Subject Disposition for Study BUP3024 and Study BUP3015

Category	Run-in Period (N=2184)	Double-blind Phase			
		BTDS (N=475)	Placebo (N=283)	BTDS 5 (N=221)	OxyIR (N=220)
Completed Period	1203 (55)	316 (67)	199 (70)	128 (58)	159 (72)
Discontinued Study Drug	981 (45)	159 (33)	84 (30)	93 (42)	61 (28)
Adverse event	383 (18)	73 (15)	20 (7)	14 (6)	16 (7)
Lack of therapeutic effect	382 (17)	47 (10)	36 (13)	52 (24)	16 (7)
Lost to follow-up	42 (2)	14 (3)	11 (4)	7 (3)	10 (5)
Subjects choice	60 (3)	17 (4)	11 (4)	11 (5)	5 (2)
Administrative	99 (5)	12 (3)	6 (2)	9 (4)	14 (6)
Confirmed or suspected diversions	3 (<1)	0	0	-	-
Did not qualify	12 (<1)	0	-	0	0

Table 6.1.3.2: Disposition of Subjects Exposed to BTDS in the Chronic Pain Studies (Group C)

	Number (%) of subjects					
Disposition	**Open-label run-in period N=4301**		**Double-blind period N=2334 [a]**		**Open-label extension period N=1576**	
Completed the period [b]	2420	(56.3)	1439	(61.7)	477	(30.3)
Discontinued BTDS use	1881	(43.7)	895	(38.4)	1099	(69.7)
Reasons for Discontinuations [c]						
Adverse event	730	(17.0)	351	(15.0)	384	(24.4)
Ineffective treatment	783	(18.2)	333	(14.3)	116	(7.4)
Death [d]	1	(<0.1)	3	(0.1)	4	(0.3)
Lost to follow-up	55	(1.3)	43	(1.8)	65	(4.1)
Protocol violation	26	(0.6)	23	(1.0)	12	(0.8)
Study discontinued	73	(1.7)	71	(3.0)	404	(25.6)
Other	220	(5.1)	107	(4.6)	130	(8.3)

Reference: Table 14. Disposition of Subjects Exposed to BTDS in the Chronic Pain Studies (Group C), ISS page 85

The discontinuation rate due to adverse events was higher with the highest BTDS dose in the nonenriched forced titration studies (Table 6.1.3.3). Discontinuations due to adverse events were 33.7% for BTDS 20, 20.4% for BTDS 10, 24.8% for BTDS 5, 18.7% for Oxy/APAP and 15% for placebo. In the double-blind period of the enriched studies the discontinuation rate due to adverse events appeared similar for the different doses of BTDS. This would be expected since subjects were required to tolerate BTDS during the run-in period to advance to the double-blind period. Across groups the higher rates of discontinuation due to AEs were seen for subjects receiving BTDS or active comparators than for those receiving placebo, while a higher rate of discontinuations due to ineffective treatment was seen for subjects receiving placebo than for those receiving active treatments.

Table 6.1.3.3: Disposition of Subjects, by Treatment and Dose of BTDS during the Double-Blind Period, in Controlled, Chronic Pain Studies

			Number (%) of subjects					
					Reason for discontinuation [a]			
Analysis group	Treatment	Number of subjects randomized	Completed	Discontinued [b]	Adverse event	Ineffective treatment	Death	Study discontinued
Group A (controlled, chronic pain studies)	Placebo	995	650 (65.3)	345 (34.7)	77 (7.7)	229 (23.0)	1 (0.1)	0
	Oxy/APAP	150	89 (59.3)	61 (40.7)	35 (23.3)	26 (17.3)	0	0
	OxyIR	353	222 (62.9)	131 (37.1)	35 (9.9)	26 (7.4)	0	34 (9.6)
	HCD/APAP	130	68 (52.3)	62 (47.7)	35 (26.9)	18 (13.8)	0	0
	Total BTDS	**2130**	**1272 (59.7)**	**858 (40.3)**	**326 (15.3)**	**330 (15.5)**	**2 (0.1)**	**71 (3.3)**
Group A1A (nonenriched, forced-titration studies)	Placebo	100	53 (53.0)	47 (47.0)	15 (15.0)	30 (30.0)	0	0
	Oxy/APAP	107	63 (58.9)	44 (41.1)	20 (18.7)	25 (23.4)	0	0
	Total BTDS	**312**	**147 (47.1)**	**165 (52.9)**	**82 (26.3)**	**62 (19.9)**	**0**	**0**
	BTDS 5	105	44 (41.9)	61 (58.1)	26 (24.8)	26 (24.8)	0	0
	BTDS 10	103	57 (55.3)	46 (44.7)	21 (20.4)	21 (20.4)	0	0
	BTDS 20	104	46 (44.2)	58 (55.8)	35 (33.7)	15 (14.4)	0	0
Group A1B (nonenriched, titration-to-effect studies)	Placebo	261	150 (57.5)	111 (42.5)	33 (12.6)	75 (28.7)	1 (0.4)	0
	Oxy/APAP	43	26 (60.5)	17 (39.5)	15 (34.9)	1 (2.3)	0	0
	HCD/APAP	130	68 (52.3)	62 (47.7)	35 (26.9)	18 (13.8)	0	0
	Total BTDS	**392**	**205 (52.3)**	**187 (47.7)**	**98 (25.0)**	**72 (18.4)**	**1 (0.3)**	**0**
Group A2A (enriched, maintenance of analgesia studies	Placebo	351	248 (70.7)	103 (29.3)	9 (2.6)	88 (25.1)	0	0
	Total BTDS	**349**	**251 (71.9)**	**98 (28.1)**	**21 (6.0)**	**65 (18.6)**	**1 (0.3)**	**0**
	BTDS 5	61	48 (78.7)	13 (21.3)	3 (4.9)	10 (16.4)	0	0
	BTDS 10	133	98 (73.7)	35 (26.3)	9 (6.8)	21 (15.8)	0	0
	BTDS 20	155	105 (67.7)	50 (32.3)	9 (5.8)	34 (21.9)	1 (0.6)	0
Group A2B (enriched, fixed duration studies)	Placebo	283	199 (70.3)	84 (29.7)	20 (7.1)	36 (12.7)	0	0
	OxyIR	353	222 (62.9)	131 (37.1)	35 (9.9)	26 (7.4)	0	34 (9.6)
	Total BTDS	**1077**	**669 (62.1)**	**408 (37.9)**	**125 (11.6)**	**131 (12.2)**	**0**	**71 (6.6)**
	BTDS 5	404	241 (59.7)	163 (40.3)	26 (6.4)	78 (19.3)	0	29 (7.2)
	BTDS 10	120	84 (70.0)	36 (30.0)	18 (15.0)	9 (7.5)	0	0
	BTDS 20	553	344 (62.2)	209 (37.8)	81 (14.6)	44 (8.0)	0	42 (7.6)

Reference: Table 15. Disposition of Subjects Exposed to BTDS in the Chronic Pain Studies (Group A and Subgroups of Group A), ISS page 87

6.1.4 Analysis of Primary Endpoint(s)

Choice of Endpoints

Applicant's Primary Endpoints for Pivotal Studies

The primary efficacy variable for Study BUP3024 (conducted under a Special Protocol Agreement) and BUP3015 was 'average pain over the last 24 hours' measured on an 11-point numerical pain scale. The primary efficacy endpoint for BUP3024 was 'average pain over the last 24 hours' at Week 12. The protocol-specified primary endpoint for BUP3015 was 'average pain over the last 24 hours' at Weeks 4, 8 and 12, with the primary comparison between BTDS 5 and BTDS 20. The applicant's primary efficacy analysis of data from Weeks 4, 8 and 12 is not consistent with the Division's current standard of a landmark analysis at three months for a chronic pain indication. Therefore the FDA statistician conducted an additional efficacy analysis using the data at Week 12 and BOCF imputation method.

Efficacy Results

BUP3024 Primary Efficacy Endpoint

The primary efficacy endpoint "average pain over the last 24 hours" score at week 12 compared to baseline was statistically superior for BTDS compared to placebo (Table 6.1.4.1). Using a "hybrid" imputation method (BOCF for subjects who discontinued study medication due to an adverse event and LOCF otherwise) agreed to under the Special Protocol Agreement, the primary efficacy analysis resulted in week 12 adjusted LS means (SE) of 3.81 (0.166) for the BTDS group and 4.39 (0.152) for the placebo group. BTDS was statistically superior (P=.0104) compared to placebo by a difference of 0.58 on an 11-point numerical rating scale. However, the confidence interval was fairly wide, showing that the effect could be between .14 and 1.02. The FDA statistician was able to verify the applicant's findings.

Table 6.1.4.1: Pain Scores at Screening, Prerandomization, and Week 12 of the Double-blind Phase – Hybrid Imputation, Full Analysis Population

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)	

Cross-references: Table 14.2.1.1; Appendices 16.2.6.1, 16.2.6.2, 16.2.6.4, and 16.1.9.2.1.
LS = least squares, SE = standard error

[a] Screening mean pain was the mean of the diary "average pain over the last 24 hours" scores during the 2 consecutive days in the screening period that qualified the subject to enter the run-in period.
[b] Prerandomization mean pain was the mean of the diary "average pain over the last 24 hours" scores during the days of the run-in period that qualified the subject for randomization to double-blind treatment.
[c] Statistics are based on a mixed effect general linear model with subject as a random component, treatment and time as fixed components, and the screening mean pain and prerandomization mean pain as fixed covariates.
[d] Does not include 1 subject who completed the study but the site did not collect the pain score.

Note: Number of subjects with data varies between visits because missing pain scores were only imputed for subjects who discontinued double-blind treatment early. Intermittent missing pain scores were not imputed.
Note: Based on the selection algorithm in the SAP, an unstructured covariance matrix was used.
Note: Pain scale is 11 points (0 = no pain to 10 = pain as bad as you can imagine).

Reference: Table 9. Summary of the "Average Pain Over the Last 24 Hours" Scores at Screening, Prerandomization, and Week 12 of the Double-blind Phase – Hybrid Imputation Using Adjudicated Reasons for Study Drug Discontinuation: Full Analysis Population, pg 109 of Clinical Study Report BUP3024

Sensitivity Analyses BUP3024

The applicant conducted a number of sensitivity analyses that demonstrated statistical significance except with BOCF imputation but the results trended in the right direction, difference -0.34, P=.1502 (Table 6.1.4.2). The FDA statistician, Jonathan Norton, confirmed the findings of the different sensitivity analyses submitted by the applicant and also noted that the statistical analysis plan for the Special Protocol Agreement did not require that the applicant demonstrate statistical significance with all of the sensitivity analyses.

Table 6.1.4.2: Sensitivity Analyses of the Primary Efficacy Variable

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

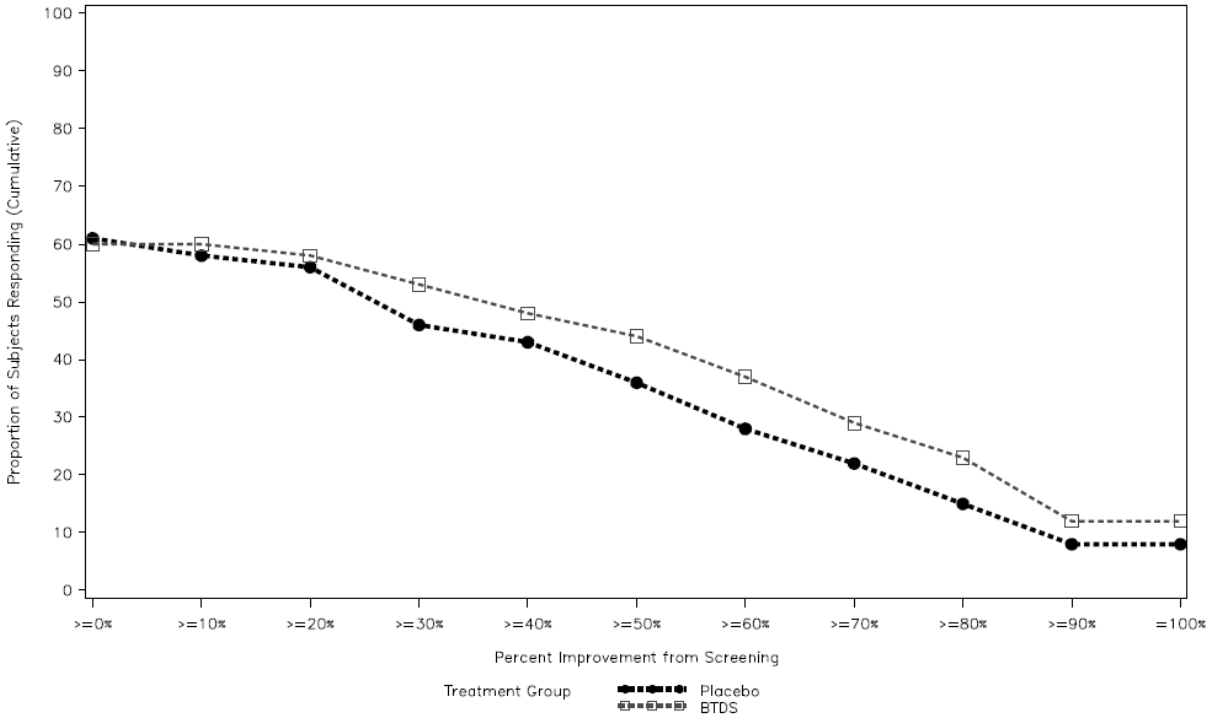
Reference: Table10. Sensitivity Analyses of the Primary Efficacy Variable, pg 110 of Clinical Study Report

More subjects had SOWS scores greater than 23 during the first week of the double-blind phase in the placebo group compared to the BTDS group, 10 subjects (8%) and 2 subjects (<1%) respectively. This may have been related to opioid withdrawal symptoms but the SOWS items are nonspecific and the relatively modest number of subjects involved is unlikely to substantially affect the efficacy results.

Responder Analysis BUP 3024

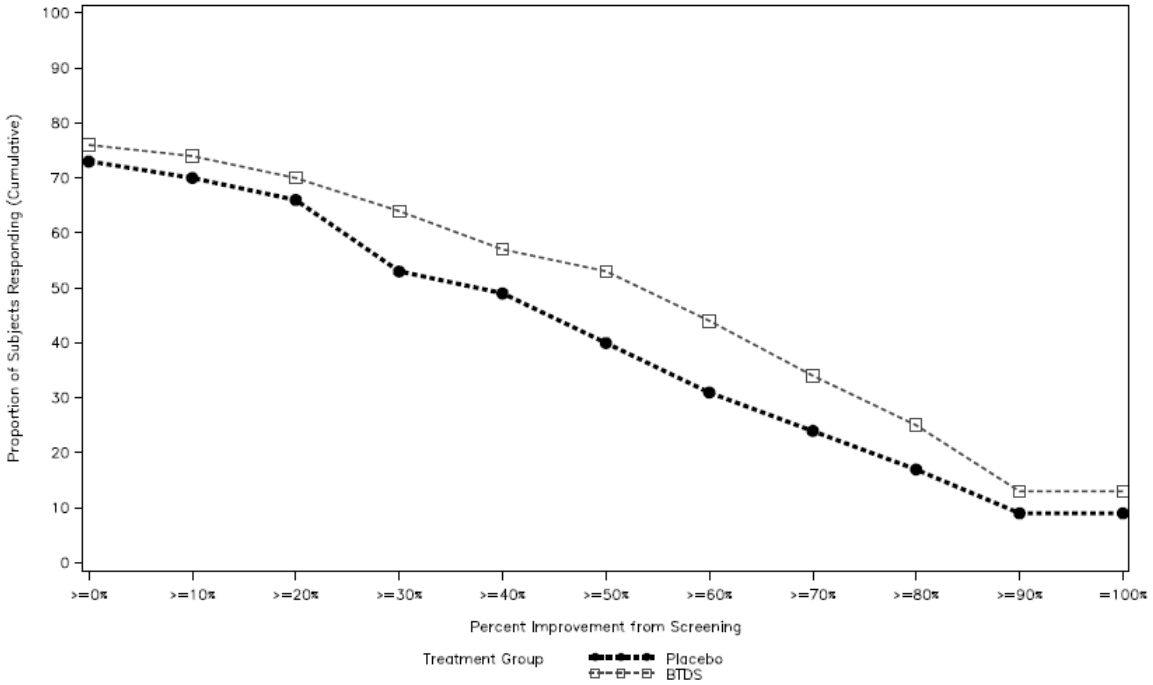
The applicant performed two versions of the responder analysis. In responder analysis 1, subjects who discontinued before week 12 were regarded as nonresponders (Figure 6.1.4.1). The plot demonstrates that subjects receiving BTDS reported a greater percent reduction in pain severity than placebo subjects but the difference was small. The number of subjects reporting a greater than or equal to 30% reduction in pain form baseline was 53% in the BTDS group versus 46% in the placebo group for responder analysis 1. The FDA statistician noted that the proportion of responders in the two treatment arms at the 30% cut point were not significantly different at the conventional .05 level (chi-square test, p=.10). The benefit of BTDS was more noticeable when a hybrid imputation methodology was used for dropouts in responder analysis 2. In responder analysis 2 the number of subjects reporting a greater than or equal to 30% reduction in pain from baseline was 64% for the BTDS group versus 53% for the placebo group (Figure 6.1.4.2).

Figure 6.1.4.1: Plot for Responder Analysis 1
Discontinuations Prior to Week 12 Regarded as Non-responders



Reference: Figure 14.2.11.9. Plot for Responder Analysis 1-discontinuations Prior to Week 12 Regarded as Non-responders, Double-blind Period, Full Analysis Population, pg 283 of Clinical Study Report

Figure 6.1.4.2: Plot for Responder Analysis 2
Hybrid Imputation Used for Dropouts Prior to Week 12



Reference: Figure 14.2.11.10. Plot for Responder Analysis 2-Hybrid Imputation, Double-blind Period, Full Analysis Population, pg 284 of Clinical Study Report

BUP3015 Protocol-Specified Primary Efficacy Endpoint

The protocol-specified primary efficacy endpoint was the "average pain over the last 24 hours" score at weeks 4, 8, and 12. Table 6.1.4.3 presents the pain scores at screening and prerandomization and the applicant's analysis at weeks 4, 8, and 12. The applicant used no imputation for missing data. For the 39 subjects who discontinued study drug but remained in the study, the applicant did not impute missing pain scores but used the available observed pain scores. Mean pain scores at screening and prerandomization were similar for all groups. At weeks 4, 8 and 12 there was a statistically significant treatment difference of -0.67 in favor of BTDS 20 versus BTDS 5, P<.001 and a statistically significant treatment difference of -0.75 in favor OxyIR versus BTDS 5, P<.001. The FDA statistician confirmed the results of the applicant's analysis of the primary endpoint.

Table 6.1.4.3: Summary of the "Average Pain Over the Last 24 Hours" Score at Screening, Prerandomization, and Weeks 4, 8, and 12 of the Double-blind Phase

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)

Reference: Table 9. Summary of the "Average Pain Over the Last 24 Hours" Scores at Screening, Prerandomization, and Weeks 4, 8, and 12 of the Double-blind Phase: Full Analysis Population, Clinical Study Report page 86

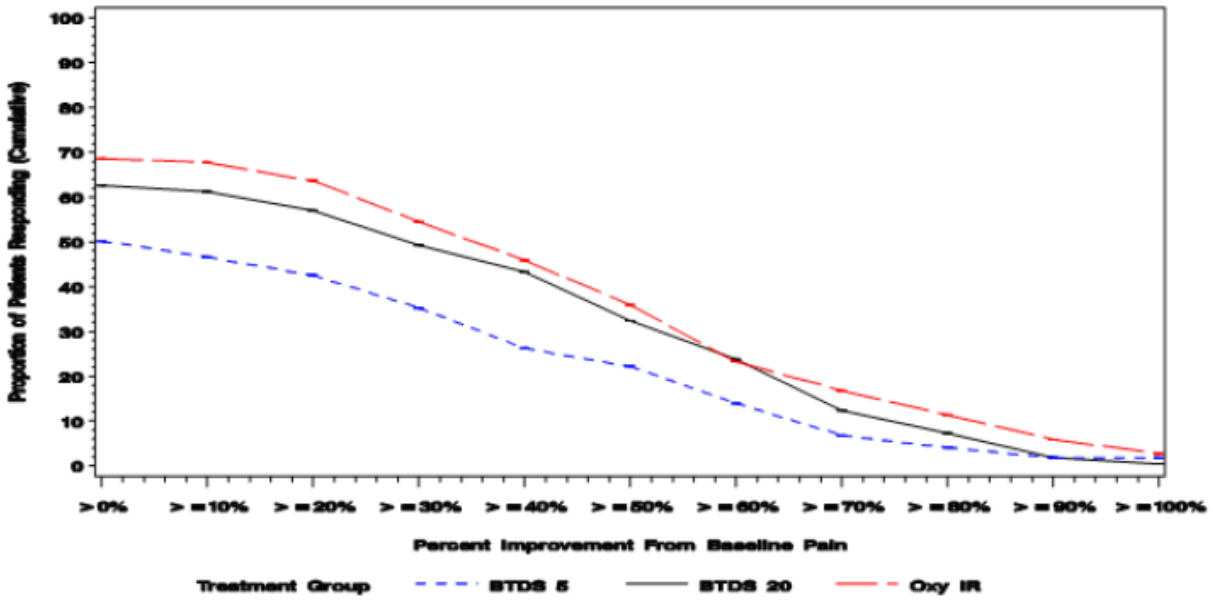
FDA Preferred Primary Endpoint for BUP3015

The applicant's primary efficacy analysis of data from Weeks 4, 8 and 12 is not consistent with the Division's current standard for a chronic pain indication. The FDA statistician analyzed the data at Week 12 using a BOCF imputation methodology. This analysis also showed BTDS 20 to be statistically superior to BTDS 5 (p<.0001). The estimated treatment effect (difference in least-squares means) was .62, with a standard error of .19. This is similar to the treatment effect of .67 found using the Applicant's analysis. The BTDS5 treatment arm showed a (least-squares) mean pain at Week 12 of 4.96, and the mean pain for the BTDS20 arm was 4.33.

Responder Analysis BUP3015

A responder was defined based on the percentage improvement from the screening mean to the means of the primary efficacy variable, "average pain over the last 24 hours" scores for weeks 4, 8, and 12. In Responder Analysis 1, the more conservative analysis, subjects who discontinued or had an increase in pain scores postrandomization were assigned a percentage improvement of zero (failure). Figure 6.1.4.3 is a graphic presentation of the results of Responder Analysis 1. For the BTDS5 treatment group 35% of subjects showed ≥30% improvement compared to 49% for BTDS 20. The analysis of the FDA statistician revealed slightly different results but the percent responding did not differ by more than 1% in any cell.

Figure 6.1.4.3: Plot for Responder Analysis 1
Discontinuations Prior to Week 12 Regarded as Non-responders



Reference: Figure 3. Percentage Change from Baseline in Average of Week 4, 8 and 12 "Average Pain over the Last 24 Hours" Scores (Responder Analysis 1): Full Analysis Population, BUP3015 Clinical Study Report, pg. 93

6.1.5 Analysis of Secondary Endpoints(s)

BUP3024

Secondary Efficacy Endpoints

- Daily number of tablets of non-opioid supplemental analgesic medications during the Double-Blind Phase
- Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale

Results of Secondary Endpoints BUP3024

Results of the analysis of the two secondary efficacy variables, sleep disturbance and use of supplemental analgesics, tested using a stepwise gate-keeping approach to control the overall Type I error-rate at 5% are shown in Table 6.1.4.4. Using the sleep disturbance subscale of the MOS-Sleep Scale there was a statistical difference between BTDS and placebo. The applicant's analysis of sleep disturbance is based on weeks 4, 8 and 12. The FDA statistician reanalyzed sleep disturbance at Week 12 to be more consistent with current Division policy and determined that the effect of BTDS is still significant (p=.035) with a similar point estimate (-3.78). No statistically significant difference was noted in the mean daily number of tablets of nonopioid supplemental analgesic used during weeks 2 to 12 of the double-blind phase but the placebo group trended toward using more supplemental analgesia.

Table 6.1.4.4. Summary of Secondary Efficacy Results

Treatments/Measurements	Treatment Difference (95% CI)	*P* Value	α-Level	Decision
Sleep disturbance subscale of the MOS-Sleep Scale at weeks 4, 8, and 12	−4.40 (−7.55, −1.25)	.0062	.025	Significant
Mean daily number of tablets of nonopioid supplemental analgesic during weeks 2 to 12 of double-blind treatment	−0.124 (−0.296, 0.048)	.1586	.05	NS

Reference: Table11. Application of a Gate-keeping Method to Assess Statistical Significance of Multiple Endpoints: BTDS vs Placebo: Full Analysis Population, pg 111 of Clinical Study Report

BUP3015

Secondary Efficacy Endpoints

- Number of tablets of rescue analgesia used in the double-blind phase
- Oswestry Disability Index
- Sleep Disturbance Subscale of the MOS Sleep Scale

Results of Secondary Efficacy Endpoints BUP3015

Secondary efficacy variables consisted of the daily number of supplemental analgesic tablets used during the double-blind phase, the Oswestry Disability Index (ODI) score, and the Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale. To address the issue of multiplicity, a gate-keeping strategy and a stepwise approach to the analysis of the secondary efficacy results were used to evaluate statistical significance. The results of the analyses of the secondary efficacy endpoints are shown in Table 6.1.4.5. The FDA statistician confirmed the findings for the MOS Sleep Scale and supplemental

analgesia, but did not look at the ODI outcome. Treatment with BTDS 20 resulted in statistically less sleep disturbance (-6.23, P<.001) and decreased use of supplemental analgesic medication (-0.5, P=.006) compared with BTDS 5. There was no statistically significant difference in the Oswestry Disability Index score between BTDS 20 and BTDS 5 treatment groups.

Number of Supplemental Analgesic Tablets
Supplemental analgesic use prior to randomization, measured during the last seven days of the run-in period, was similar for all groups. During the double-blind treatment, least squares mean doses were 3.8 tablets for the BTDS 5 treatment group, 3.3 tablets for the BTDS 20 treatment group, and 3.5 tablets for the OxyIR treatment group.

Oswestry Disability Index (ODI) Score
Mean ODI scores were similar across treatment groups at screening and prerandomization. There was no significant difference in scores between the treatment groups at weeks 4, 8 and 12.

Sleep Disturbance Subscale of MOS-Sleep Scale at Weeks 4, 8, and 12
Mean Sleep Disturbance Subscale scores were similar for all treatment groups at screening and prerandomization. Mean scores at week 12 for the three treatment groups were the following: 40.85 (BTDS 5), 33.65 (BTDS 20), and 41.60 (OxyIR). The difference in scores was statistically significant and in favor of the BTDS 20 group compared to the BTDS 5 group.

Other (Exploratory) Efficacy Endpoints
Patient Global Impression of Change (PGIC)
More subjects reported “very much improved” or “much improved” at the end of study in the BTDS 20 and OxyIR treatment groups compared to the BTDS 5 group. The percentage of subjects reporting “very much improved” or “much improved” was 33% in BTDS 5 group, 54% in BTDS 20 group and 56% in OxyIR group.

Table 6.1.4.5: Summary of Secondary Efficacy Results

Treatments/Measurements	Treatment Difference (95% CI)	*P* Value	α-Level	Decision
BTDS 20 vs BTDS 5				
MOS Sleep Scale - Sleep Disturbance Subscale	−6.23 (−9.64, −2.82)	< .001	.0167	Significant
Supplemental analgesic medication	−0.5 (−0.90, −0.13)	.006	.025	Significant
ODI Score	−1.72 (−3.55, 0.11)	.065	.05	NS
OxyIR® vs BTDS 5				
ODI Score	−1.99 (−3.79, −0.18)	.031	.0167	NS
MOS Sleep Scale- Sleep Disturbance Subscale	−2.65 (−6.01, 0.70)	.121	.025	NS
Supplemental analgesic medication	−0.3 (−0.70, 0.09)	.158	.05	NS

Reference: Table 12. Application of a Gate-keeping Method to Assess Statistical Significance of Multiple Endpoints, Clinical Study Report page 90

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

The FDA statistician verified that the efficacy findings in both pivotal studies (BUP3024 and BUP3015) were not significantly affected by age, sex or race. It was noted that older subjects reported less pain in study BUP3015 but there was no interaction between age and treatment. The comparison of race was between white and black subjects since the small numbers in other categories precluded meaningful interpretation.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing recommendations for BTDS are supported by the pivotal efficacy studies conducted by the applicant. In study BUP3024, opioid-naïve subjects were started on BTDS 5 and titrated to BTDS 10 or 20 based on efficacy and tolerability during the open-label period. Subjects successfully treated with BTDS 10 or 20 during the open-label period were randomized to their self-selected dose or placebo. Approximately half the subjects (47%) remained on BTDS 10 and half (53%) remained on BTDS 20. BTDS10 and 20 both provided effective treatment. Study results from BUP3024 support BTDS 5 as a starting dose for opioid naïve subjects and the effectiveness of BTDS 10 and BTDS 20.

In Study BUP3015, opioid-experienced subjects were started on BTDS 10 for three days and if tolerated the dose was increased to BTDS 20. Results of this

study demonstrated that BTDS 10 was tolerated as a starting dose in opioid-experienced subjects and that BTDS 20 was more effective than BTDS 5.

It was noted that BTDS 5 was the preferred dose for some subjects in supportive studies. The efficacy results reported by the applicant for these studies was not reviewed by the statistician but support the use of this dose in subjects who respond favorably.

Efficacy of BTDS 10
For Study BUP3024 the primary efficacy analysis included subjects on BTDS 10 and BTDS 20 combined. In order to asses whether BTDS 10 was effective the FDA statistician, Dr. Jonathan Norton, analyzed the proportion of subjects who completed the study and stayed on drug by treatment arm and by the dose they were on when the began the double-blind treatment (Table 6.1.10.1). The completion rate for BTDS 10 is higher than for BTDS 20. However, it was noted that subjects on BTDS 10 had less pain at screening. The statistician concluded that the comparative completion rates show no evidence that BTDS 10 is less effective when administered to the proper subject population.

Table 6.1.4.1: Disposition by Starting Dose and Arm, Full Analysis Set Study BUP3024

Starting Dose (Patch Size)	Completed?	BTDS	Placebo
10	Y (%)	84 (70%)	106 (77%)
	N (%)	36 (30%)	31 (23%)
20	Y (%)	86 (63%)	93 (63%)
	N (%)	51 (37%)	54 (37%)

Reference: FDA statistical review, page 9 Table 2: Disposition by Starting Dose and Arm, Full Analysis Set

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was demonstrated in both pivotal studies at three months. This is consistent with the current Division's requirement for demonstrating evidence of efficacy at three months for a chronic pain indication.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Exposure: The BTDS development program provided adequate exposure to assess safety with a total of 6,042 subjects treated with BTDS including 183 subjects for greater than one year in the 35 completed studies.

The applicant reports that worldwide there is over 280 million patient days of exposure to a variety of buprenorphine patches ranging in strength from 5 mcg/h to 70 mcg/h.

Safety Issues
The following safety issues were identified:

Respiratory Depression
There were three nonfatal SAEs and two deaths coded as respiratory depression. One of the SAEs was likely due to pneumonia and another was due to pulmonary edema. The third nonfatal SAE of respiratory depression may have been related to the use of a heating pad and concomitant use of a benzodiazepine. There were confounding medical issues in the two deaths making it impossible to determine an exact cause but there was no strong evidence to suggest that BTDS played a contributory role. One adverse event of respiratory depression not considered an SAE was of concern due to the severity of the respiratory depression that occurred in an opioid naïve subject treated with BTDS 20 who also received promethazine for nausea.

There is no evidence of severe respiratory depression in the BTDS development program when the product was used as recommended. As with all opioids respiratory depression is a concern. The proposed label adequately addresses the respiratory issues discussed above. There is sufficient warning in the label against using a heating pad and concomitant CNS depressants. Opioid naïve subjects are to start treatment with BTDS 5 and titrate no sooner than every three days.

In the original NDA review there was concern about respiratory depression in the immediate postoperative period. The additional studies submitted for this review do not study BTDS in the postoperative period; therefore the recommendation remains that postoperative subjects not be treated with BTDS.

Overdose
There were no cases of intentional overdose reported. There was one case (Subject 51012 study BUP3015) of respiratory depression, also coded as overdose occurring in a subject who was using a heating pad and concomitant

benzodiazepines. No cases of overdose were reported during the development program when the product was used as recommended. However, as with any opioid there is a risk of overdose. In fact the large amount of residual buprenorphine remaining after use may increase the risk of overdose if the patch is abused.

Drug Abuse

Eleven subjects were coded with an adverse event to "drug abuse." Of these 11 subjects, it was observed that 3 abused cannabis, 2 abused cocaine, 3 abused OxyIR, 2 abused Vicodin, and 1 abused Percocet/Soma. One subject who drowned tested positive for cocaine. As with all opioids the potential for abuse with a fatal outcome exists but there was no evidence from the development program the Butrans is more likely to be abused.

Withdrawal

There were 17 subjects in the BTDS clinical development program reported to have drug withdrawal syndrome including: 15 of 6042 (0.25%) BTDS-treated subjects and 2 of 1085 (0.18%) placebo-treated subjects. The applicant reports that withdrawal syndrome was never reported as an SAE but my search of the ISS dataset identified one subject (Subject 75019 Study BUP3019) coded as "Drug withdrawal syndrome" hospitalized for withdrawal symptoms nine days after discontinuing treatment with BTDS 20 following a 5-month exposure. It is well known that opioids can lead to withdrawal symptoms when discontinued abruptly and BTDS is no exception. The label adequately addresses the issue of potential withdrawal as follows:

> When the patient no longer requires therapy with BuTrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

Residual buprenorphine: The amount of residual buprenorphine remaining (b) (4)) in the patch after use poses a significant safety risk as well as abuse risk. In the development program there was no evidence of tampering with the patch to remove residual opioid. However, subjects with a history of drug abuse were excluded from the chronic pain studies. The applicant has reduced the potential for inadvertent exposure to children by providing two methods for ensuring safe disposal of used patches: fold-and-flush disposal method and occlusive-type disposal system when the primary fold-and-flush method is not possible. However, it is unclear how effective the occlusive-type disposal system will be in preventing children from accessing the drug.

I believe that the original requirement for patch modification was appropriate but that the risk can still be adequately managed with a proper Risk Evaluation and Mitigation Strategy (REMS). The applicant has theoretically reduced the potential for inadvertent exposure to children by providing two methods for ensuring safe disposal of used patches: fold-and-flush disposal method and occlusive-type disposal system when the primary fold-and-flush method is not possible.

Need for Risk Management: A Risk Evaluation and Mitigation Strategies (REMS) program will be necessary to address the issues of residual buprenorphine in the patch after use in addition to the typical problems of abuse encountered with opioid use.

Pancreatitis
Four SAEs due to pancreatitis were identified but no definite conclusions could be made regarding the role of BTDS in these individual cases. However, it is known that opioids can increase sphincter of Oddi pressure which has been implicated as a cause of pancreatitis. Given a theoretical basis for opioids causing pancreatitis and the increased incidence of pancreatitis observed in BTDS-treated subjects compared to placebo, it appears reasonable to conclude that there may be an association between BTDS and pancreatitis. The proposed label with the standard opioid warning appears adequate to address this risk:

> Buprenorphine may cause spasm of the sphincter of Oddi. Use with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase.

QT Interval Prolongation/Cardiac
In the thorough QT study a supratherapeutic dose of BTDS (40 mcg/h) prolonged QTcI by 9.2 ms (90% CI:5.2-13.3), an effect similar to that of 400 mg of moxifloxacin used in the same study. The therapeutic dose of BTDS 10 had no clinically meaningful effect on QTcI. The BTDS 20 dose was not studied but the exposure with the supratherapuetic dose would be twice that of the BTDS 20 dose. The cardiologist form the Division of Cardio-Renal Products concluded QTc outliers, QTc duration or QTc increases over baseline data showed a modest unbalance between placebo and BTDS arms, in particular at the highest dose studed (BTDS 20). In none of the groups analyzed mean changes from baseline in QTc were over 5.7 ms. The highest effect was seen in the BTDS 20 arm. There was a low incidence rate of AEs and SAEs related to E14 ICH Guidance even at the highest dose tested. Syncope was the AE and SAE with higher rate (0.1-0.3%) that was not necessarily linked to QT prolongation.
We performed an MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration including PR, QRS and QT events and arrhythmias. The cardiologist detected no signals for Torsades and

QT prolongation. I reviewed the two cases of ventricular tachycardia and determined that they were unrelated to BTDS. There were six cases of SAEs involving seizures and syncope: 2 cases were unrelated to BTDS, for 4 cases there was insufficient information to make a determination as to the role of BTDS but there was no evidence that BTDS contributed to the event.

Although the risk of a proarrhythmic effect is low based on the QT data the label appropriately informs prescribers to consider these observation when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide) should consider the risk of adding BuTrans treatment.

Serious Adverse Events of the Skin

Five subjects (<0.1%) of the 6042 BTDS-treated subjects developed serious adverse events of the skin. One subject developed erytherma multiforme unrelated to BTDS. Four subjects developed either a rash or skin ulcers/necrosis. BTDS was probably the cause for only one of these subjects who developed a generalized rash requiring hospitalization. BTDS was not the cause for two subjects with ulcers/necrosis and unlikely the cause of one subject with a rash starting after two days on nambutone. There were frequent local skin irritations but this would be expected with use of a patch.

Laboratory Findings

Potentially elevated LFTs: Review of the shift tables from normal to high for LFTs suggested a possible weak signal for hepatotoxicty. The applicant reports that no subjects were discontinued form the study due to elevated LFTs and conducted an analysis of adverse events coded to liver related signs and symptoms and found the rates were similar during the double-blind period of the controlled chronic pain studies (Group A). The incidence of all AEs under this subSMQ for BTDS-treated subjects was 0.6%, placebo-treated subjects 0.4%, and OxyIR-treated subjects 1.1%. There was one case meeting the definition of Hy's law that was due to acute cholecystitis. The issue is adequately addressed with the information in the proposed label:

> Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative

or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected.

Hematologic Laboratory Changes: Subjects treated with BTDS appear to have slightly lower hemoglobin, WBC and ANC values. This effect also appears to be present with other opioids but may be greater with BTDS on ANC. These changes are not felt to be clinically relevant.

Pending Issues
The 120 day safety update was not submitted by the applicant at the time of completion of this review. The applicant is currently working on the update.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In support of this NDA, the Applicant submitted 35 completed studies that are included in the integrated database: 18 pharmacokinetic studies and 17 phase 2 and 3 studies. In addition safety data from ongoing chronic pain study BUP3025 is reported separately but not included in the integrated database. The *safety population* is composed of all subjects who were enrolled in any of the studies integrated in the ISS, received at least 1 dose of any study drug, and had at least 1 safety assessment during exposure to study medication with the following exceptions:

- Subjects in BUP3018 who received hydrocodone/acetaminophen during the open-label run-in period, but were not randomized to the double-blind period
- Subjects in BUP1011 who were randomized to moxifloxacin

The *randomized safety population* is composed of subjects who were enrolled in studies integrated in the ISS, who were randomized to treatment groups, received at least 1 dose of double-blind study drug, and had at least 1 safety assessment during the double-blind period. This population is used for comparative analyses based on data recorded during the double-blind period.

Purdue's integrated safety analyses are based on the following groupings for the 35 studies, each group is represented by a letter (Figure 7.1.1.1):

- Studies in chronic pain (Group C)
- Studies in nonchronic pain (Group B)

- Clinical pharmacology studies (Group D)

The applicant, in general, provided safety summaries and analyses for each of these groups separately but used summaries across groups C, B, and D for analysis of AEs, deaths, and SAEs.

Group C consists of fifteen controlled and uncontrolled, chronic pain, phase 3 studies

- 13 controlled, double-blind, multiple-dose phase 3 studies in subjects with chronic pain (Group A)
  - 7 of these 13 studies (BUP3002, BUP3011, BUP3012, BUP3014, BUP3015, BUP3019, BUP3201) had open-label extension periods
  - Subjects from 3 of the 13 studies (BP96-0101, BP96-0102, BP96-0604) were allowed to enroll in an open-label extension study (BP96-0103)
- 2 uncontrolled studies in subjects with chronic pain
  - 1 uncontrolled, open-label long-term phase 3 study (BP96-0103)
  - 1 uncontrolled, multiple-dose, double-blind phase 3 conversion study (BUP3018)

Group B consists of 2 studies in nonchronic pain

- 2 placebo-controlled, double-blind, single- and multiple-dose phase 2 studies (BP96-0104, BUP2003) in subjects with nonchronic pain (post-operative)

Group D consists of clinical pharmacology studies

- 18 controlled and uncontrolled, single- and multiple-dose clinical pharmacology studies

Group C, chronic pain studies, are subdivided into controlled chronic pain studies designated as Group A. Group A is composed of the nonenriched chronic pain studies (Group A1) and the enriched chronic pain studies (Group A2). Group A1 consists of forced titration (Group A1A) and titration to effect (Group A1B). Group A2B is composed of the 4 enriched, fixed duration studies and Group A2A consists of 3 enriched, maintenance of analgesia (randomized withdrawal) studies.

Figure 7.1.1.1: Summary of Study Design and Analysis Groupings for the 35 Completed Studies

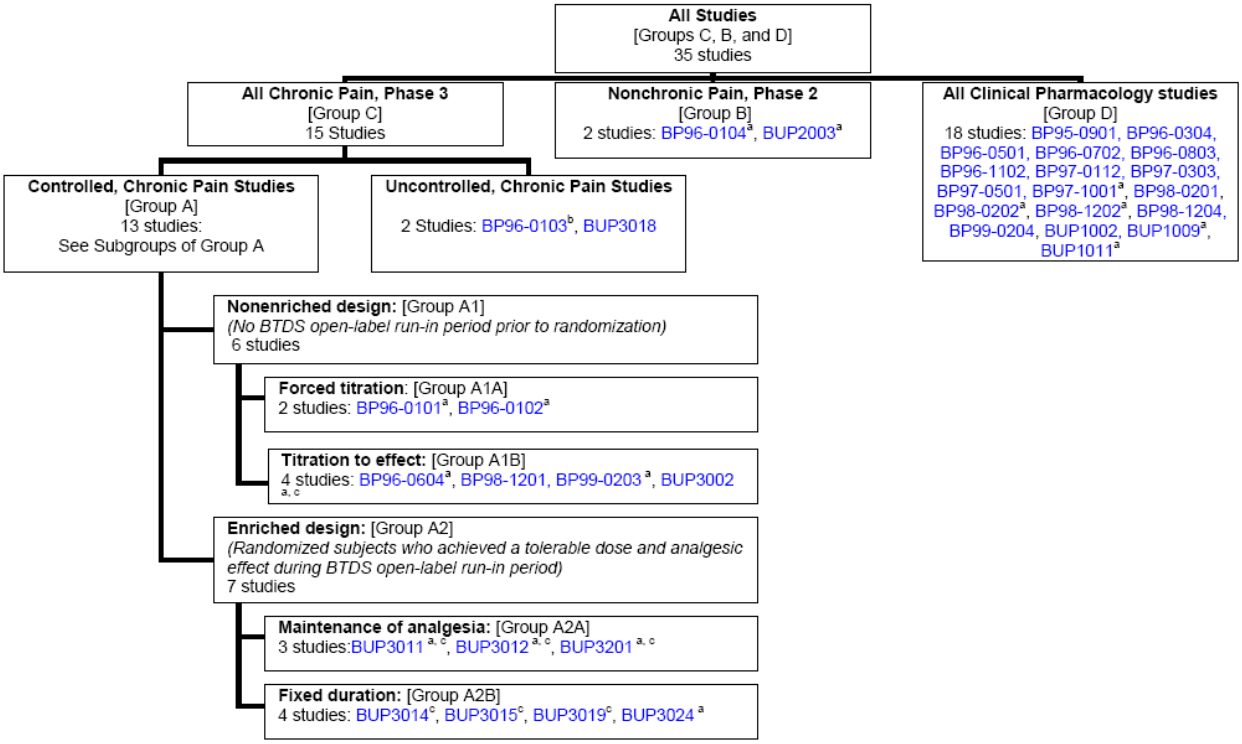


Figure 1. Overview of Analysis Groups and Designations

[a] Placebo-controlled studies.
[b] Subjects from studies BP96-0101, BP96-0102, BP96-0604 entered study BP96-0103.
[c] 7 studies with extension periods were BUP3002, BUP3011, BUP3012, BUP3014, BUP3015, BUP3019, and BUP3201.

Reference: ISS, pg. 40

Safety data from one ongoing study (BUP3025) was not included in the integrated safety data but reported separately. BUP3025 was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial evaluating the analgesic efficacy and safety of BTDS 10/20 versus placebo in opioid-naïve subjects with moderate to severe chronic pain due to OA of the knee; 1149 subjects entered the open-label run-in period and were exposed to BTDS; 571 of these subjects were randomized into the double-blind period. At the time of this submission data from the double-blind period of this study was still blinded. The adverse events were consistent with adverse events observed in the completed studies.

Applicant's Response to Deficiency #56 in the Not Approvable Letter:

The applicant reanalyzed the prior safety data for the 22 studies included in the original submission and one additional study, BUP1002, completed shortly after the submission. The reanalysis included the following: source documentation was remonitored; safety data was reviewed for discrepancies; errors or discrepancies in the safety database were reconciled; all AEs were recoded

using COSTART; and all revised analyses based on updated safety data were documented. The applicant reports that this safety re-analysis did not change the overall conclusions provided in the original clinical study reports. The new study reports for these 23 studies are denoted with the letter "R" following the clinical study report number.

The applicant submitted an updated Summary of Clinical Safety dated 29 Dec 2009 to correct minor changes noted in the original report. The updated report was reviewed in detail and none of the changes impacted on the overall safety impression based on original report. The changes occurred as the result of three clinical data errors: 1) Study BUP3201 - miscoding some adverse events to a general skin reaction that should have been coded specifically to patch-application-site reactions; 2) Study BP99-0203 and BP98-1201 - classifying some subjects as opioid-experienced when they were opioid naïve; 3) Study BUP3001 - omitting concomitant medications started and/or stopped during the extension period of the study. These errors affected approximately 200 subjects in the four studies. The changes were small e.g. "Application site pruritus" changed from 12.1% to 14.3% and pruritus changed from 6.1% to 4.9%.

Adverse events from all studies for the current ISS were recoded into MedDRA version 10.0.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 terminology. AEs considered treatment emergent were those:

- Whose onset occurred during exposure to study drug or within 7 days after the last dose of study drug, having been absent prior to receiving study drug
- Whose onset reoccurred during exposure to study drug or within 7 days after the last dose of study drug, having been present but stopping prior to or during exposure to study drug
- That worsen in severity during exposure to study drug or within 7 days after the last dose of study drug

The applicant performed analyses of AEs that can signal potential proarrhythmic effects (AEs listed in the ICH E14 guideline) and other relevant AEs such as seizures/ convulsions. Standard MedDRA Queries (SMQs) were conducted by the applicant for accidents and injuries, acute central respiratory depression, adverse pregnancy outcome/reproductive toxicity, agranulocytosis, cardiac failure, cardiac arrhythmias, dementia, drug abuse/dependence/withdrawal, hepatic disorders, leucopenia and severe cutaneous adverse reactions.

AEs, serious AEs and AEs leading to study-drug discontinuation for Group A (double-blind) and Group C (overall BTDS exposure) were presented.

The applicant evaluated the interaction between drug and demographic characteristics (age, sex, pain site/etiology, race and previous opioid experience) for subjects in the nonenriched controlled, chronic pain studies (Group A1). Analyses were not performed for the group of enriched chronic pain studies (Group A2) because the open-label run-in period in which all subjects received BTDS prior to randomization limited the usefulness of the data.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As noted in section 7.1.1 the safety dataset included both the safety population and the randomized safety population. The randomized safety population was utilized for making comparisons between treatment groups.

7.2 Adequacy of Safety Assessments

A total of 6,042 subjects were treated with BTDS in the 35 completed studies. The safety database allowed for analyses of all subjects who received BTDS and randomized subjects who received BTDS. Safety assessments included adverse events, laboratory evaluations (hematology, chemistry), vital signs, ECGs and a through QT study. The applicant submitted data of adequate quality and completeness to allow for a comprehensive safety review. The safety assessments were considered adequate to asses the overall safety of BTDS in chronic pain subjects.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 6,042 subjects were treated with BTDS in the 35 completed studies: 5415 subjects in the chronic pain studies (Group C), 107 subjects in the nonchronic pain studies (Group B) and 520 subjects in the clinical pharmacology studies (Group D). Table 7.2.1 displays the duration of exposure for BTDS in the chronic pain studies calculated by the applicant using 28 day months.

Table 7.2.1: Number (%) of Subjects with Continuous Exposure to BTDS in the Chronic Pain Studies (Group C)	
Continuous exposure categories [a,b]	**Number (%) of BTDS treated subjects**
Any duration	5415 (100)
≥3 months	1611 (29.8)
≥6 months	924 (17.1)
≥12 months	220 (4.1)
≥365 days	183 (3.4)
Reference: Table 11. Number (%) of Subjects with Continuous Exposure to BTDS in the Chronic Pain Studies (Group C), page 81 of ISS [a] 1 month is defined as 28 days [b] Continuous exposure is defined as the longest time a subject is exposed to BTDS without any gaps (≥7 days) in treatment	

In the controlled, chronic pain studies (Group A), 2130 subjects were exposed to BTDS. Table 7.2.2 displays the duration of exposure to BTDS and placebo for subjects during the double-blind period of the controlled chronic pain studies. The overall exposure was adequate to assess the use of BTDS for the management of chronic pain.

Table 7.2.2: Number (%) of Subjects with Cumulative Exposure to BTDS or Placebo During the Double-Blind Treatment in All Controlled, Chronic Pain Studies (Group A)		
Cumulative exposure categories	**Number (%) of subjects**	
	BTDS	**Placebo**
Any duration	2130 (100)	995 (100)
≥7 days	1964 (92.2)	866 (87.0)
≥14 days	1701 (79.9)	700 (70.4)
≥21 days	1478 (69.4)	580 (58.3
≥28 days	1399 (65.7)	537 (54.0)
≥2 months	1028 (48.3)	316 (31.8)
≥3 months	598 (28.1)	200 (20.1)
Median cumulative days of exposure	28	45
Reference: Table 12. Number (%) of Subjects with Cumulative Exposure to BTDS or Placebo During the Double-Blind Treatment in All Controlled, Chronic Pain Studies (Group A), page 82 of ISS		

7.2.2 Explorations for Dose Response

The applicant analyzed the incidence of AEs and BTDS dose (Table 7.2.2). There was a dose-response relationship, with an increased incidence of AEs associated with higher BTDS strengths. No dose-response relationship for AEs was observed in nonenriched, forced-titration studies (GroupA1A) but this group had the highest AE rates (>90%) making it difficult to identify any difference in rates with dose. This group also had the highest discontinuation rate. In the nonenriched titration-to-effect studies (Group A1B) whose design approximates the clinical setting, a dose-response relationship was observed for the most common AEs, eg, incidence of constipation was 3.6% for subjects receiving BTDS 5, 6.2% for subjects treated with BTDS 10, and 8.6% for subjects treated with BTDS 20.

Table 7.2.2: Number (%) of Subjects with Adverse Events and Adverse Events that Led to Study Drug Discointinuation by BTDS Dose in Group A studies

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	*	*

(Reference: Appendix 11, Tables: Group A1A double-blind: Tables 4.2.1.6, 4.5.5.6; Group A1B double-blind: Table 4.2.1.7.2; Group A2A open-label run-in: Table 4.2.1.2.2; Group A2A double blind: Tables 4.2.1.9, 4.5.5.9; Group A2B open-label run-in: Table 4.2.1.3.2; Group A2B double-blind: Tables 4.2.1.10, 4.5.5.10).
[a] AEs leading to discontinuation.
N=number of subjects who received BTDS.
n=number of subjects with adverse events.
* Not available (Incidence of AEs leading to study-drug discontinuation in the double-blind period of Group A1B are provided in Appendix 11, 4.5.5.7.1).

Reference: Table 28, ISS, pg. 124

7.2.3 Special Animal and/or In Vitro Testing

As a 505(b)(1) submission with a proposed chronic indication, a complete nonclinical dataset was required including reproductive toxicology and carcinogenicity.

Special animal testing showed that nalmefene, an opioid antagonist and analog of naltrexone, could not reverse or attenuate respiratory depression induced by buprenorphine pretreatment in rats. Simulated accidental ingestion (swallowing of patches or chewing before swallowing) of up to 20 mg buprenorphine in beagle dogs, the amount of buprenorphine in one 20 mcg/h patch, did not result in significant clinical effects. Simulated accidental buccal absorption of 5 or 20 mcg/h patches in beagle dogs identified a potentially significant safety issue due to significant absorption of buprenorphine, which may occur if children were to chew used (discarded) or unused patches. Warm water immersion did not increase dermal absorption of buprenorphine from applied dermal patches in minipigs

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of Butrans appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review of Dr.Shettal Agarwal.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The opioid class of drugs has been associated with the potentially serious adverse events of respiratory depression, drug abuse and overdose. Opioids can also result in central nervous system adverse events of sedation, dizziness, somnolence and headache. Gastrointestinal system adverse events include nausea, vomiting and constipation. Opioids, in particular methadone have been associated with QTc prolongation and torsade de pointes. The causality assessment of QT prolongation and adverse events can be difficult to interpret due to confounding medical conditions.

7.3 Major Safety Results

7.3.1 Deaths

There were 18 deaths in the BTDS clinical program: 17 in completed studies and one in ongoing chronic pain study (BUP3025). Fifteen deaths occurred in BTDS-treated subjects: 14 in completed studies and one in the ongoing chronic pain study. In the completed studies of BTDS-treated subjects there were 14 deaths out of 6042 subjects (0.23%). According to the applicant this resulted in 12.2 deaths per 1,000 subject-years. There was one death in placebo-treated subjects out of 1085 placebo-treated subjects (0.09%). This resulted in 9.4 deaths per 1,000 subject-years. In the hydrocodone/acetaminophen group there was one death out of 130 subjects (0.77%). One subject died during the screening period and never received study drug. The one subject who died during the open-label run-in period of BUP3025 (n=1149) received BTDS. This resulted in 15 deaths out of 7191 BTDS-treated subjects (completed and ongoing studies) for an incidenc 0.21%.

Deaths in the original NDA submission of November 2000 were reviewed in detail by Dr. Gerald Dal Pan, the medical officer. There were three deaths which all occurred in BTDS treated subjects. Excerpts from his review of those three patients along with my review of the additional deaths follow.

Individual Patient Death Summaries

Subject 47005 (Study BUP3011)
Subject 47005 was a 70-year-old white man with a past medical history of coronary artery disease, diabetes mellitus, and hypertension enrolled in study BUP3011 for chronic osteoarthritic pain of the right hip. A prior exercise myocardial perfusion scan from (b) (6) was positive for severe left ventricular dilatation with 25% ejection fraction, global hypokinesis and ischemic ECG changes. No significant arrhythmias were noted. Screening ECG prior to starting the study was consistent with inferior MI and ST depression and inverted T waves. The subject began treatment with BTDS 5 on (b) (6). He was randomized to BTDS 20 on (b) (6). On (b) (6) the subject was found by a passer-by to be blue in a wheelchair at an airport. He received CPR and defibrillation approximately 12 times on the way to the hospital. Monitors revealed ventricular fibrillation in both the ambulance and the hospital. Serial CK-MB and troponin levels were elevated. The subject apparently did not regain consciousness and died on (b) (6) after the family requested for extubation. No autopsy was performed. The investigator considered the acute MI unrelated to BTDS but associated with cardiovascular disease.

Impression
The presumed cause of death, acute MI, is consistent with the patient's history of myocardial ischemia and severely impaired left ventricular function. Assessing the contributory role BTDS may have had in his MI or ventricular fibrillation is confounded by his comorbidities.

Subject 16 (Study BUP3002)
Subject 16 was an 86-year-old woman enrolled in the study with left shoulder pain. The subject's past medical history was significant for pulmonary embolus, congestive heart failure, coronary artery disease, transient ischemic attack, insulin-dependent diabetes mellitus, glaucoma, COPD, osteoporosis, bronchopneumonia, degenerative joint disease of the spine and extremities and chronic lymphocytic leukemia. The subject began treatment on (b) (6) with BTDS 5 and increased to BTDS 10 on (b) (6). On (b) (6) after 13 days exposure to BTDS the subject had a myocardial infarction which led to death on (b) (6). Concomitant medications included Vicodin, morphine, prednisone, glyceryl trinitrate, levofloxacin, furosemide, lorazepam, bisacodyl, metolazone, potassium, Humulin 70/30, fluconazole, and nystatin.

Impression
The subject's acute myocardial infarction may have been related to his pre-existing cardiac disease but there is insufficient information to exclude BTDS as having a contributory role.

Subject 118 (Study BUP3002)
This 91-year-old white woman enrolled in the study with right shoulder pain. Her past medical history was significant for congestive heart failure, hypertension, transient ischemic attack, edema, pleural effusion, degenerative joint disease, diarrhea, urinary incontinence, insominia, depression, senile dementia and nausea. The subject began treatment on (b) (6) with BTDS 5 and increased to BTDS on (b) (6). She completed the study on (b) (6). She was in hospice care for treatment of congestive heart failure and on (b) (6), 5 days after completing the study, the subject experienced an increase in her congestive heart failure that led to her death later the same day. Concomitant medications included digoxin, furosemide, potassium, prochlorperazine, levofloxacin, zolpidem, propranolol and Vicodin.

Impression
The increased congestive heart failure is consistent with the patient's past medical history of congestive heart failure. It is impossible to exclude BTDS as having a contributory role in her failure but this seems unlikely.

Subject 46002 (Study BUP3015S)
Subject 46002 was a 74-year-old white man with low back pain. The subject's past medical history included: tobacco abuse, gout, hypertension, hypertriglyceridemia, diverticulosis, hiatal hernia, glucose intolerance, insomnia, lumbar 3-4 anterolisthesis and severe stenosis, and degenerative joint disease. Screening visit ECG results indicated: first degree AV block and intraventricular conduction defect.

On (b) (6), the subject began the opioid taper and began discontinuation of Vicodin. On (b) (6), the subject began treatment in the run-in period with BTDS 10 and increased to BTDS 20 on (b) (6). On (b) (6), the subject was randomized to BTDS 5. On (b) (6), the subject completed the double-blind phase and began treatment in the extension phase with open-label BTDS 5. On (b) (6) the study drug was increased to BTDS 10. On (b) (6), the study drug was increased to BTDS 20.

On (b) (6), the subject began experiencing nausea, anorexia, and became febrile. On (b) (6) the subject underwent colonoscopy, which revealed two lesions in the rectosigmoid area. The subject was diagnosed with sigmoid colon cancer, A nuclear stress test on (b) (6) showed an ejection fraction of 46% and evidence of an inferior wall infarct, but was negative for ischemia. On (b) (6), the subject underwent lower anterior resection for sigmoid colon cancer. On (b) (6), the subject was discharged from the hospital and the sigmoid colon cancer and polyps were considered resolved. On (b) (6), the subject experienced acute cardiac death, which was considered by the investigator to not be related to study drug. On that date, the subject had been found unresponsive at home by his son who attempted CPR unsuccessfully. No autopsy was performed. The subject remained on BTDS 20 up to the time of death. ECG results on (b) (6) and (b) (6) indicated: intraventricular conduction defect. ECG results on (b) (6) and (b) (6) indicated: first degree AV block and intraventricular conduction defect.

Impression
The presumed cause of death was an acute cardiac death that occurred after being on BTDS for over one year and approximately one week after resection of the sigmoid colon for cancer. The sequence of events makes it unlikely that BTDS resulted in the death but a contributory role cannot be completely excluded.

Subject 93019 (Study BUP3025-ongoing)
Subject 93019, a 59-year-old (opioid-naïve) white male was enrolled in the ongoing study BUP3025 for osteoarthritic knee pain. Past medical history was notable for HTN, hypercholesterolemia, and a 45 pack-year smoking history. Medications included hydrochlorothiazide/lisinopril. On (b) (6), he began

the open-label run-in period receiving treatment with BTDS 5, which was increased to BTDS 10 on (b) (6) and to BTDS 20 on (b) (6) On (b) (6) he was discovered, dead, by his family. The applicant provides the following information:

> Autopsy revealed cardiomegaly and remote MI, and cause of death was listed as hypertensive atherosclerotic cardiovascular disease, deemed not related to study medication. Of note, the transdermal patch was reportedly on the patient when he died (the patch tested positive for buprenorphine), even though buprenorphine was not detected on toxicology testing (per forensic pathology report).

Impression
The presumed cause of acute cardiac death, hypertensive atherosclerotic cardiovascular disease does not necessarily exclude the possibility of a contributory role of BTDS given the death occurred approximately two weeks after starting study medication. The negative toxicology test for buprenorphine if accurate would make it unlikely that BTDS contributed to his death. However, the subject was reported to have been found with the transdermal patch on him which would make it difficult to explain the test results.

Subject 0106 (Study BUP3002S)
Subject 0106, a 73-year-old woman, entered the extension study BUP3002S on (b) (6) with osteoarthritic pain of the left shoulder. At the start of the core study the subject's ongoing medical conditions included: congestive heart failure, hypertension, edema, gastritis, Type II diabetes mellitus, cerebrovascular accident and diabetic neuropathy. The subject was randomized to BTDS in the core study on (b) (6) and completed the core study on (b) (6) in the BTDS 10 treatment group. The subject began the extension phase with BTDS 5 on (b) (6) (Day 0) then increased to BTDS 10 on (b) (6) 1. The subject was maintained on BTDS 10 until discontinuation of study drug on (b) (6). On (b) (6) (Day 109 of the extension), after 173 days of cumulative exposure to BTDS, the subject developed metabolic encephalopathy and sepsis at which time the subject stopped taking study drug. On (b) (6) (41 days after discontinuation from the extension), after 173 days of cumulative exposure to BTDS, the subject experienced bradycardia leading to death, which was considered by the investigator not related to study drug. The subject died on (b) (6)

Impression
I concur with the investigator's impression that this subject's bradycardia leading to death 41 days after discontinuation of study medication was not related to BTDS.

Subject 5 (Study BUP3002)
Subject 5, an 89-year-old, white female entered the study with low back pain. The subject's medical history was significant for congestive heart failure, hypertension, hypercholesterolemia, osteoarthritis of the neck and back and malnutrition. The subject began treatment on (b) (6) with BTDS 5 (Day 0), increasing to BTDS 10 on (b) (6), which was further increased to BTDS 20 on (b) (6). On (b) (6), after 20 days of exposure to BTDS, the subject discontinued the study due to an adverse event, stupor, which was considered by the investigator to be not serious and having a possible relationship to study drug. On (b) (6) 9 days following BTDS patch removal, the subject had the following serious adverse event, cerebrovascular accident, which was considered by the investigator to be severe and not related to study drug. The subject died on (b) (6)

Impression
This patient's cerebrovascular accident occurring nine days after BTDS patch removal does not appear related to study drug. The adverse event "stupor" occurring while on study drug may have been related to BTDS but as noted previously would not explain her stroke.

Subject 142 (Study BUP3002S)
Subject 142, an 89 year-old white female entered the extension study on (b) (6) with osteoarthritis and pain in multiple joints. At the beginning of the extension, the subject's ongoing medical conditions included anorexia, Addison's disease, incontinence, osteoporosis, depression, hypertension, gout, transient ischemic attacks and right hemiplegia, aphasia, and myopia associated with cerebrovascular disease. The subject was randomized to BTDS in the core study (b) (6) and completed the core study on (b) (6) on BTDS 20. The subject began the extension phase treatment with BTDS 5 on (b) (6) (Day 0), increasing to BTDS 10 on (b) (6), then increasing to BTDS 20 on (b) (6) The last recorded date the patch was applied was (b) (6) On (b) (6) (Day 81), after 18 days without treatment and after 123 days of cumulative exposure to BTDS, the subject was coded with cerebrovascular disease, considered by the investigator to be unrelated to study drug, which resulted in death on the same day.

Impression
I concur with the investigator's opinion that this subject's death from cerebrovascular disease was unrelated to study drug but consistent with her history of prior stroke and TIA.

Subject 32004 (Study BUP3019S)
Subject 32004 was a 64-year-old woman enrolled in BUP3019S with osteoarthritic pain of the left knee. The subject's past medical history included:

morbid obesity, type II diabetes, hypothyroidism, osteoarthritis, pulmonary embolus and left deep vein thrombosis (2003), depression, mild anxiety, chronic renal insufficiency, hypertension and stasis dermatitis of the lower extremities. The subject was taking the following medications at onset of study: lisinopril, levothyroxine, furosemide, metformin, warfarin, ammonium lactate (Lac-Hydrin) and propoxyphene/ acetaminophen. On (b) (6), the subject began the opioid taper of propoxyphene/acetaminophen. On (b) (6), the subject began treatment in the run-in period with open-label BTDS 10. On (b) (6), study drug was increased to BTDS 20. On (b) (6), the subject was randomized to BTDS 20. On (b) (6), the subject completed the double-blind phase, and began treatment in the extension phase with open-label BTDS 5, increased to BTDS 10 on (b) (6), and BTDS 20 on (b) (6). On (b) (6) the subject began experiencing worsening cellulitis of the right lower extremity and was treated with a 10-day course of cephalexin. On (b) (6) the subject developed moderate gout in the right foot and was treated with allopurinol and a 7-day course of prednisone. On (b) (6) the subject discontinued treatment with warfarin, which the subject had been taking since 2003. On (b) (6), the subject discontinued study drug following the sponsor's decision to discontinue the study due to non-safety related considerations. At the time of study discontinuation, the gout on the right foot was considered ongoing. On (b) (6), the subject was found dead at her home after experiencing a pulmonary embolism. Coworkers reported that she had been short of breath for a few days prior to her death. An autopsy was not performed. The investigator considered the pulmonary embolism which led to death to be a serious adverse event and not related to study drug.

Impression
The presumed cause of death, pulmonary embolism, appears unrelated to BTDS-treatment. Her history supports the diagnosis of pulmonary embolism but no confirmatory imaging studies were reported. It is unlikely that BTDS contributed to her death since it occurred approximately two weeks after discontinuing study drug.

Subject 0079 (Study BP96-0104)
Patient 79 in Study BP96-0104 was a 90-year-old woman who underwent a right total knee revision on (b) (6). The patient's past medical history included cardiovascular disease (hypertension and chronic atrial fibrillation) and a cerebrovascular accident in 1996, resulting in right lower extremity weakness and minimal aphasia. Baseline ECG (b) (6) revealed coarse atrial fibrillation with a ventricular response of 63 and probable left ventricular hypertrophy with ST-T abnormalities.

Postoperative medications included metoprolol, cefazolin, docusate, ranitidine, nifedipine, bacitracin, and polymyxin. In the recovery room the patient was

treated with 2 doses of labetolol. The patient received BTDS 10 on (b) (6) at approximately 8:00 AM (0 hour). The same day the subject was started on hydrochlorothiazide, enoxaparin SC, famotidine IV and furosemide. At 20:47 the patient experienced mild agitation and was treated with lorazepam 2 mg IV. At 22:00 the patient experienced ventricular tachycardia, respiratory failure, and cardiac arrest. She required cardioversion, converted to an atrial fibrillation rhythm, and was intubated; Swan-Ganz catheterization revealed evidence of congestive heart failure. At approximately 22:55 at 39 hours, the patient was discontinued from study drug.

The subject was also reported to have post-op anemia and moderate acute oliguric renal failure. That same day, the postbaseline ECG findings included: atrial fibrillation with a ventricular response of 79 and diffuse ST-T abnormalities. Multiple CXRs post-cardiac arrest were suggestive of either atelectasis or left lower lobe infiltrate. On (b) (6), an M-mode and 2-D echocardiogram revealed an ejection fraction of 25%. There was mild concentric left ventricular hypertrophy with diffuse hypokinesis. Post-cardiac arrest cardiac enzymes were consistent with a myocardial infarction. The patient was transfused several units of blood for her anemia. On (b) (6), the post-op anemia was considered resolved by the investigator. On the same date, the patient was extubated. On (b) (6), the acute renal failure was considered resolved by the investigator. On (b) (6) after 2 days total exposure to BTDS 10, and 5 days post-removal of patch, the patient died due to presumed heart failure secondary to atrial fibrillation, respiratory failure, congestive heart failure, and acute renal failure. No autopsy was performed.

This death was reviewed in the initial NDA submission by Dr. Del Pan who concluded the following:

> In review of the above narrative, it is not clear if the hypoxia and apnea preceded the ventricular tachycardia, or if they followed it. If the initial event was the respiratory decompensation, then BTDS may certainly have played a role. The basis of the investigator's judgement that the apnea and tachycardia were not related to the study drug, but that the cardiac arrest may possibly have been related, is not clear. Of note, two other patients in post-operative study BP96-0104 had life threatening serious adverse events of apnea. The Sponsor notes in Section 8.13.6.2 (Deaths) of the ISS that "BTDS is indicated for the management of pain in patients requiring continuous opioid analgesia, not for postoperative use.

Impression
I concur with Dr. Del Pan's assessment that it is unclear from the sequence of events whether BTDS may have played a role in the respiratory decompensation. I also note Dr. Del Pan's concern about life threatening serious adverse events of apnea in two other post-operative patients. Use of long-acting opioids is not

consistent with the current standard of care for acute post-operative pain management. The applicant is not seeking a postoperative pain indication for BTDS which would mitigate any concern about the potential role BTDS may have on postoperative respiratory depression. This subject's ventricular tachycardia and cardiac arrest may have been related to her pre-existing cardiovascular disease (atrial fibrillation) and possible hypoxia but a contributory role of BTDS cannot be completely excluded.

Subject 0061 (Study BUP3002S)
Subject 0061 was a 77 year-old white female with arthritis and pain in the neck, upper back and left hand who entered the extension study on (b) (6) At the beginning of the core study (BUP3002), the subject's ongoing medical conditions included: shortness of breath on exertion; hypertension; urinary incontinence; chronic dehydration; Parkinson's Disease; migraine headaches; depression and psychosis with hallucinations and Lewy Body Disease. Additional surgical history included tonsillectomy; hysterectomy; mastectomy and resection of a mass in her neck. The subject was randomized to BTDS in the core study on (b) (6) and completed the core study on BTDS 10 on (b) (6) . The subject began the extension phase treatment with BTDS 5 on (b) (6) (Day 0), increasing to BTDS 10 on (b) (6) and was then increased to BTDS 20 on (b) (6). On (b) (6) (Day 139 of the extension), after 191 days of cumulative exposure to BTDS, the subject had the following serious adverse event: cardiac-respiratory arrest which lead to her death that day and was considered by the investigator to be not related to study drug.

Impression
From the available information it is not clear whether the presumed cardiac-respiratory arrest was related to BTDS. Given the event occurred after 191 days of cumulative exposure to BTDS and approximately 3 months after the last dose titration, BTDS appears to be an unlikely factor in her cardiac arrest but cannot be completely excluded.

Subject 20304 (Study BP96-0103) also Subject 20209 (Study BP96-0102)
Patient summary obtained from Dr. Del Pan's review:

Patient 20304, a 76-year-old woman in open-label study BP96-0103, had originally participated in Study BP96-0102, a forced-titration study in patients with chronic back pain. Her patient number in Study BP96-0102 was 20209. Her medical history was notable for cardiovascular disease (hypertension, angina, carotid artery disease, water retention, and a balloon angioplasty about four or five years prior to study entry). She also had gastroesophageal reflux disease and chronic depression. Concomitant medications included naproxen (Naprosyn®), azathioprine (Imuran®), furosemide (Lasix®), prednisone, folic

acid, calcium carbonate (Tums®), metoprolol/hydrochlorothiazide (Lopressor HCT®), nifedipine (Procardia XL®), ticlopidine (Ticlid®), diazepam (Valium®), lansoprazole (Prevacid®), and propoxyphene apsylate/acetaminophen (Darvocet®) prn. In BP96-0102, the patient had been randomized to BTDS, which she received for 58 days (BTDS 20 for the last 44 days). In Study BP96-0103, she experienced intermittent drowsiness, intermittent dry mouth, intermittent itchiness, and an episode of fatigue, all of which were rated as severe. Intermittent upset stomach and an episode of itching were each rated as mild. One episode of an adverse event described as "weak" was rated as moderate. No serious adverse events were reported for her during Study BP96-0102. She completed this study on Day 58, at which time the BTDS 20 patch was removed. That same day, she entered into Study BP96-0103 (Study Day 0), and was started on a BTDS 5 patch. The dose was increased to BTDS 10 on Day 4, but was then decreased back to BTDS 5 on Day 65, because she reported that she did not think she needed the higher dose. She remained on BTDS 5 through Day 525. No adverse events were reported for the first 12 months of the open-label study. On Day 481, she fell at home and was hospitalized with shortness of breath and a lumbar fracture. She was taken to an emergency room that day, and was admitted to the hospital the next day. On Day 524 (day 42 of the hospitalization), she had a deterioration in her clinical course. An ECG showed atrial fibrillation and rapid ventricular response, and an anteroseptal and inferior wall infarct. Chest X-ray showed cardiac enlargement, pulmonary edema, and bilateral infarcts. She was managed with "cardiopulmonary assist". She was weaned from bypass, but then developed a myopathy and required re-intubation. The BTDS 5 patch was removed on Study Day 525, with no change in her clinical status. She was extubated, but could not maintain ventilation. She died on Study Day 529. The investigator judged that this death was not related to study drug.

Dr Del Pan's Impression: Review of the above narrative suggests that cardiopulmonary disease was the cause of the patient's death, though the reason for the in-hospital deterioration is not clear. In addition, the reason for the fall, which prompted the hospitalization, is not clear. While the buprenorphine in the BTDS patch could have contributed to her ventilatory insufficiency, it is certainly possible that her cardiopulmonary disease was extensive, and that it would have resulted in death regardless of the presence of an opiate. There are no details of her hepatic or renal function during her terminal acute illness. If she had concomitant extensive hepatic insufficiency, it is possible that buprenorphine levels would have been higher than during the period prior to her acute illness. Higher buprenorphine levels may have contributed to her inability to maintain ventilation.

Impression
There are insufficient details to determine the exact sequence of events leading to her death but it appears unlikely that this subject's respiratory failure and acute myocardial infarction occurring after being on BTDS 5 patch for over one year was related to study drug. She had a history of cardiovascular disease and her decline appeared to be initially related to an acute myocardial infarction and respiratory failure.

Subject 040 (Study BUP3201)
This 76 year old woman with hip pain due to osteoarthritis completed the core study and entered the extension study on (b) (6). Her medical conditions included osteoarthritis of both knees, status post left knee replacement 1992, left hip replacement 1992, acid reflux and upper respiratory infection 2001. The subject began taking prednisone 20 mg for inflammation. She developed failure to thrive and congestive heart failure that led to her death.

The subject began the open-label run-in phase on (b) (6) with BTDS 5, increasing to BTDS 10 on (b) (6), and to BTDS 20 on (b) (6). The subject was randomized to placebo in the double-blind phase on (b) (6), and discontinued the double-blind phase due to ineffective treatment. The subject's final study visit was on (b) (6) The subject began the extension phase treatment with BTDS 5 on (b) (6) (Day 0), increasing to BTDS 10 on (b) (6) (Day 3) and to BTDS 20 on (b) (6) (Day 6).

On (b) (4) (Day 39), the subject was hospitalized due to acute congestive heart failure. The BTDS patch was removed on (b) (4) due to congestive heart failure and failure to thrive. On (b) (4) (Day 54), after 11 days without study drug, the subject died due to failure to thrive. The subject's total exposure to BTDS was 54 days.

Impression
It is unclear form the records the basis for making the diagnosis of "failure to thrive." However, it does not appear likely that BTDS contributed to her congestive heart failure or failure to thrive that eventually led to her death.

Subject 05043 (Study BUP3015)
Subject 05043 was a 25 year old woman, with low back pain due to intervertebral disc disease. The subject's past medical and surgical history included: intervertebral disc disease, anxiety, headaches, and insomnia. The subject reported no medical history of substance or alcohol abuse.
The subject was taking the following medications: alprazolam (Xanax), and zolpidem tartrate (Ambien). On (b) (6), the subject began the opioid taper and began discontinuation of hydrocodone and acetaminophen.

On [redacted], the subject began run-in treatment with open-label BTDS 10. On [redacted] the subject died due to cocaine toxicity, arrhythmia, and drowning. Autopsy performed on [redacted] indicated that the subject died as a result of drowning associated with the toxic effect of cocaine. However, the applicant notes that it is likely that she suffered an arrhythmia associated with the use of cocaine and subsequently became submerged and drowned in the water. Multiple track marks were seen on the subject's arms. The subject was noted to have detectable levels of cocaine, butalbital (0.6 mcg/ml) and caffeine in her system. The investigator noted that subject had not reported history of illicit drug use at time of screening and did not exhibit any indication of abuse during the study.

Impression
There is insufficient information to determine the exact cause of her drowning. Cocaine toxicity may have resulted in her death but BTDS cannot be excluded as a contributing factor.

Subject 9019 (Study BUP3018)
Subject 9019 was a 64 year old man with right knee pain due to osteoarthritis, enrolled in BUP3018. The subject's past medical and surgical history included: renal stones, obesity and left knee osteoarthritis. On [redacted], the subject entered the open-label run-in period, and began taking sponsor-provided ibuprofen. On [redacted], the subject was randomized to BTDS 20 and on [redacted], the subject was discontinued from acetaminophen/hydrocodone. On [redacted], BTDS 20 was stopped due to shakiness, but with no improvement of symptoms. On [redacted], the subject discontinued from the study and was examined by a neurologist. On [redacted], the subject was admitted to the hospital with approximately a one month course of progressive confusion, somnolence, tremor, myoclonus, dysarthria and oral-facial dyskinesia. Brain MRI with and without contrast revealed increased T2 signal intensity and diffusion signal intensity in lentiform nuclei bilaterally. EEG revealed diffuse abnormality. On [redacted], brain biopsy revealed CJD spongiform changes. On [redacted], the subject became unresponsive. On [redacted] the subject died. Final diagnosis by brain biopsy of Creutzfeld-Jakob disease was reported. Hospital consult notes indicated that although the introduction of the acetaminophen/ hydrocodone and BTDS was coincident with subject symptoms, withdrawal of the medications did not improve these symptoms; the medications may have unmasked an underlying neurodegenerative condition. No autopsy was performed.

Impression
The cause of death in this individual, Creutzfeldt-Jakob disease, is unrelated to use of BTDS.

Subject 3016 (Study BP98-1201) (Hydrocodone/APAP)
Patient 3016 a 74 year old, white male, with low back pain due to lumbar spondylosis was enrolled in the comparator arm of Study BP98-1201. The patient's past medical and surgical history included: duodenal ulcer, hypertension, osteoarthritis, pedal edema, NSAID gastropathy, restless leg syndrome, and congestive heart failure. The patient was taking the following medications from the onset of study to onset of event: furosemide, omeprazole, pilocarpine, ketorolac, potassium, nifedipine, carbamazepine, timolol, trazodone, pramipexole, hydrochlorothiazide, and lisinopril. The patient began treatment on (b) (6) with hydrocodone/APAP. On (b) (6), the patient was reported to have a dry mouth, and drowsiness, which were considered by the investigator to be mild, and possibly related to study drug. On (b) (6), the patient was reported to have ataxia, which was considered by the investigator to be moderate, and not related to study drug. On (b) (6) the patient discontinued hydrocodone/APAP due to ineffective treatment. That same day, the ataxia resolved, and the patient was reported to have a low potassium level of 3.3, which was considered by the investigator to be possibly due to the diuretic. On (b) (6), the dry mouth and drowsiness resolved. On (b) (6), the patient reportedly had a myocardial infarction. On (b) (6), after 22 days exposure to hydrocodone/APAP and after 36 days of stopping study drug, the patient was reported to have died due to strangulated hernia, stroke, kidney failure, and heart attack.

Impression
This subject's myocardial infraction does not appear related to hydrocodone/APAP which was discontinued approximately one month earlier. The other adverse events of strangulated hernia, stroke and kidney failure eventually leading to death also do not appear to be related to hydrocodone/APAP.

Subject 0011 (Study BUP 3002) (Placebo)
Subject 0011, a 78 year old white male with CAD, CHF, pneumonia, and history of MRSA, enrolled in study BUP3002 for his chronic low back pain. He was randomized to placebo on (b) (6) Lethargy developed on (b) (6), and placebo was discontinued. On (b) (6) the subject developed sepsis and pneumonia, considered severe but unrelated to placebo, and died 2 days later.

Impression
This subject on placebo died from pneumonia and sepsis unrelated to study drug.

Subject 1139 (Study BP96-0101)
Died during screening prior to initiation of study drug
Subject 1139, a 71 year old white male, died in (b) (6), during the screening period of study BP96-0101, prior to initiation of study drug.

Cause of Death			
	BTDS N=7191*	**PBO N=1085**	**HC/APAP N=130**
Number of Deaths	15 (.21%)	1 (.09%)	1 (.77%)
Acute MI**	3 (2 possibly, 1 unlikely)		1 (unrelated)
Acute Cardiac Death/ Cardiac Arrest**	4 (3 possibly, 1 unlikely)		
CHF	2 (1 unlikely, 1 unrelated)		
Bradycardia	1 (unrelated)		
Stroke	2 (unrelated)		
Pulmonary Embolism	1 (unrelated)		
CocaineToxicity/Drowning	1 (possible)		
Creutzfeldt-Jacob Disease	1 (unrelated)		
Pneumonia		1 (unrelated)	

* Includes ongoing study BUP3025
** Subject 20304 included under acute MI and Subject 0079 included under cardiac arrest also had respiratory failure.

Summary of Deaths
The deaths of all subjects on BTDS were reviewed with special attention to potential cardiac related events. For many deaths there was insufficient information to determine an exact etiology. For cardiac deaths there were underlying medical problems which could explain the death but BTDS-treatment could not be conclusively excluded as a cause of death in some subjects. Dr. Monica Friszman from the Division of Cardio-Renal Drug Products reviewed some of the more concerning cardiac deaths. Her review has not yet been finalized but her preliminary conclusions are that there is no clear cardiac signal. The non-cardiac deaths were unrelated to BTDs with the possible exception of drowning in a subject abusing cocaine.

7.3.2 Nonfatal Serious Adverse Events

In the BTDS development program 210 of 6042 BTDS-treated subjects (3.5%) experienced a total of 384 nonfatal SAEs (Table 7.3.2.1). Four of these subjects also had fatal SAEs and are discussed in the section on deaths. Table 7.3.2.3 presents the number of subjects in all studies with nonfatal serious adverse events by preferred term that occurred in at least two subjects.

Table 7.3.2.1: Number (%) of BTDS-Treated Subjects with ≥1 Nonfatal Serious Adverse Events in All Studies – Groups C, B, and D

Analysis group	Number of BTDS-treated subjects	Number (%) of BTDS-treated subjects with ≥1 nonfatal serious adverse events	Number of nonfatal serious adverse events [a]
C (chronic pain studies)	5415	204 (3.8)	374
B (nonchronic pain studies)	107	5 (4.7)	9
D (clinical pharmacology studies)	520	1 (0.2)	1
Total (Groups C, B, and D)	6042	210 (3.5)	384

Reference: Table 43. Number (%) of BTDS-Treated Subjects with ≥1 Nonfatal Serious Adverse Events in All Studies – Groups C, B, and D, page 154 of ISS

Table 7.3.2.2: Number (%) of Subjects with Nonfatal Serious Adverse Events, by System Organ Class and by Preferred Term, that Occurred in ≥2 Subjects Across All Studies - Groups C, B and D (page 1 of 2)

MedDRA SOC/ preferred term [a]	Number (%) of BTDS-treated subjects N=6042 [b]
All SOCs/all preferred terms	**210 (3.5)**
Cardiac disorders	**31 (0.5)**
Myocardial infarction	5 (0.1)
Cardiac failure congestive	4 (0.1)
Acute coronary syndrome	3 (<0.1)
Acute myocardial infarction	3 (<0.1)
Angina pectoris	3 (<0.1)
Angina unstable	3 (<0.1)
Bradycardia	2 (<0.1)
Coronary artery disease	2 (<0.1)
Supraventricular tachycardia	2 (<0.1)
Gastrointestinal disorder	**33 (0.5)**
Vomiting	7 (0.1)
Abdominal pain	5 (0.1)
Nausea	5 (0.1)
Gastrointestinal haemorrhage	3 (<0.1)
Pancreatitis	3 (<0.1)
Abdominal pain upper	2 (<0.1)
Diarrhoea	2 (<0.1)
General disorders and administration site conditions	**27 (0.4)**
Chest pain	21 (0.3)
Chest discomfort	3 (<0.1)
Pain	2 (<0.1)
Hepatobiliary disorders	**12 (0.2)**
Cholecystitis	4 (0.1)
Cholecystitis acute	3 (<0.1)
Cholelithiasis	3 (<0.1)
Infections and infestations	**34 (0.6)**
Pneumonia	6 (0.1)
Cellulitis	5 (0.1)
Gastroenteritis	4 (0.1)
Lobar pneumonia	2 (<0.1)
Osteomyelitis	2 (<0.1)
Sepsis	2 (<0.1)
Urinary tract infection	2 (<0.1)
Injury, poisoning and procedural complications	**23 (0.4)**
Fall	6 (0.1)
Hip fracture	5 (0.1)
Road traffic accident	2 (<0.1)

Table 7.3.2.2: Number (%) of Subjects with Nonfatal Serious Adverse Events, by System Organ Class and by Preferred Term, that Occurred in ≥2 Subjects Across All Studies - Groups C, B and D (page 2 of 2)

MedDRA SOC/ preferred term [a]	Number (%) of BTDS-treated subjects N=6042 [b]
Investigations	**4 (0.1)**
Blood pressure increased	2 (<0.1)
Metabolism and nutrition disorders	**12 (0.2)**
Dehydration	9 (0.1)
Musculoskeletal and connective tissue disorders	**23 (0.4)**
Osteoarthritis	6 (0.1)
Intervertebral disc protrusion	3 (<0.1)
Back pain	2 (<0.1)
Lumbar spinal stenosis	2 (<0.1)
Pain in extremity	2 (<0.1)
Nervous system disorders	**28 (0.5)**
Transient ischaemic attack	5 (0.1)
Cerebrovascular accident	4 (0.1)
Convulsion	3 (<0.1)
Syncope	3 (<0.1)
Dizziness	2 (<0.1)
Headache	2 (<0.1)
Subarachnoid haemorrhage	2 (<0.1)
Psychiatric disorders	**9 (0.1)**
Depression	2 (<0.1)
Major depression	2 (<0.1)
Renal and urinary disorders	**6 (0.1)**
Nephrolithiasis	2 (<0.1)
Respiratory, thoracic and mediastinal disorders	**25 (0.4)**
Dyspnoea	7 (0.1)
Chronic obstructive pulmonary disease	5 (0.1)
Pulmonary embolism	4 (0.1)
Asthma	2 (<0.1)
Pleural effusion	2 (<0.1)
Skin and subcutaneous tissue disorders	**8 (0.1)**
Hyperhidrosis	3 (<0.1)
Rash generalized	2 (<0.1)
Social circumstances	**3 (<0.1)**
Drug abuser	3 (<0.1)
Surgical and medical procedures	**4 (0.1)**
Knee arthroplasty	3 (<0.1)
Vascular disorders	**9 (0.1)**
Deep vein thrombosis	2 (<0.1)
Hypertension	2 (<0.1)

(Reference: Appendix 11, Tables 4.5.4.1.2, 4.5.4.2, 4.5.4.3).
[a] Treatment-emergent adverse events are presented alphabetically by SOC and by descending frequency within each SOC .
[b] A subject may have ≥1 SAE.

Reference: Table 44 from ISS, pages 154-155

Table 7.3.2.3 presents the number of BTDS-treated subjects in all studies with nonfatal SAEs that occurred in four or more subjects. The incidence of the more frequent SAEs appears consistent with subjects on opioids and the study population (elderly chronic pain population with multiple comorbidities) except for the apparently high number of subjects with chest pain.

Table 7.3.2.3: Nonfatal Serious Adverse Events by Preferred Term which Occurred in ≥4 BTDS-treated Subjects in All Studies – Groups C, B and D

Preferred Term	Number (%) of BTDS-treated subjects with nonfatal serious adverse events N=6042	Number of nonfatal serious adverse events in BTDS-treated subjects
All Preferred Terms	**210 (3.5)**	**384**
Chest pain	21 (0.3)	21
Dehydration	9 (0.1)	9
Vomiting	7 (0.1)	10
Dyspnoea	7 (0.1)	7
Fall	6 (0.1)	6
Osteoarthritis	6 (0.1)	6
Pneumonia	6 (0.1)	6
Abdominal pain	5 (0.1)	5
Cellulitis	5 (0.1)	5
Chronic obstructive pulmonary disease	5 (0.1)	7
Hip fracture	5 (0.1)	5
Myocardial infarction	5 (0.1)	5
Nausea	5 (0.1)	7
Transient ischaemic attack	5 (0.1)	5
Cardiac failure congestive	4 (0.1)	4
Cerebrovascular accident	4 (0.1)	4
Cholecystitis	4 (0.1)	5
Gastroenteritis	4 (0.1)	4
Pulmonary embolism	4 (0.1)	4

Reference: Table 45. Non Nonfatal Serious Adverse Events which Occurred in ≥4 BTDS-treated Subjects in All Studies – Groups C, B and D, page 157 of ISS

Table 7.3.2.4 presents the number of subjects with nonfatal serious adverse events by system organ class and by preferred term occurring in at least two or more subjects in the double-blind period of controlled chronic pain studies (Group A).

Table 7.3.2.4: Number (%) of Subjects with Nonfatal Serious Adverse Events by System Organ Class and by Preferred Term in ≥ 2 Subjects in the Double-Blind Period of Controlled, Chronic Pain Studies (Group A)

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.

The incidence of cardiac SAEs was similar in the BTDS and placebo groups in the controlled studies. The number of SAEs by preferred term in the BTDS group with an incidence of two or more subjects greater than in the placebo group were the following: pancreatitis, cellulits, gastroenteritis, fall, transient

ischemic attack, nephroliathiasis, COPD, and drug abuser. There is some evidence that opioids may induce pancreatitis and therefore the SAEs involving pancreatitis were reviewed. Given the concern of opioid abuse, the drug abuse SAEs were also reviewed. It is well known that opioids can cause drowsiness and result in falls and therefore SAEs related to falls were not reviewed. Given the experience with other opioids and different formulations of buprenorphine, there is no reason to suspect that the other SAEs listed above were related to BTDS and therefore these SAEs were not reviewed. Below is a review of SAE of special interest.

Individual Serious Adverse Event Summaries

Pancreatitis
To identify all SAEs involving pancreatitis the dataset was searched with the terms "pancreatitis and acute pancreatitis" for the Dictionary-Derived Term (variable AEDECOD). Four cases of pancreatitis with subjects on BTDS were identified and are reviewed below.

Subject 14008 (Study BUP3015)
This was a 47 year old man with low back pain and a history of perforated diverticulitis and sigmoid resection who developed pancreatitis 27 days after starting BTDS 5. He was on no medications prior to the study and there was no history of alcohol or drug abuse. He was admitted to the hospital with abdominal pain associated with nausea and diarrhea. WBC count was 7500, amylase 207 and lipase 130. Amylase decreased to 187 the following day and the reported event of pancreatitis was considered resolved. BTDS was discontinued and the event was considered possibly related by the investigator. His abdominal pain resolved within one week of hospital admission.

Impression
This subject developed pancreatitis possibly related to BTDS.

Subject 57002 (Study BUP3015)
This was a 55 year old man with a history of diabetes and hyperlipidemia who was diagnosed with abdominal pain and pancreatitis 28 days after exposure to BTDS 5. The subject was hospitalized with abdominal pain and laboratory test results included amylase 119, lipase 134, lactic acid 2.1, and WBC 11.1. An ultrasound of the gallbladder was unremarkable. The SAE resolved in two days and was considered possibly related to study drug. The subject was readmitted to the hospital the following day for gastroenteritis which lasted 8 days.

Impression
This subject was coded for pancreatitis but also diagnosed with gastroenteritis. It is unclear whether he had mild pancreatitis which resolved in a couple of days.

Subject 1301 (Study BUP3015) also Subject 1003 (Study BP96-0101)
This was a 49 year old woman with a history of pancreatitis and pancreatic stent placement, hypercalcemia, and hyperparathyroidism who developed acute pancreatitis approximately 35 days after initiation of treatment with BTDS. She was previously enrolled in BP96-0101 (Patient 1003), randomized to BTDS 10. The patient experienced no serious adverse events in this study. On 21-Mar-1997, she began treatment with open-label BTDS 5, increased to BTDS 10 and on 04-Apr-1997 increased to BTDS 20. On 25-Apr-1997, she developed acute pancreatitis. Her amylase was greater than 400. She was temporarily discontinued from BTDS but reapplied it on her own. On 10-May-1997 her pancreatitis was considered resolved. The BTDS was discontinued due to a rash on 10-Nov-1997.

Impression
It is difficult to assess the cause of this subject's pancreatitis due to her prior history of pancreatitis. BTDS cannot be excluded as a contributing factor.

Subject 4316 (BP96-0103) also Subject 4014 (BP96-0101)
This was a 53 year old woman with rheumatoid arthritis, osteoarthritis, cervical spondylosis and lumbar spondylosis previously enrolled in BP96-0101, randomized to Oxy/APAP. The patient experienced no serious adverse events in this study. Her past medical history was significant for diabetes, hypertension, thyroid problems, gastric bypass surgery and cholecystectomy. On 11-Jul-1997 she began treatment with open-label BTDS 5, increased to BTDS 10 on 25-Jul-1997 and then increased to BTDS 20 on 8-Aug-1997. On (b) (6), the study drug was interrupted due to hospitalization for symptoms of abdominal pain, chills, fever, nausea and vomiting. During her hospitalization she was diagnosed with pneumonia, small bowel obstruction and GI bleed. Approximately 11 days after being hospitalized she was diagnosed with chemical pancreatitis which was considered by the investigator not related to study drug. On (b) (6), she was discharged. She restarted BTDS and on 09-Mar-1999, the patient completed the study. At the time of study completion, the chemical pancreatitis was reported as ongoing.

Impression
This subject's pancreatitis does not appear to be related to BTDS.

<u>Summary of Pancreatitis Cases</u>
Due to confounding medical comorbidities in the four cases of pancreatitis, no definite conclusions can be made regarding the role of BTDS in the individual cases. It is known that opioids can increase sphincter of Oddi pressure which has been implicated as a cause of pancreatitis. Given a theoretical basis for opioids causing pancreatitis and the increased incidence of pancreatitis observed

in BTDS-treated subjects compared to placebo it appears reasonable to conclude that there may be an association between BTDS and pancreatitis. The proposed label provides the standard opioid warning about pancreatitis:

> Buprenorphine may cause spasm of the sphincter of Oddi. Use with caution in patients with biliary tract disease, including acute pancreatitis. Opioids may cause increases in the serum amylase.

This warning appears adequate to address the findings of pancreatitis observed in the BTDS development program.

Drug Abuse
Three subjects with SAEs related to drug abuse were identified:

Subject 36020 (BUP3015)
The subject was a 47 year old man with low back pain who completed the double-blind period of BUP3015 and began treatment in the extension phase eventually being titrated to BTDS 20. During the extension phase he developed erythema multiforme requiring hospitalization (described in section on SAEs of the skin). During the hospitalization he tested positive for cocaine metabolites and admitted to occasional use of cocaine. He was discontinued from study drug due to cocaine abuse. The erythemal multiforme was probably unrelated to BTDS. The rash developed approximately five days after starting ciprofloxacin.

Impression
This subject was discovered to be using cocaine following an admission to the hospital for a rash. His cocaine use was unrelated to BTDS-treatment.

Subject 71003 (BUP3019)
The subject was a 50 year old man with left knee pain due to osteoarthritis enrolled in BUP3019. At the time of screening he was taking oxycodone/acetaminophen (Percocet) and oxycodone (OxyContin) but provided no history of substance abuse or alcohol abuse. The subject was randomized to BTDS 20 and provided oxycodone for use as supplemental analgesia. The subject missed his appointment because he had been in a car accident. He returned two empty bottles of oxycodone and no transdermal systems were returned. He failed to complete his study rescue medication use diary. The subject was reported to experience anxiety at the visit and left abruptly when questioned. The subject was therefore removed from the study for suspected abuse of oxycodone. On a follow-up questionnaire the subject admitted to receiving a prescription fo oxycodone (OxyContin) 20 mg BID for pain from the emergency room after his car accident.

Impression
This subject on BTDS 20 was also taking additional oxycodone not provided by the study.

Subject 10019 (BUP3024)
The subject was a 45 year old man with a history of chronic low back pain enrolled in study BUP3024. During his screening evaluation he denied any past history of abuse. The subject was randomized to BTDS 20 and provided oxycodone for use during week 1 as sponsor provided supplemental analgesic medication. The subject took three capsules of oxycodone on several days instead of the protocol specified maximum of two capsules per day. On his visit he was unable to account for three capsules of oxycodone and was discontinued from BTDS 20 due to suspected oxycodone abuse. The investigator reported the subject was not seen with any signs or symptoms of excessive drug effect.

Impression
This subject was using more oxycodone than allowed by the protocol.

Summary of Drug Abuse SAEs
There were two cases of subjects taking additional opioid beyond the protocol specified allowed amount and one case of concomitant use of cocaine with BTDS. The abuse of opioids is well known and not unexpected.

Drug Withdrawal
There was one nonfatal SAE of drug withdrawal symptoms (Subject 75019) reviewed below.

Subject 75019 (BUP3019)
The subject was a 75 year old woman with osteoarthritis of the left knee enrolled in BUP3019. The subject completed the double-blind phase of the study and began treatment in the extension phase. She was started on BTDS 5 and increased to BTDS 10 and then to BTDS 20. The subject was discontinued from the study due to the sponsor's decision to discontinue the study due to non-safety related considerations. Nine days after discontinuation of BTDS 20 and after approximately 5 months of exposure to BTDS she was hospitalized complaining of withdrawal symptoms. She had not restarted analgesic treatment since study drug was discontinued. She was discharged from the hospital with the diagnosis of depression with probable component of narcotic withdrawal.

Summary of Drug Withdrawal SAE
This subject was hospitalized for withdrawal symptoms nine days after discontinuing treatment with BTDS 20 following a 5-month exposure. The label adequately addresses the issue of potential withdrawal with the following instructions:

When the patient no longer requires therapy with BuTrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

Respiratory Failure
There were three nonfatal SAEs and two deaths coded as respiratory failure. There was also one adverse event coded as respiratory depression reviewed below do to the seriousness of the case.

Subject 0088 (BP96-0104)
This was an 84 year old woman entered into BP96-0104 after undergoing right hip open reduction and internal fixation surgery on (b) (6). The patient's past medical history was significant for diabetes, chronic anemia, CVA, arteriosclerotic heart disease and rales right lung base. The day after surgery she started treatment with BTDS 5. The day after starting BTDS-treatment she experienced diaphoresis, shortness of breath, wheezing and respiratory failure after a blood transfusion. The patient was treated with Bumex. The same day the subject developed changes consistent with a myocardial infarction.

Impression
This subject's respiratory failure appears to be related to a postoperative blood transfusion that resulted in pulmonary edema. There is no evidence that BTDS contributed to her respiratory failure.

Subject 51012 (BUP3015) This subject was a 68-year-old woman who enrolled in study BUP3015 for osteoarthritic back pain. At screening she reported no history of substance or alcohol abuse. Her medications included: tramadol/acetaminophen (Ultracet), hydrocodone/acetaminophen (Lortab), clorazepate, and amitriptyline (Elavil). The subject successfully completed the opioid taper and run-in period on BTDS 20. Three days after randomization to treatment with BTDS 5, the subject presented to an emergency room with depressed respiration, which was considered by the investigator to be a serious adverse event and definitely related to study drug. The study drug was discontinued due to the depressed respiration. A drug panel, performed in the emergency room was positive for benzodiazepines, amphetamines, and barbiturates. The emergency records are difficult to read but no pulse ox reading was lower than 97% or respiratory rate less than 14. The investigator indicated that the subject had possibly abused study drug based on the report of the subject's daughter that the subject had a heating pad in bed, and the investigator suspected that the subject had been applying a heating pad to the patch. The impression of the emergency room physician was sedation due to pain medication. The subject was treated in the emergency room with oxygen.

Several months after the event, the investigator noted that the subject had been admitted to a rehabilitation center a little over one year prior to enrollment into the study. Had this information been available at screening the subject would not have been eligible for enrollment.

Impression
This subject with reported respiratory depression did not appear to have a life threatening condition based on the respiratory rate and pulse ox recorded in the emergency room. Furthermore it is unclear to what extent the use of BTDS resulted in her symptoms since she also tested positive for benzodiazepines, amphetamines and barbiturates. Even if BTDS contributed to her respiratory depression her possible use of a heating pad makes it impossible to draw any safety conclusions with respect to the recommended use of BTDS. The proposed label adequately addresses the issue of use of heat over the patch and use of concomitant CNS depressants that may depress respirations.

Subject 20304 (BP96-0103) also Subject 20209 (BP96-0102)
This case is reviewed in the section on deaths.
Impression
It appears unlikely that this subject's respiratory failure occurring after being on BTDS 5 patch for over one year was related to BTDS. She had a history of cardiovascular disease and her decline appeared to be initially related to an acute myocardial infarction but a contributory role of BTDS in her respiratory failure cannot be completely excluded.

Subject 0079 (Study BP96-0104)
This death in a postoperative 90 year old woman is reviewed in detail in the section on deaths.

Impression
I concur with Dr. Del Pan's assessment that it is unclear from the sequence of events whether BTDS may have played a role in the respiratory decompensation. I also note Dr. Del Pan's concern about life threatening serious adverse events of apnea in two other post-operative patients. Use of long-acting opioids is not consistent with the current standard of care for acute post-operative pain management. Since the applicant is not seeking a postoperative pain indication for BTDS this would mitigate any concern about the potential role BTDS played in postoperative respiratory decompensation. This subject's ventricular tachycardia and cardiac arrest may have been related to her pre-existing cardiovascular disease (atrial fibrillation) and possible hypoxia but a contributory role of BTDS cannot be completely excluded.

Subject 0034 (Study BUP3002S)
This was a 78 year old man with a history of COPD, asthma, rheumatoid arthritis and low back pain randomized to placebo in the core study. He was enrolled in the open-label extension study and began treatment with BTDS 5 on 06-Apr-2001. His dose was increased to BTDS 20 on 13-Apr-2001. The subject developed pneumonia and respiratory distress after 144 days of exposure to BTDS that led to hospitalization and study drug discontinuation.

Impression
This subject with a history of respiratory disease developed respiratory distress and pneumonia after treatment with BTDS for 144 days. It appears unlikely that the respiratory distress was related to the BTDS.

Subject 0001 (BP96-0304)
This was a 40 year old healthy male volunteer who enrolled in a randomized, three-way crossover, single dose bioequivalence and dose proportionality study. The subject began treatment on 10-Sep-1996 with BTDS 10. Over the next eight days, the subject experienced nausea, emesis, urinary hesitancy, pruritus at patch site and headache. Following a washout period of approximately 10 days, the subject received BTDS 5 (x2) on 24-Sep-1996. Over the next three days, the subject experienced headache, nausea, and emesis, dizziness, and pallor. The nausea and emesis were treated on 25-Sep-1996 with Phenergan (promethazine) 25 mg IM and Reglan (metoclopramide) 5 mg IM. All events resolved within four days of onset. The BTDS 5 (x2) were removed on 27-Sep-1996.

On 08-Oct-1996, after a washout period of approximately 10 days, the subject received BTDS 20. Over the next two days, the subject experienced emesis, nausea, headache, and respiratory depression. The test medication was interrupted on 08-Oct-1996 at 20:45. The buprenorphine patch was removed 10/9/96 at 12:30. The nausea was treated on 09-Oct-1996 with Phenergan (promethazine) 12.5 mg IV. The subject was placed on a datascope monitor with continuous pulse oximetry. On 09-Oct-1996, the subject experienced intermittent events of respiratory depression. Respiratory rate was recorded as low as 3 breaths per minute with a corresponding pulse oximetry of 86%. The subject recovered from the respiratory depression on 09-Oct-1996 at 17:11 and all other events resolved within one day of onset.

Impression
This subject was not coded as a SAE but is included in this section based on the severity of the event which could have resulted in respiratory arrest and death in an unmonitored subject. The subject received promethazine 12.5 mg IV which may have contributed to the respiratory depression but when previously administered promethazine on a lower dose of BTDS no respiratory depression

was reported. The analysis of PK data for this subject did not reveal any unusually high exposure which might suggest patch failure. The respiratory depression in this subject highlights both the importance of initiating BTDS therapy with a low dose in opioid naïve subjects and avoiding concomitant use of drugs which result in respiratory depression.

Summary of Respiratory Depression
There were three nonfatal SAEs and two deaths coded as respiratory depression in the ISS database. One of the SAEs was likely due to pneumonia and another was due to pulmonary edema. The third nonfatal SAE of respiratory depression may have been related to the use of a heating pad and concomitant CNS depressants. There were confounding medical issues in the two deaths making it impossible to determine the role of BTDS but there is no convincing evidence that BTDS played a contributory role. The one adverse event of respiratory depression not considered an SAE was of concern due to the severity of the respiratory depression. This event occurred in an opioid naïve subject treated with BTDS 20 who also received promethazine for nausea. The proposed label adequately addresses the respiratory issues discussed above. There is sufficient warning in the label against using a heating pad and concomitant CNS depressants. Opioid naïve subjects are to start treatment with BTDS 5 and titrate no sooner than every three days.

It is noted that in the review of Dr Del Pan there was concern about respiratory depression in the immediate postoperative period. The additional studies submitted after Dr. Del Pan's review do not study BTDS in the postoperative period and therefore no conclusions regarding the safety of BTDS in postoperative subjects can be made based on this review. Therefore, the recommendation is that postoperative subjects not be treated with BTDS.

Convulsion
Convulsion was reported as a SAE in three subjects.

Subject 22302 (BP96-0103) also Subject 22205 (BP96-0102)
This was a 70 year old man who while enrolled in open-label BP96-0103 experienced adverse events of stroke, syncopal episode (related to ventricular asystole), heart block (ventricular asystole), cardiac arrhythmia and seizure. The patient was previously enrolled in BP96-0102, randomized to BTDS 10. The patient experienced no serious adverse events.

The patient's past medical and surgical history included: coronary artery bypass graft, abdominal aortic aneurysm repair/graft, atherosclerosis, abdominal aortic graft, coronary artery disease, hypertension, constipation, diverticulitis, prostatic hypertrophy, low back pain, hypothyroidism, hypercholesterolemia, blackouts, nocturnal myoclonus, narcolepsy, postherpetic neuralgia, history of depression,

myocardial infarction, syncopal episodes, and history of substance abuse (alcohol). The patient was taking the following medications from onset of study to onset of events: baby aspirin, dicyclomine, chlorzoxazone, isosorbide, clonazepam, lactulose, metoprolol, levothyroxine, nitroglycerin, fluvastatin, and naproxen.

On (b) (6), the patient began treatment with open-label BTDS 5, increased to BTDS 10 on (b) (6). On (b) (6), the study drug was increased to BTDS 20. On (b) (6) the patient began treatment with valproic acid for blackouts that was later discontinued. On (b) (6), the patient experienced a stroke and a seizure, which led to hospitalization and were considered by the investigator not related to study drug. An evaluation on (b) (6) revealed no deficits, and the patient was released. On (b) (6), the patient was treated with heparin for an unknown number of days for possible stroke. On (b) (6), an MRI that was performed revealed an occluded vessel. That same day, the patient was hospitalized and underwent a vertebral arteriogram that showed right vertebral artery stenosis and the left vertebral artery occluded. On (b) (6), the stroke was considered resolved and the patient was discharged from the hospital and re-started treatment with valproic acid. On (b) (6), the valproic acid was discontinued. On (b) (6), the patient experienced a syncopal episode attribute to ventricular asystole which led to hospitalization. The investigator noted that the patient was wearing a heart monitor and experienced a syncopal episode, at the time of heart block. On (b) (6), the subject underwent emergency pacemaker implant. On (b) (6), the heart block and cardiac arrhythmia were considered resolved and the patient was then discharged from the hospital. On (b) (6), the patient completed the study and discontinued study drug.

Impression
This subject apparently experienced a syncopal episode and possible seizure secondary to heart block and ventricular asystole. Given his history of cardiovascular disease and prior syncopal events it is unlikely that BTDS played a contributory role.

Subject 36007 (BUP3012)
Subject 36007 was a 66 year old woman with left knee pain due to osteoarthritis who experienced the serious adverse events of intraventricular hemorrhage and seizure after 123 days on BTDS in the open-label study BUP3012S. During the double-blind study BUP3012 the subject experienced dizziness while on BTDS 20. The study drug was reduced to BTDS 10 and the dizziness resolved. She entered the extension phase on (b) (6). Her dose was increased from BTDS 5 to BTDS 10 on (b) (6). On (b) (6), the subject began experiencing confusion, nausea, and delirium. On (b) (6), her BTDS was discontinued due to confusion, delirium and nausea. On (b) (6) the subject

experienced a syncopal episode that resulted in a fall and right hip fracture. Labs on admission to the hospital were significant for a WBC of 17,000 with 89% segs. She was diagnosed with a left lateral intraventricular cerebral hemorrhage. She also had a seizure.

Impression
This subject's seizure does not appear to be related to BTDS treatment but was probably a result of her intraventricular bleed. However, treatment with BTDS may have contributed to her fall and resultant hip fracture.

Subject 38027 (BUP3015)
Subject 38027 was a 79 year old man with low back pain enrolled the double-blind and extension phase of study BUP3015. His past medical history was significant for hypertension, hypercholesterolemia, coronary artery disease, coronary artery bypass, pacemaker, left ventricular diastolic dysfunction and mild renal insufficiency. On (b) (6), the subject completed the double-blind phase and began treatment in the extension phase with BTDS 5, increased to BTDS 10 on (b) (6), and then increased to BTDS 20 on (b) (6). On (b) (6), the subject began experiencing disorientation and on (b) (6), he began experiencing shaking, confusion, yawning and an episode of incontinence. In the emergency room he was noted to have weakness on the left side and confusion, both of which improved over time. He was hospitalized for a probable seizure disorder which was not considered by the investigator to be related to study drug. ECG showed a paced rhythm without ischemic changes.

Impression
The cause of this subject's possible seizure is unclear but the fact that the seizure occurred over seven months after starting BTDS treatment makes it less likely that BTDS played a contributory role.

Summary of Seizures
There were three SAEs due to seizures. Review of these cases does not reveal a clear relationship to BTDS-treatment. For one subject with a history of cardiovascular disease the seizure appeared to be due to heart block.

Cardiac Disorders
Thirty one of 6042 BTDS-treated subjects (0.5%) across all studies (Groups C, B and D) experienced 42 nonfatal SAE cardiac disorders (Table 7.3.3). Twelve subjects in this group reported 16 SAEs related to cardiac arrhythmias or cardiac arrest. The two cases of SAEs coded as ventricular tachycardia were reviewed under the section on deaths (Subject 0079 and Subject 20304). There was no strong evidence that either case was related to BTDS-treatment and both cases appear unlikely. Subject 20304 developed atrial fibrillation with rapid ventricular response following a myocardial infarction after she had been on BTDS for over

one year. Subject 0079 a 90 year old woman with atrial fibrillation developed ventricular tachycardia and cardiac arrest the day after undergoing a total knee revision and may have had congestive heart failure preceding her cardiac arrest.

Dr. Monica Fiszman, from the Division of Cardio-Renal Products reviewed cases based on the E14ICH recommendation for QT prolongation. She concluded that there was a low incidence rate of AEs and SAEs related to E14 ICH Guidance even at the highest dose tested. Syncope was the AE and SAE with higher rate (0.1-0.3%) that was not necessarily linked to QT prolongation. She also performed an MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration including PR, QRS and QT events and arrhythmias. The cardiologist detected no signals for Torsades and QT prolongation. Table 7.3.2.4 presents the number of subjects with nonfatal serious adverse events by system organ class and by preferred term occurring in at least two or more subjects in the double-blind period of controlled chronic pain studies (Group A). In the controlled studies there does not appear to be an imbalance between placebo and BTDS-treatment in the incidence of cardiac adverse events.

I reviewed the two cases of ventricular tachycardia and determined that they were unrelated to BTDS. I also reviewed the six cases of SAEs involving seizures and syncope.

Table 7.3.2.5: Number (%) of BTDS-Treated Subjects Across all Studies with Nonfatal Serious Adverse Events in the Cardiac Disorders System Organ Class (Groups C, B, and D)

Cardiac disorders SOC/ Preferred Term [a]	Number (%) of BTDS-treated subjects with nonfatal serious adverse events N=6042
All preferred terms	**31 (0.5)**
Myocardial infarction	5 (0.1)
Cardiac failure congestive	4 (0.1)
Acute coronary syndrome	3 (<0.1)
Acute myocardial infarction	3 (<0.1)
Angina pectoris	3 (<0.1)
Angina unstable	3 (<0.1)
Bradycardia	2 (<0.1)
Coronary artery disease	2 (<0.1)
Supraventricular tachycardia	2 (<0.1)
Arrhythmia	1 (<0.1)
Atrial fibrillation	1 (<0.1)
Atrial flutter	1 (<0.1)
Atrioventricular block	1 (<0.1)
Atrioventricular block complete	1 (<0.1)
Bradyarrhythmia	1 (<0.1)
Cardiac arrest	1 (<0.1)
Cardiogenic shock	1 (<0.1)
Mitral valve incompetence	1 (<0.1)
Palpitations	1 (<0.1)
Right atrial dilatation	1 (<0.1)
Tachycardia	1 (<0.1)
Ventricular asystole	1 (<0.1)
Ventricular tachycardia	1 (<0.1)

Reference: Table 47. Number (%) of BTDS-Treated Subjects Across all Studies with Nonfatal Serious Adverse Events in the Cardiac Disorders System Organ Class (Groups C, B, and D), Page 164, ISS

Summary of Cardiac Disorders

Impression

Dr. Monica Fiszman reviewed approximately 25 narratives of cardiac SAEs and reports that no cardiac signal was observed. Her review of the ECG data revealed a slight increase in QTc, more in the BTDS 20 dose but less than 10 msec. There was no evidence of torsades. There did not appear to be an imbalance in cardiac events between BTDS and control groups. Overall there is no convincing evidence that BTDS-treatment resulted in an increased cardiac risk for SAEs.

Syncope

Using the preferred terms "syncope" and "presyncope" four subjects (one in the placebo group and three in the BTDS group) were identified. The case narratives and case report forms for the three BTDS subjects were reviewed.

Subject 29002 (Study BUP3011S)

Subject 29002 was a 70-year-old Caucasian male with right hip pain due to osteoarthritis, enrolled in BUP3011. The subject's past medical and surgical history included: non-insulin dependent diabetes mellitus type II, osteomyelitis cervical spine, hypertension, hyperlipidemia, osteoarthritis, herniated lumbar disc, chronic renal insufficiency, head trauma, sick sinus syndrome, pacer, myocardial infarction and CVA. The subject was taking the following medications at onset of study: naproxen, temazepam, lorazepam, glipizide, hydrochlorothiazide, fosinopril (Monopril), simvastatin and hydromorphone. On (b) (6), the subject entered the opioid taper period and began discontinuation of hydromorphone. On (b) (6) the subject began treatment in the run-in period with open-label BTDS 5, and was provided oxycodone (OxyIR) for use as supplemental analgesia. On (b) (6) study drug was increased to BTDS 10. On (b) (6), the subject was randomized to BTDS 10. On (b) (6), the subject began treatment with rosiglitazone (Avandia). On (b) (6), the subject began experiencing an altered mental status, which was considered possibly related to study drug. On (b) (6), rosiglitazone (Avandia) was discontinued. On (b) (6), the altered mental status was considered resolved. On (b) (6), the subject completed the double-blind phase, and began treatment in the extension phase with open-label BTDS 5. On (b) (6), study drug increased to BTDS 10, and then increased to BTDS 20 on (b) (6). On (b) (6), the subject fell (unspecified etiology). On (b) (6), the subject was brought to the emergency room by his wife after experiencing chest discomfort, confusion, and a near syncope episode. On arrival to the hospital he was noted to have hypoglycemia with blood glucose 48. The subject was treated with D5W and subsequently became more alert and his confusion began to resolve. EKG indicated normal sinus rhythm, inferior wall Q waves compatible with a prior inferior wall MI of indeterminate age.

Impression
The near-syncopal episode in this subject appears related to hypoglycemia and unrelated to BTDS.

Subject 6612 (Study BP960604)
Applicant's narrative for this subject is as follows:

> Patient 6612 was a 61-year-old white female with a history of non–insulin-dependent diabetes mellitus, vasopressor syncope, Lyme disease, migraines, arthritis, and sciatica. She had intervertebral disc disease with nerve as the predominant pain site for about 4 years. On baseline Day 1, (b) (6), she received BTDS at level 1 and was increased to level 3 by Day 25. On Day 3, she developed a mild rash at the system site, which lasted 1 day but was followed on Day 4 by itching at the system site, which continued. A moderate rash at the system site was reported on Day 64. The rash was considered definitely related to study medication. Study medication was discontinued on Day 74. The rash resolved by Day 93. This patient also experienced a serious adverse event, syncope, on Day 50, which required hospitalization. This event was considered possibly related to study medication. The event resolved the same day.

The CRF was reviewed and contained the hospital discharge summary which is summarized below.

She was known to have neurocardiogenic syncope with a positive tilt table test last year. Of note, the tilt table was only positive after 52 minutes of standing. She improved then with beta-blockers. She was taking Inderal 80 mg q.d. She was admitted with syncope and had mild wheezing on admission. Theophylline was added. Discontinuing the opioid patch was discussed with the patient but she did not want to stop the patch since this was the first time she has had complete relief of her pain in many years. She had one episode of blackout while in bed, lying flat, and without any obvious change in her pulse rate. Etiology for this event was unclear.

Impression:
The lack of information makes it impossible to definitively determine the cause of this subject's syncope. She was evaluated by a cardiologist in the hospital but unfortunately there was no mention of ECG findings or vital signs in the discharge summary. Assuming that any significant ECG findings or arrhythmia would have been included in the discharge summary and given her history of prior syncope, it appears unlikely that her syncope was related to an arrhythmia from her BTDS.

Subject 36007 (Study BUP3012S)
This subject was also reviewed under the section SAEs due to seizures. This subject was coded for a "syncopal" event resulting in a fall prior to her "seizure" in the hospital.
The subject was a 66-year-old woman with left knee pain due to osteoarthritis, enrolled in BUP3012S. Her past medical and surgical history included: migraine headaches, endometriosis, hysterectomy, appendectomy, anemia, angina, hypercholesteremia and hypertension. On (b) (6), the subject completed the double-blind Phase in the placebo group and began treatment in the extension Phase with open-label BTDS 5 and increased to BTDS 10 on (b) (6). On (b) (6) the subject began experiencing confusion, nausea, and delirium and BTDS 10 was discontinued on (b) (6) On (b) (6), the subject experienced a syncopal episode that resulted in a fall leading to hospitalization for a right hip fracture.

The patient was diagnosed with an intraventricular cerebral hemorrhage. While in the hospital she had a seizure and required a ventriculoperitoneal shunt for hydrocephalous.

Impression:
There is insufficient information to determine whether this subject's syncopal episode was related to BTDS. She was later diagnosed with an intraventricular cerebral hemorrhage but it is unclear whether this was the cause of her fall.

Summary of Serious Adverse Events due to Syncope
There were three subjects with a syncope in the BTDS group. Syncope was due to hypoglycemia in one subject and unrelated to BTDS. There is insufficient data for the other two subjects to determine a definitive cause for their syncope but a contributory role of BTDS cannot be excluded. Hypotension and possible falls are a known risk of opioids.

Skin and Subcutaneous Serious Adverse Events
Eight subjects (0.1%) of the 6042 BTDS-treated subjects in all studies (Groups C, B and D) developed 10 skin and subcutaneous nonfatal SAEs (Table 7.3.2.6). One subject developed erytherma multiforme unrelated to BTDS. Four subjects developed either a rash or skin ulcers/necrosis. The case narratives of these subjects are reviewed below. BTDS was probably the cause for only one of these subjects who developed a generalized rash requiring hospitalization. BTDS was not the cause for two subjects with ulcers/necrosis and unlikely the cause of one subjects with a rash starting two days on nambutone. The other four subjects were not reviewed since the SAEs were not related to skin.

Subject 1722 (BP98-1201)
This was a 43-year-old, white male, with a past medical history significant for diabetes, leg ulcerations, neuropathy, toe ulceration and right great toe amputation enrolled in Study BP98-1201 with back pain due to intervertebral disc disease. After 4 days of exposure to BTDS, the patient was reported to have necrotic cellulitis of the right foot. The next day the patient was reported to have mild ulcers both upper extremities but not at the patch site, which was considered by the investigator not related to study drug. After 11 days of exposure to BTDS, the patient was discontinued from study drug due to necrotic cellulitis right foot, osteomyelitis right foot, infectious tenosynovitis right foot, and ulcer right toe. He underwent several debridment procedures and eventually an amputation of the second right toe.

Impression
This subject's skin necrosis is consistent with his history of diabetes and prior ulcerations and appears unrelated to treatment with BTDS.

Subject 27005 (BUP3018)
This was a 72 year old man with right hip pain secondary to osteoarthritis, enrolled in BUP3018. On (b) (6) the subject was randomized to BTDS 10. On (b) (6) the subject experienced increased blood pressure and generalized rashes of the chest, arms, and face. The subject immediately removed the BTDS 10 patch, and his high blood pressure (unspecified value) was treated with a hypertensive medication. He apparently was seen in the ER but it is unclear whether he was admitted to the hospital (subject refused to give information regarding his hospitalization). These events were considered by the investigator to be moderate and probably related to study drug. On (b) (6), all these events were resolved. However, that same day, the subject called the site and noted that his skin currently had a dark discoloration that he believed to be a remnant of the rash. On (b) (6), the subject was seen at the site to return study drug and materials, but refused to perform the protocol-specified discontinuation procedures and refused to provide details regarding the hospitalization. The dark discoloration of the skin was considered to be mild in severity and probably related to study drug. The investigator considered the increased blood pressure (no value reported) resolved, rashes resolved but discoloration of his skin was ongoing as of his last visit on 22-Apr-2004 (approximately 20 days after rash appeared).

Impression
This subject's generalized rash involving his chest, arms, and face occurring one day after BTDS 10 application was probably related to study drug. The rashes resolved but there was a residual dark discoloration of the skin at the time of his last visit. This subject was coded for both the SAE rash and rash generalized.

Subject 7015 (BP96-0101) also Subject 07311 (BP96-0103)
This was a 76 year old man with osteoarthritis of the lumbar spine previously enrolled in BP96-0101 as Patient 7015, randomized to placebo. On (b) (6), the patient began treatment with open-label BTDS 5. On 2 (b) (6) open-label study drug was increased to BTDS 10. On that same day, the patient began experiencing a scab on the left upper arm where a patch had been placed and removed, which was considered by the investigator to be mild and not related to study drug. On (b) (6) open-label study drug was increased to BTDS 20. On (b) (6) he began taking Relafen (nabumetone) for pain. On (b) (6) the patient developed a blistering rash on his back which later spread to his legs. He started to have itching and welts on stomach, arms, head, and slightly on his feet. On (b) (6), the patient was weak and could not move and lost balance while using a walker. On (b) (6), the rash was treated with topical betamethasone cream. On this same day he developed a fever (degrees not specified). On (b) (6), the patient was admitted to the hospital for a full body rash, which was considered by the investigator to be severe and possibly related to study drug. Nabumetone was discontinued and the patch was removed and permanently discontinued due to the rash. The patient was treated with diphenhydramine and on (b) (6) he began a tapering dose of prednisone (50 mg to 5 mg over 17 days) and was discharged from the hospital. On (b) (6), the full body rash was assessed as resolved

Impression
This subject developed a severe generalized rash that required treatment with steroids and hospitalization, two days after starting nabumetone. Since the subject was on BTDS for approximately five months prior to the rash developing, it appears more likely that the rash was due to the nabumetone. Of note the patient did develop a scab on the upper arm at the location of where a patch had been applied. There is no further mention of the scab and therefore I assume that it resolved without any sequlae.

Subject 20213 (BP96-0102) also Subject 20306 (BP96-0103)
This 81 year old woman with osteoarthritis was previously enrolled in BP96-0102 as Patient 20213, randomized to Oxy/APAP. The patient experienced no serious adverse events in this study. Her past medical history was significant for coronary bypass, foot surgery, osteomyelitis, non-healing ulcer of the left foot, peripheral vascular disease and diabetes. On 1 (b) (6), the patient began treatment with open-label BTDS 5 and increased to BTDS 10 on (b) (6). On (b) (6), the patient was admitted to the hospital for cellulitis. Her right foot ulcer failed to heal with oral antibiotics and eventually she required a right popliteal to dorsalis pedis artery saphenous bypass graft and revision of left femoral below knee popliteal bypass graft.

Impression
The foot ulcer (cellulitis) in this diabetic patient with peripheral vascular disease does not appear at all related to the use of BTDS.

Subject 36020 (BUP3015S)
This was a 47 year old man with low back pain enrolled in Study BUP3015. He received BTDS during the open-label run-in of this study but was randomized to OxyIR. After completing the randomized phase he began treatment in the extension phase with BTDS 5. After being on BTDS 20 for approximately 4 months he developed fever, chills, and diarrhea treated with ciprofloxacin. Approximately five days after treatment with ciprofloxacin he developed an allergic reaction with swelling in his hands and a pruritic rash occuriring on most of his body. He was hospitalized and a dermatology consult diagnosed the rash as erythemal multiforme.

Impression
This case of erythema multiforme was probably related to ciprofloxacin. He had been on BTDS for over four months prior to developing his rash approximately five days after starting ciprofloxacin.

Table 7.3.2.6: Number (%) of BTDS-Treated Subjects in all Studies with Nonfatal SAEs in the Skin and Subcutaneous Tissue

Skin and subcutaneous disorders SOC/ preferred term [a]	Number (%) of BTDS-treated subjects with nonfatal serious adverse events N=6042
All preferred terms	**8 (0.1)**
Hyperhidrosis	3 (<0.1)
Rash generalized	2 (<0.1)
Hypoaesthesia facial	1 (<0.1)
Rash	1 (<0.1)
Skin necrosis	1 (<0.1)
Skin ulcer	1 (<0.1)

(Reference: Appendix 11, Tables 4.5.4.1.2, 4.5.4.2, 4.5.4.3).
[a] Adverse events are treatment-emergent events sorted by descending frequency in the Total BTDS group and alphabetically by SOC.

Drug Withdrawal
There was one subject with an SAE of drug withdrawal symptoms. The subject was a 70 year old woman who was discontinued form BTDS 20 after a 5-month

exposure. She was not restarted on another opioid analgesic medication and developed the symptoms of opioid withdrawal.

In the BTDS development program a total of 17 subjects were reported to have drug withdrawal syndrome: 15 of 6042 (0.25%) BTDS-treated subjects and 2 of 1085 (0.18%) placebo-treated subjects.

Impresssion
It is well known that opioids in general can lead to withdrawal symptoms when discontinued abruptly and BTDS is no exception.

7.3.3 Dropouts and/or Discontinuations

Dropouts Due to Adverse Events
In the chronic pain studies (Group C) 26.4% of BTDS-treated subjects discontinued due to adverse events (Table 7.3.3.1). The most common reasons for discontinuation were gastrointestinal (11.6%), nervous system disorders (9.3%), and application site disorders (4.2%). The reasons for discontinuations with BTDS are consistent with other opioids and patches.

Table 7.3.3.1: Number (%) of Subjects with Adverse Events Leading to Study-Drug Discontinuation (≥1% of Subjects) During Overall Exposure to BTDS in the Chronic Pain Studies (Group C)

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)

Reference: Table 61. Number (%) of Subjects with Adverse Events Leading to Study-Drug Discontinuation (≥1% of Subjects) During Overall Exposure to BTDS in the Chronic Pain Studies (Group C), page 197 of ISS

Table 7.3.3.2 summarizes the rate of discontinuations during the double-blind period of the enriched fixed duration chronic pain studies (Group A2B). The rate of discontinuations for the BTDS group was dose dependent and higher than for placebo. The rate of discontinuations was similar for BTDs and OxyIR treatment groups. As expected for an opioid the highest rate of discontinuations for adverse events was related to nausea, vomiting and dizziness. The high rate of discontinuations for application site disorders is consistent with use of a patch.

Table 7.3.3.2. Number (%) of Subjects with Adverse Events Leading to Study-Drug Discontinuation in ≥1% of Subjects by Treatment Group During the Double-Blind Period of Enriched, Fixed Duration, Chronic Pain Studies (Group A2B)

	Number (%) subjects with at least one adverse event leading to discontinuation					
MedDRA system organ class/ preferred term	Placebo (n=283)	OxyIR (n=353)	Total BTDS (N = 1077)	BTDS 5 (n=404)	BTDS 10 (n=120)	BTDS 20 (n=553)
All SOCs/all preferred terms	**15 (5.3)**	**32 (9.1)**	**113 (10.5)**	**25 (6.2)**	**16 (13.3)**	**72 (13.0)**
Gastrointestinal disorders	**3 (1.1)**	**11 (3.1)**	**38 (3.5)**	**7 (1.7)**	**11 (9.2)**	**20 (3.6)**
Nausea	3 (1.1)	10 (2.8)	20 (1.9)	2 (0.5)	8 (6.7)	10 (1.8)
Vomiting	0	4 (1.1)	9 (0.8)	1 (0.2)	2 (1.7)	6 (1.1)
General disorders and administration site conditions	**2 (0.7)**	**8 (2.3)**	**37 (3.4)**	**11 (2.7)**	**4 (3.3)**	**22 (4.0)**
Application site pruritus	0	2 (0.6)	11 (1.0)	3 (0.7)	1 (0.8)	7 (1.3)
Application site rash	0	1 (0.3)	9 (0.8)	3 (0.7)	0	6 (1.1)
Application site irritation	0	0	8 (0.7)	2 (0.5)	0	6 (1.1)
Application site erythema	0	2 (0.6)	7 (0.6)	1 (0.2)	0	6 (1.1)
Nervous system disorders	**3 (1.1)**	**12 (3.4)**	**19 (1.8)**	**4 (1.0)**	**3 (2.5)**	**12 (2.2)**
Dizziness	0	3 (0.8)	8 (0.7)	2 (0.5)	2 (1.7)	4 (0.7)
Somnolence	0	6 (1.7)	2 (0.2)	0	0	2 (0.4)
Psychiatric disorders	**1 (0.4)**	**1 (0.3)**	**13 (1.2)**	**2 (0.5)**	**4 (3.3)**	**7 (1.3)**
Anxiety	1 (0.4)	1 (0.3)	3 (0.3)	0	2 (1.7)	1 (0.2)

Reference: Table 64. Number (%) of Subjects with Adverse Events Leading to StudyDrug Discontinuation in ≥1% of Subjects by Treatment Group During the Double-Blind Period of Enriched, Fixed Duration, Chronic Pain Studies (Group A2B), pg. 201 of ISS

Dose Reductions Due to Adverse Events

The most common reasons by system organ class for dose reductions during the open-label extension period of the chronic pain studies were gastrointestinal disorders (2.0%) and nervous system disorders (1.8%). The most common reasons for dose reduction by preferred term were: nausea (1.6%); vomiting (0.4%); application site erythema (0.4%); fatigue (0/4%); dizziness (0.8%) and somnolence (0.6%). In the enriched, fixed-duration studies (Group A2B), only study BUP3024 allowed dose reduction. In this study during the open-label run-in period, 2/1024 (0.2%) subjects experienced AEs that led to dose reduction. In the double-blind period, 6/256 (2.3%) BTDS-treated subjects and 2/283 (0.7%) placebo-treated subjects experienced AEs that led to dose-reduction.

7.3.4 Significant Adverse Events

Discussed in section 7.3.2

7.3.5 Submission Specific Primary Safety Concerns

Thorough QT Study (BUP1011)
Study BUP1011 was a Phase 1, randomized, placebo- and positive-controlled, parallel group, dose-escalating study in132 healthy subjects randomized into three groups: placebo, moxifloxacin (positive control), and BTDS. The BTDS group consisted of a therapeutic dose (BTDS 10) and supratherapeutic dose (2 x BTDS 20). The FDA Interdisciplinary Review Team (IRT) concluded that the therapeutic dose of BTDS 10 has no clinically meaningful effect on QT. However, for the supratherapeutic dose of BTDS 40, the maximum mean ΔΔQTcF was 11 ms (upper 90% CI: 15 ms) at 2 hours postdose and exceeded the 10-ms threshold at 6 additional timepoints. This dose level provides a 2-fold exposure margin over the 20-mg dose, which is sufficient to cover the increased exposure for patients with severe renal impairment. The FDA IRT agreed with the applicants proposed language in the label (except for what appears in strikeout):

7.4 Supportive Safety Results

None

7.4.1 Common Adverse Events

The most common adverse events in BTDS-treated subjects from all chronic pain studies (Group C) were: gastrointestinal disorders, administration site and skin disorders and nervous system disorders. In study BUP3024, in opioid naïve subjects, the most common adverse events are listed in Table 7.4.1.1. In Study BUP3015, in opioid-experienced subjects, the most common adverse events are listed in Table 7.4.1.2. The most common adverse events in the two pivotal studies are similar to the chronic pain studies and expected with use of an opioid

and patch. As expected the incidence is higher in opioid-naïve subjects compared to opioid-experienced subjects. In the open-label period nausea occurred in 23% of the opioid naïve subjects compared to 15% of the opioid experienced subjects.

Table 7.4.1.1: Treatment-Emergent Adverse Events Reported in ≥ 5.0% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period of BUP3024 (12-Week Study in Opioid-Naïve Patients)

	Open-Label Titration Period	Double-Blind Treatment Period	
	BuTrans	BuTrans	Placebo
Preferred Term	**(N = 1024)**	**(N = 256)**	**(N = 283)**
Nausea	23.3%	12.5%	11.0%
Dizziness	10.0%	3.9%	1.1%
Headache	9.8%	5.5%	4.9%
Application site pruritus	8.5%	4.3%	6.7%
Somnolence	8.2%	1.6%	2.1%
Vomiting	7.5%	4.3%	1.8%
Constipation	6.5%	3.5%	1.1%

Reference: Table 15: Incidence of Treatment-Emergent Adverse Events Reported in ≥ 5% of Subjects: Safety Population (Run-in Period) and Randomized Safety Population (Double-blind Phase), Clinical Study Report BUP3024, pg 123

Table 7.4.1.2: Treatment-Emergent Adverse Events Reported in ≥ 5.0% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period of BUP3015 (12-Week Study in Opioid-Experienced Patients)

	Open-Label Titration Period	Double-Blind Treatment Period		
	BuTrans	BuTrans 20	OxyIR*	BuTrans 5
Preferred Term	**(N = 1160)**	**(N = 219)**	**(N=220)**	**(N = 221)**
Nausea	14.9%	12.3%	8.2%	8.1%
Headache	10.8%	11.4%	9.5%	5.0%
Application site pruritus	8.8%	13.2%	9.1%	5.4%
Somnolence	5.9%	4.6%	5.0%	1.8%
Vomiting	5.3%	5.0%	4.1%	2.3%
Dizziness	5.3%	4.6%	3.6%	2.3%
Constipation	4.1%	6.4%	6.4%	3.2%
Application site erythema	3.3%	10.0%	8.6%	4.5%
Application site rash	2.7%	8.7%	5.9%	5.9%
Application site irritation	2.4%	5.5%	3.2%	2.7%

* OxyIR dosed two 5 mg tablets every 6 hours (40 mg/day)
Reference: Table 15. Incidence of TEAEs Reported in ≥ 5% of Subjects in the Core Study:Safety Population (Run-in Period) and Randomized Safety Population (Double-blind Phase), Clinical Study Report BUP3015, pg. 98

7.4.2 Laboratory Findings

The mean changes and shifts in clinical laboratory test data were summarized at screening, end of open-label run-in for enriched studies, and at end of the double-blind period.

Hematologic Values
More BTDS-treated subjects had a shift in hemoglobin from normal to low than placebo subjects but the percentages in BTDS-treated subjects were similar to those seen in active-comparator-treated subjects (Table 7.4.2.1). In the controlled chronic pain studies (Group A), a decrease in hemoglobin occurred in 5.0% of BTDS-treated subjects, 3.7% of placebo-treated subjects, 7.6% Oxy/APAP-treated subjects, 3.3% in OxyIR-treated subjects, and 13.4% in HCD/APAP-treated subjects. There were also more BTDS-treated subjects who had a shift in ANC and WBC from normal to low than placebo subjects but the differences were slight and percentages in BTDS-treated subjects were similar to those seen in active-comparator-treated subjects (Table 7.4.2.1). In controlled chronic pain studies (Group A) a decrease in ANC occurred in 1.7% of BTDS-treated subjects compared to 1.4% of placebo treated subjects. A decrease in WBC occurred in 2.1% of BTDS-treated subjects compared to 1.4% of placebo treated subjects. The shift from normal to low for hemoglobin, WBC and ANC was greater with BTDS 20 than BTDS 10 or BTDS 5 for subjects in the nonenriched forced titration studies (Group A1A). A decrease in hemoglobin occurred in 10.7% of BTDS 20, 5.8% of BTDS 10 and 3.7% of BTDS 5 and a decrease in ANC occurred 5.7% of BTDS 20, 2.3% of BTDS 10, and 3.6% of BTDS 5.

Table 7.4.2.1: Number (%) of Subjects Who Had Shifts in Hematologic Values from Normal at Baseline to Abnormal (High or Low) at the End of the Double-Blind Period in the Controlled, Chronic Pain Studies (Group A)

Direction of change/ Laboratory value	Number (%) of subjects who had shifts from normal to abnormal in laboratory values [a]														
	Placebo			Oxy/APAP			OxyIR			HCD/APAP			BTDS		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Normal to high															
Red blood cells (x10^{12}/L)	736	8	1.1	132	2	1.5	271	4	1.5	112	0	0	1620	13	0.8
Hemoglobin (g/L)	734	3	0.4	131	1	0.8	271	7	2.6	112	1	0.9	1614	21	1.3
Hematocrit (fraction)	735	13	1.8	132	0	0	271	14	5.2	112	1	0.9	1620	41	2.5
Platelet (x10^{9}/L)	735	8	1.1	132	4	3.0	266	5	1.9	112	1	0.9	1609	13	0.8
White blood cells (x10^{9}/L)	736	31	4.2	132	4	3.0	271	13	4.8	112	1	0.9	1620	49	3.0
Neutrophils (fraction)	746	26	3.5	132	10	7.6	270	14	5.2	112	6	5.4	1626	58	3.6
Bands (fraction)	42	0	0	49	0	0	0	0	0	0	0	0	150	0	0
Lymphocytes (fraction)	746	12	1.6	132	3	2.3	270	1	0.4	112	6	5.4	1626	34	2.1
Monocytes (fraction)	743	9	1.2	130	6	4.6	270	3	1.1	112	3	2.7	1618	26	1.6
Eosinophils (fraction)	744	16	2.2	129	2	1.6	270	7	2.6	112	6	5.4	1615	49	3.0
Basophils (fraction)	743	5	0.7	128	7	5.5	271	1	0.4	112	2	1.8	1612	6	0.4
Absolute neutrophil count (x10^{6}/L)	736	19	2.6	132	2	1.5	270	14	5.2	112	0	0	1619	42	2.6
Normal to low															
Red blood cells (x10^{12}/L)	736	24	3.3	132	9	6.8	271	8	3.0	112	13	11.6	1620	70	4.3
Hemoglobin (g/L)	734	27	3.7	131	10	7.6	271	9	3.3	112	15	13.4	1614	81	5.0
Hematocrit (fraction)	735	29	3.9	132	12	9.1	271	7	2.6	112	14	12.5	1620	89	5.5
Platelet (x10^{9}/L)	735	4	0.5	132	1	0.8	266	1	0.4	112	1	0.9	1609	10	0.6
White blood cells (x10^{9}/L)	736	10	1.4	132	1	0.8	271	5	1.8	112	3	2.7	1620	34	2.1
Neutrophils (fraction)	746	7	0.9	132	4	3.0	270	1	0.4	112	4	3.6	1626	21	1.3
Bands (fraction)	42	0	0	49	0	0	0	0	0	0	0	0	150	1	0.7
Lymphocytes (fraction)	746	17	2.3	132	11	8.3	270	1	0.4	112	5	4.5	1626	36	2.2
Monocytes (fraction)	743	6	0.8	130	3	2.3	270	2	0.7	112	0	0	1618	17	1.1
Eosinophils (fraction)	744	0	0	129	2	1.6	270	0	0	112	0	0	1615	6	0.4
Basophils (fraction)	743	0	0	128	0	0	271	0	0	112	0	0	1612	0	0
Absolute neutrophil count (x10^{6}/L)	736	10	1.4	132	3	2.3	270	1	0.4	112	5	4.5	1619	28	1.7

(Reference: Appendix 11, Table 5.2.4).
[a] Group A is composed of Group A1 and Group A2. Baseline value for the controlled, chronic pain studies (Group A) was the prerandomization (end of open-label run-in period) value. Baseline value for the nonenriched studies (Group A1) was the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.
N=number of subjects with a laboratory value at baseline and a postbaseline value.
n=number of subjects with a shift from normal to abnormal.

Reference: Table 79. Number (%) of Subjects Who Had Shifts in Hematologic Values from Normal at Baseline to Abnormal (High or Low) at the End of the Double-Blind Period in the Controlled, Chronic Pain Studies (Group A), page 37 of ISS

In Group A studies change in means for hematologic values was small but in nonenriched studies (Group A1) there was a greater mean decrease in ANC with BTDS than with comparators (Table 7.4.2.2). A smaller decrease vs comparators was seen in enriched studies (Group A2):

- Group A1: the mean change in ANC from baseline to the end of the double-blind period was -201 x10^{6}/L in BTDS-treated subjects compared to 53 x10^{6}/L in placebo-treated subjects, -85 x10^{6}/L in Oxy/APAP-treated subjects, and -29 x10^{6}/L in HCD/APAP-treated subjects.
- Group A2: the mean change in ANC for the BTDS-treated subjects was -245 x10^{6}/L from baseline to the end of open-label run-in period compared to 173 x10^{6}/L from the end of the open-label run-in period to the end of the double-blind period. In the double-blind period, the mean change in ANC for subjects receiving BTDS was 173 x10^{6}/L compared to 315 x10^{6}/L for placebo-treated subjects and 317 x10^{6}/L for OxyIR-treated subjects.

The largest decreases in mean change occurred at the highest dose, BTDS 20, in red blood cells, hemoglobin, hematocrit, platelets, neutrophils, basophils and in ANC in Group A1A but an association between increases in BTDS dose and changes in any hematologic parameters, including ANC was not observed during the double-blind period of the nonenriched, chronic pain studies,Group A2 (Table 7.4.2.2).

- Group A1A (Baseline ANC 4606 $x10^6$/L): the mean change in ANC from baseline to the end of the double-blind period was: -414 $x10^6$/L in BTDS 20, -177 $x10^6$/L in BTDS 10 and -62 $x10^6$/L in BTDS 5

Table 7.4.2.2. Mean Hematologic Values and Changes from Baseline by BTDS Dose to the End of the Double-Blind Period of the Nonenriched, Forced-Titration Chronic Pain Studies (Groups A1A) and the Enriched Chronic Pain Studies (Group A2) (page 1 of 2)

		Double-blind period							
		Total BTDS		BTDS 5		BTDS 10		BTDS 20	
		Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)
Parameter	Analysis Group	N(A1A)=236 to 310 N(A2)=1242 to 1248	NN(A1A)=190 to 257 NN(A2)=1026 to 1040	N(A1A)=82 to 104 N(A2)=423 to 424	NN(A1A)=63 to 83 NN(A2)=352 to 356	N(A1A)=76 to 102 N(A2)=204 to 205	NN(A1A)=63 to 87 NN(A2)=178 to 180	N(A1A)=78 to 104 N(A2)=615 to 619	NN(A1A)=64 to 87 NN(A2)=496 to 504
Red blood cell (10^{12}/L)	A1A	4.502	-0.026 (0.0244)	4.49	0.031 (0.0598)	4.489	-0.016 (0.0339)	4.528	-0.091 (0.0277)
	A2	4.445	0.038 (0.0078)	4.426	0.063 (0.0137)	4.474	0.002 (0.0176)	4.448	0.032 (0.0112)
Hemoglobin (g/L)	A1A	137.6	-2.4 (0.57)	137.9	-1.4 (0.97)	136.5	-1.1 (1.02)	138.3	-4.7 (0.92)
	A2	136.1	0.4 (0.24)	136.8	1.7 (0.43)	135.6	-0.5 (0.49)	135.7	-0.1 (0.33)
Hematocrit (fraction)	A1A	0.409	0.0083 (0.01384)	0.4103	0.0391 (0.04261)	0.4071	-0.0021 (0.00313)	0.4097	-0.0107 (0.00262)
	A2	0.4077	0.0007 (0.00074)	0.4098	0.0038 (0.00135)	0.4066	-0.0029 (0.00158)	0.4066	-0.0002 (0.00105)
Platelet (10^9/L)	A1A	246.4	-4.2 (2.57)	247.2	-3.6 (3.51)	248.2	0.2 (5.12)	243.9	-9.3 (4.5)
	A2	258.6	-0.7 (1.1)	254.0	3.1 (1.87)	257.1	-5.6 (2.5)	262.3	-1.7 (1.6)
White blood cells (10^9/L)	A1A	7.37	-0.24 (0.106)	7.23	0.04 (0.162)	7.40	-0.27 (0.217)	7.49	-0.48 (0.161)
	A2	6.84	0.19 (0.05)	6.86	0.28 (0.085)	6.79	0.05 (0.109)	6.84	0.19 (0.074)
Neutrophils (fraction)	A1A	0.6103	-0.0081 (0.00544)	0.6164	-0.0099 (0.00941)	0.6049	0.0018 (0.01018)	0.6094	-0.0163 (0.00865)
	A2	0.6019	0.0097 (0.00278)	0.6034	0.0156 (0.00461)	0.6037	-0.0046 (0.00594)	0.6002	0.0107 (0.00421)
Bands (fraction)	A1A	0.004	-0.001 (0.0013)	0.004	-0.002 (0.0035)	0.003	-0.001 (0.0012)	0.004	-0.002 (0.0017)
	A2	*	*	*	*	*	*	*	*

Parameter	Analysis group	Double-blind period							
		Total BTDS		BTDS 5		BTDS 10		BTDS 20	
		Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)	Mean baseline value	Mean change (SE)
		N(A1A)=236 to 310 N(A2)=1242 to 1248	NN(A1A)=190 to 257 NN(A2)=1026 to 1040	N(A1A)=82 to 104 N(A2)=423 to 424	NN(A1A)=63 to 83 NN(A2)=352 to 356	N(A1A)=76 to 102 N(A2)=204 to 205	NN(A1A)=63 to 87 NN(A2)=178 to 180	N(A1A)=78 to 104 N(A2)=615 to 619	NN(A1A)=64 to 87 NN(A2)=496 to 504
Lymphocytes (fraction)	A1A	0.2861	0.008 (0.00478)	0.279	0.0089 (0.00883)	0.2922	0.0017 (0.0089)	0.2872	0.0132 (0.00709)
	A2	0.3076	-0.0045 (0.00242)	0.3051	-0.0067 (0.0039)	0.3073	0.0049 (0.00515)	0.3094	-0.0062 (0.00374)
Monocytes (fraction)	A1A	0.0688	0.0014 (0.00199)	0.0651	0.0041 (0.00279)	0.0713	-0.0023 (0.00411)	0.0699	0.0026 (0.00328)
	A2	0.0576	-0.0032 (0.00067)	0.0575	-0.0047 (0.00113)	0.0563	-0.0011 (0.00167)	0.0581	-0.0028 (0.00095)
Eosinophils (fraction)	A1A	0.0275	0.0009 (0.00145)	0.0316	-0.0016 (0.00244)	0.0257	0.001 (0.00285)	0.0255	0.0031 (0.0022)
	A2	0.0298	-0.0019 (0.00059)	0.0307	-0.0038 (0.00116)	0.0298	0.001 (0.00121)	0.0293	-0.0017 (0.00078)
Basophils (fraction)	A1A	0.0065	-0.0003 (0.00056)	0.0063	0.0002 (0.00088)	0.0057	0.001 (0.00083)	0.0075	-0.0021 (0.00113)
	A2	0.0029	-0.0001 (0.00010)	0.0028	-0.0001 (0.00017)	0.003	-0.0001 (0.00028)	0.0029	-0.0002 (0.00015)
Absolute neutrophil count (10^6/L)	A1A	4606.4	-220.4 (93.62)	4524.0	-62.3 (153.61)	4616.6	-177.1 (184.36)	4678.7	-414 (145.14)
	A2	4204.6	172.6 (47.02)	4214.3	267.6 (77.36)	4186.1	11.1 (101.68)	4204.1	162.9 (71.37)

(References: Appendix 11, Tables 5.1.6 and 5.1.8).
*Bands were not counted separately for all studies in Group A2.
N=number of subjects with a baseline value.
NN=number of subjects with a baseline and a postbaseline value.
Note: Baseline value for the nonenriched, forced-titration studies (Group A1A) was the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.

Reference: Table 86. Mean Hematologic Values and Changes from Baseline by BTDS Dose to the End of the Double-Blind Period of the Nonenriched, Forced-Titration Chronic Pain Studies (Groups A1A) and the Enriched Chronic Pain Studies (Group A2), pate 252 of ISS

Summary of Hematologic Laboratory Changes

Subjects treated with BTDS appear to have slightly lower hemoglobin, WBC and ANC values. This effect also appears to be present with other opioids but may be greater with BTDS on ANC. The effect was more noticeable with higher doses of BTDS.

Blood Chemistry Values

Review of the tables on the number of subjects with shifts in blood chemistry values from normal to abnormal and mean changes from baseline in chemistry values revealed no clinically significant changes with the possible exception of LFTs discussed below.

Liver Function Tests

The applicant defined markedly abnormal LFT values as >3x ULN for AST or ALT or >1.5x ULN for bilirubin. The majority of studies in the BTDS clinical development program excluded subjects with markedly abnormal baseline LFT values.

Summary of Abnormal LFT Findings
Four thousand nine hundred seventy-two (4972) BTDS-treated subjects in all studies (Groups C, B, and D) had a postbaseline LFT value; 41 of these subjects (0.8%) had markedly abnormal LFT values (either AST, ALT, or bilirubin). None of the subjects discontinued BTDS treatment due to elevated LFT values. Of these 41 subjects, 1 subject (Subject 0011 BP970303) had ALT and AST values >5 to ≤10x ULN, and met criteria for Hy's Law. This subject's abnormal LFTs were due to acute cholecystitis.

Subject 00111 (BP970303)
The subject was a 37-year-old woman, enrolled in clinical pharmacology study BP97-0303. She completed the 14-day treatment with BTDS 5 and BTDS 20. Her LFT values were normal at baseline. On her final study visit, 3 days after discontinuing BTDS 20 treatment, she had upper right quadrant abdominal pain and elevated liver function tests. She was subsequently hospitalized with acute cholecystitis. The total bili was 4.8 mg/dL, ALT was 492 U/L, AST was 199 U/L and ALP was 182 U/, meeting Hy's Law criteria. She underwent cholecystectomy 5 days after discontinuing BTDS treatment that revealed a diseased gall bladder which required removal. After discharge from the hospital she developed evidence of continued common duct obstruction and a stent was placed in the common duct. No follow-up laboratory tests were provided for this subject.

Impression
This subject had abnormal LFTs meeting Hy's Law criteria secondary to acute cholecystitis.

The distribution of the 41 subjects with markedly abnormal LFTs is the following:
- 1 case ALT and AST >3x ULN with bilirubin > 1.5 x ULN (Hy's Law criteria)
- 6 (0.1%) ALT and AST >3xULN with bilirubin <1.5x ULN
- 26 (0.5%) had either AST or ALT >3xULN with bilirubin <1.5x ULN
- 8 (0.1%) bilirubin >1.5 x ULN with ALT and AST <3xULN

Table 7.4.2.3 summarizes by treatment group the cases of abnormal ALT, AST and bilirubin values in controlled, chronic pain studies (Group A). Four subjects in the BTDS group had ALT and/or AST > 3x ULN, compared to no subjects in the active comparator groups and only one subject in placebo group. However, the higher number of subjects enrolled in the BTDS group make it difficult to compare rates.

Table 7.4.2.3: Distribution of subjects with peak ALT, AST and Bilirubin Abnormalities During BTDS Exposure in the Double-Blind Period of the Controlled, Chronic Pain Studies (Group A)

Laboratory evaluations [a]		Number (%) of subjects				
Bilirubin category	Peak treatment-emergent AST/ALT value	Placebo (N=679)	Oxy/APAP (N=118)	OxyIR (N=232)	HCD/APAP (N=98)	BTDS (N=1474)
≤1.5x ULN	ALT and AST ≤1x ULN	673 (99.1)	116 (98.3)	228 (98.3)	97 (99.0)	1455 (98.7)
	1x ULN <AST and ALT ≤1x ULN	4 (0.6)	1 (0.8)	3 (1.3)	1 (1.0)	14 (0.9)
	ALT ≤3x ULN and AST >3x ULN	0	0	0	0	0
	ALT >3x ULN and AST ≤3x ULN	1 (0.1)	0	0	0	3 (0.2)
	ALT and AST >3x ULN	0	0	0	0	1 (0.1)
>1.5x ULN	ALT and AST ≤1x ULN	1 (0.1)	1 (0.8)	1 (0.4)	0	1 (0.1)
	1x ULN <AST and ALT ≤1x ULN	0	0	0	0	0
	ALT ≤3x ULN and AST >3x ULN	0	0	0	0	0
	ALT >3x ULN and AST ≤3x ULN	0	0	0	0	0
	ALT and AST >3x ULN	0	0	0	0	0

(References: Appendix 11, Table 5.6.4).
[a] These laboratory categories were applied to the same test date.
[b] Subjects with or without baseline were included.
Note: Peak treatment-emergent AST/ALT value is defined as occurring ≤7 days from last study drug exposure

Reference: Sponsor provided Table 117 from page 304 of the ISS

Table 7.4.2.4 summarizes the percentage of subjects who had shifts from normal to abnormal in blood chemistry values in the enriched and nonenriched chronic pain studies (Groups A1 and A2). In the nonenriched pain studies there was a higher incidence of subjects on BTDS that showed a shift in AST and ALT compared to the placebo and active comparator groups. There was the suggestion of a weak dose response for shift in AST (Table 7.4.2.5)

Table 7.4.2.4: Number (%) of Subjects Who Had Shifts in Blood Chemistry Values from Normal at Baseline to Abnormal (High) at the End of the Open-Label Run-In Period and at the End of the Double-Blind Period in Nonenriched and Enriched Chronic Pain Studies (Groups A1 and A2)

Direction of change/ laboratory parameter	Analysis group	Number (%) of subjects who had shifts in blood chemistry values																	
		Open-label run-in period BTDS			Double-blind period [a]														
					Placebo			Oxy/APAP			OxyIR			HCD/APAP			BTDS		
		N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Normal to high																			
Phosphorus/inorganic phosphate (mmol/L)	A1	*	*	*	295	16	5.4	130	3	2.3	*	*	*	110	2	1.8	573	24	4.2
	A2	3266	87	2.7	446	13	2.9	*	*	*	281	9	3.2	*	*	*	1084	32	3.0
Alkaline phosphatase (U/L)	A1	*	*	*	298	6	2.0	132	1	0.8	*	*	*	110	0	0	580	7	1.2
	A2	3262	20	0.6	445	4	0.9	*	*	*	279	1	0.4	*	*	*	1084	5	0.5
Aspartate transferase (U/L)	A1	*	*	*	298	4	1.3	132	2	1.5	*	*	*	110	1	0.9	580	14	2.4
	A2	3262	100	3.1	446	5	1.1	*	*	*	279	5	1.8	*	*	*	1085	25	2.3
Alanine transferase (U/L)	A1	*	*	*	296	4	1.4	131	3	2.3	*	*	*	110	3	2.7	578	20	3.5
	A2	3265	132	4.0	446	11	2.5	*	*	*	279	12	4.3	*	*	*	1085	23	2.1
Lactic dehydrogenase (U/L)	A1	*	*	*	298	2	0.7	132	3	2.3	*	*	*	110	3	2.7	580	14	2.4
	A2	3264	60	1.8	445	8	1.8	*	*	*	280	2	0.7	*	*	*	1085	18	1.7
Gamma glutamyl-transferase (U/L)	A1	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	A2	699	20	2.9	206	2	1.0	*	*	*	0	0	0	*	*	*	203	1	0.5
Total bilirubin (µmol/L)	A1	*	*	*	298	2	0.7	132	0	0	*	*	*	110	1	0.9	580	2	0.3
	A2	3265	14	0.4	446	4	0.9	*	*	*	279	2	0.7	*	*	*	1085	4	0.4
Triglycerides (mmol/L)	A1	*	*	*	287	32	11.1	122	10	8.2	*	*	*	110	26	23.6	553	49	8.9
	A2	3265	257	7.9	446	55	12.3	*	*	*	279	26	9.3	*	*	*	1085	121	11.2
Total cholesterol (mmol/L)	A1	*	*	*	298	16	5.4	132	8	6.1	*	*	*	110	11	10	581	34	5.9
	A2	3265	202	6.2	446	55	12.3	*	*	*	279	34	12.2	*	*	*	1085	110	10.1
Bilirubin direct (µmol/L)	A1	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
	A2	2704	1	<0.1	284	0	0	*	*	*	280	1	0.4	*	*	*	927	1	0.1

(Reference: Appendix 11, Tables 5.2.1, 5.2.5, 5.2.11).
[a] Baseline value for the nonenriched studies (Group A1) and the open-label run-in period of the enriched studies (Group A2) was the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.
* No open-label run-in period for Group A1. In double-blind period, treatment group was not represented.
N=number of subjects with a baseline and a postbaseline value.
n=number of subjects with a shift from normal to abnormal.

Reference: Sponsor provided Table 107 from page 278 of the ISS

Table 7.4.2.4: Number (%) of Subjects Who Had Shifts in Blood Chemistry Values from Normal at Baseline to Abnormal (High) at the End of Double-Blind Period, by BTDS Dose, in the Nonenriched, Forced-Titration Chronic Pain Studies (Group A1A) and Enriched Chronic Pain Studies (Group A2) (page 2 of 2)

Direction of change/ laboratory parameter	Analysis groups [a]	Number (%) of subjects who had shifts from normal to abnormal											
		Total BTDS			BTDS 5			BTDS 10			BTDS 20		
		N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Normal to high (continued)													
Phosphorus/inorganic phosphate (mmol/L)	A1A	248	9	3.6	79	4	5.1	83	4	4.8	86	1	1.2
	A2	1084	32	3.0	376	10	2.7	186	5	2.7	522	17	3.3
Alkaline phosphatase (U/L)	A1A	255	4	1.6	82	2	2.4	87	2	2.3	86	0	0
	A2	1084	5	0.5	375	1	0.3	186	0	0	523	4	0.8
Aspartate transferase (U/L)	A1A	255	5	2.0	82	3	3.7	86	2	2.3	87	0	0
	A2	1085	25	2.3	376	5	1.3	186	4	2.2	523	16	3.1
Alanine transferase (U/L)	A1A	253	7	2.8	80	2	2.5	86	5	5.8	87	0	0
	A2	1085	23	2.1	376	9	2.4	186	1	0.5	523	13	2.5
Lactic dehydrogenase (U/L)	A1A	255	7	2.7	82	2	2.4	86	0	0	87	5	5.7
	A2	1085	18	1.7	376	4	1.1	186	2	1.1	523	12	2.3
Gamma glutamyl-transferase (U/L)	A1A	*	*	*	*	*	*	*	*	*	*	*	*
	A2	203	1	0.5	42	0	0	82	1	1.2	79	0	0
Total bilirubin (µmol/L)	A1A	256	0	0	82	0	0	87	0	0	87	0	0
	A2	1085	4	0.4	376	1	0.3	186	0	0	523	3	0.6
Triglycerides (mmol/L)	A1A	228	20	8.8	73	6	8.2	76	8	10.5	79	6	7.6
	A2	1085	121	11.2	376	57	15.2	186	13	7.0	523	51	9.8
Total cholesterol (mmol/L)	A1A	256	16	6.3	82	3	3.7	87	8	9.2	87	5	5.7
	A2	1085	110	10.1	376	50	13.3	186	15	8.1	523	45	8.6
Bilirubin direct (µmol/L)	A1A	*	*	*	*	*	*	*	*	*	*	*	*
	A2	927	1	0.1	334	0	0	126	0	0	467	1	0.2

(Reference: Appendix 11, Tables 5.2.6 and 5.2.11).
[a] Baseline value for the nonenriched studies (Group A1A) was the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.
* Not applicable; laboratory parameter was not collected for studies in Group A1A.
N=number of subjects with a baseline and a postbaseline value.
n=number of subjects with shift from normal to abnormal.

Reference: Sponsor provided Table 109 from page 283 of the ISS

The applicant conducted an analysis of adverse events coded to liver related signs and symptoms and found the rates were similar during the double-blind period of the controlled chronic pain studies (Group A). The incidence of all AEs under this subSMQ for BTDS-treated subjects was 0.6%, placebo-treated subjects 0.4%, and OxyIR-treated subjects 1.1%. There were no AEs within this sub SMQ for subjects receiving Oxy/APAP or HCD/APAP.

7.4.3 Vital Signs

Mean Changes in Vital Signs

The mean changes in vital sign parameters from baseline to end of BTDS-treatment for all chronic pain studies (Group C) were small (Table 7.4.3.1)

Table 7.4.3.1. Mean Changes in Vital Sign Values from Baseline to the End of BTDS Treatment (Group C)

	Mean values, changes, and standard deviation for BTDS-treated subjects in Group C				
	Baseline [a]		Change from baseline		
Vital sign parameter	N	Mean value	NN	Mean Value	Standard deviation
Heart rate (bpm)	5407	74.5	5008	-0.4	10.44
Systolic BP (mmHg)	5408	129.9	5037	-1.4	15.02
Diastolic BP (mmHg)	5408	78.8	5037	-1.3	9.38
Temperature (°C)	2352	36.6	2077	0	1.43
Respiratory rate (bpm)	3247	17.0	2951	-0.1	2.94
Weight (kg)	5397	89.9	3672	-0.7	3.51

(Reference: Appendix 11, Table 7.1.13).

[a] Baseline value was the screening value.

N=number of subjects with a baseline value.

NN=number of subjects with baseline and post-baseline values.

Reference: Table 123. Mean Changes in Vital Sign Values from Baseline to the End of BTDS Treatment (Group C), page 322 of ISS

Table 7.4.3.2 summarizes the changes in vital signs during the double-blind period in controlled chronic pain studies (Group A). The mean changes for vital sign parameters in the BTDS-treatment group appeared small and similar to placebo and other opioids. There did not appear to be a dose response.

Table 7.4.3.2. Mean Baseline Vital Sign Values and Mean Changes in the Double-Blind Period in the Controlled, Nonenriched and Enriched, Chronic Pain Studies (Group A)

	Double-blind period									
	Placebo		Oxy/APAP		OxyIR		HCD/APAP		BTDS	
Parameter	Mean baseline value N=638 to 993	Mean change NN=501 to 956	Mean baseline value N=147 to 149	Mean change NN=71 to 139	Mean baseline value N=353	Mean change NN=347	Mean baseline value N=130	Mean change NN=125	Mean baseline value N=828 to 2125	Mean change NN=753 to 2051
Heart rate (bpm)	73.2	1.5	74.3	0.3	74.5	-0.1	74.9	0.4	73.8	-0.1
Systolic BP (mm Hg)	129.1	1.3	135.1	-1.9	125.4	2.1	129.3	-0.2	128.9	0.2
Diastolic BP (mm Hg)	77.5	0.9	80.9	-1.0	76.6	1.1	78.5	0.8	77.7	0
Temperature (°C)	36.6	0	36.8	0	*	*	*	*	36.6	0
Respiratory rate (bpm)	17.1	0	17.1	-0.1	*	*	18.0	-0.4	17.2	-0.1
Weight (kg)	88.7	-0.1	80.6	-0.1	93.0	-1.0	85.8	*	89.5	-0.7

(References: Appendix 11, Table 7.1.2).
* Temperature was not recorded at the study level for studies BP98-1201, BP99-0203, BUP3011, BUP3201, BUP3014, BUP3015, and BUP3019; respiratory rate was not recorded for studies BUP3011, BUP3014, BUP3015, BUP3019; post-baseline weight was not recorded for studies BUP3012, BUP3014, BUP3015, BUP3018, BUP3019, BUP3024, BP96-0101, BP96-0102 and BP96-0604.
N = number of subjects with a baseline value.
NN =number of subjects with a baseline and a postbaseline value.
Note: Group A is composed of Group A1 and Group A2. Baseline values for the controlled, chronic pain studies (Group A) was the prerandomization (end of open-label run-in period) value. Baseline value for the nonenriched studies (Group A1) was the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.

Reference: Table 124. Mean Baseline Vital Sign Values and Mean Changes in the Double-Blind Period in the Controlled, Nonenriched and Enriched, Chronic Pain Studies (Group A), page 323 of ISS

Vital Sign Outliers

Vital sign outliers were defined by the following criteria:

- Heart rate: <50 beats per minute (bpm) or >100 bpm
- Systolic blood pressure: <90 mm Hg or >160 mm Hg
- Diastolic blood pressure: <55 mm Hg or >95 mm Hg
- Respiratory rate: <12 breaths a minute or >20 breaths a minute
- Weight: change from prerandomization of ≥5%

Table 7.4.3.3 summarizes the incidence of vital sign outliers during the double-blind period of the controlled, chronic pain studies (Group A). The percentages of BTDS-treated subjects with abnormally low vital signs during the double-blind period were within one percent of placebo with the exception of decrease of ≥5% in body weight.

Table 7.4.3.3: Number of Subjects with of Abnormally Low Vital Signs during the Double-Blind Period of the Controlled, Chronic Pain Studies (Group A)

Vital sign parameter	Number (%) of subjects with abnormally low vital signs during the double-blind period														
	Placebo			Oxy/APAP			OxyIR			HCD/APAP			BTDS		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Heart rate (bpm)	949	4	0.4	134	0	0	347	4	1.2	125	2	1.6	2016	18	0.9
Systolic BP (mm Hg)	957	9	0.9	141	0	0	347	1	0.3	125	1	0.8	2054	9	0.4
Diastolic BP (mm Hg)	957	22	2.3	141	4	2.8	347	7	2.0	125	2	1.6	2054	51	2.5
Respiratory rate (bpm)	900	5	0.6	134	0	0	*	*	*	125	6	4.8	1173	13	1.1
Weight (kg)	501	21	4.2	71	2	2.8	347	40	11.5	*	*	*	1373	118	8.6

(References: Appendix 11, Table 7.2.2).
* Not applicable; weight was not collected for this treatment group. No respiratory rate was collected for OxyIR.
N= number of subjects with vital sign measurements at baseline and at any other timepoint (week) during the study.
n= number of subjects with the defined vital sign outlier.
Note: Abnormally low temperature was not a defined parameter.

Reference: Table 128. Number (%) of Subjects with of Abnormally Low Vital Signs at Any Time During the Double-Blind Period of the Controlled, Chronic Pain Studies (Group A), pg 329 ISS

Clinically Significant Decreases in Blood Pressure

Clinically significant changes in blood pressure were defined as:

- Decrease in systolic blood pressure to <100 mm Hg during treatment and decrease in systolic blood pressure ≥30 mm Hg from baseline value
- Decrease in diastolic blood pressure to <60 mm Hg during treatment and decrease in diastolic blood pressure ≥15 mm Hg from baseline value

The incidence of clinically significant decreases in blood pressure during exposure to BTDS in subjects from the chronic pain studies (Group C) for systolic BP was 1.2% (59/5037) and for diastolic BP was 3.0% (151/5037). Table 7.4.3.4 summarizes the incidence of clinically significant blood pressure decreases during the open-label run-in and double-blind periods of controlled, nonenriched and enriched chronic pain studies (Groups A, A1 and A2). During the double-blind period the incidences of "clinically significant" decreases in systolic and diastolic blood pressure were comparable with placebo and other opioids.

Table 7.4.3.4: Number (%) of Subjects with Clinically Significant Blood Pressure Decreases at Any Time During the Open-Label Run-In and Double-Blind Periods of Controlled, Nonenriched and Enriched, Chronic Pain Studies (Groups A, A1, and A2)

Number (%) of subjects with clinically significant blood pressure decreases

Vital sign parameter	Analysis groups	Open-label run-in period			Double-blind period													
		BTDS			Placebo			Oxy/APAP			OxyIR			HCD/APAP			BTDS		
		N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Systolic BP (mm Hg)	A	*	*	*	955	10	1.0	139	1	0.7	347	1	0.3	125	3	2.4	2051	24	1.2
	A1	*	*	*	341	7	2.1	139	1	0.7	*	*	*	125	3	2.4	671	15	2.2
	A2	4033	11	0.3	614	3	0.5	*	*	*	347	1	0.3	*	*	*	1380	9	0.7
Diastolic BP (mm Hg)	A	*	*	*	955	26	2.7	139	3	2.2	347	10	2.9	125	4	3.2	2051	47	2.3
	A1	*	*	*	341	11	3.2	139	3	2.2	*	*	*	125	4	3.2	671	24	3.6
	A2	4033	45	1.1	614	15	2.4	*	*	*	347	10	2.9	*	*	*	1380	23	1.7

(Reference: Appendix 11, Tables 7.3.1. 7.3.2, 7.3.3, and 7.3.4).

* No open-label run-in period for Group A1. In the double-blind period, the treatment group was not represented.

N= number of subjects with a baseline and postbaseline value.

n=number of subjects with clinically significant decreases in blood pressure.

Baseline values for the nonenriched studies (Group A1) and for the open-label run-in period of the enriched studies (Group A2) were the screening value. Baseline value for the double-blind period of the enriched studies (Group A2) was the prerandomization (end of open-label run-in period) value.

Reference: Table 133 from page 335 of ISS

7.4.4 Electrocardiograms (ECGs)

Dr. Monica Fiszman from the Division of Cardio-Renal Products analyzed the ECG data. At the time this report was completed her review had not been finalized but her preliminary findings were as follows:

> Slight changes from baseline in QTcB (3.2 ms; BTDS 20 group) and QTcF (3.8 ms; BTDS 20 group) were seen compared to placebo. Those increases over baseline were slightly higher than those seen in the OxyIR arm (Table 7.4.4.1). In group A2 there were 4 subjects with QTcF >500 ms, all belonged to the BTDS 20 arm, none were from the placebo arm. Eight subjects had a QTcB >500ms in the BTDS arm and one in the placebo arm. (Table 7.4.4.2).
>
> Outliers data in study A2 revealed that in all BTDS arms there is a higher incidence in changes from baseline in QTcF and QTcB >30ms compared to placebo. The percentage of subjects with changes from baseline in QTcF >60 ms is higher in the BTDS 5 and 20-mg arm than in the placebo arm. Similar trend was seen with QTcB. Either for QTcB or QTcF the number of outliers is higher in the BTDS 20mg arm than at lower doses.
>
> In group A2B, mean changes from baseline in QTcF ranged from 1 to 5.7 ms for BTDS 20. Very modest changes in mean QTcF from baseline were observed in the group treated with 5-mg BTDS and no changes were seen in the placebo group.

A low incidence in AE and SAEs as per ICH E14 Guidance was reported. The highest incidence for AEs was syncope (0.3%) and for SAEs were convulsion, syncope and presyncope (all of them were < 0.1%) when considering all safety population from all groups. By analyzing the placebo phase of Group A we found that the incidence rate for syncope and presyncope was balanced with placebo.

We performed an MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration including PR, QRS and QT events and arrhythmias. We detected no signals for Torsades and QT prolongation.

Table 7.4.4.1: Mean Baseline ECG Values and Mean Changes from Baseline to the End of Open-Label Run-in Period and to the End of the Double-Blind period of the Enriched, Chronic Pain Studies (Group A2)

	Open-label run-in period		Double-blind period											
	BTDS		Placebo		OxyIR		Total BTDS		BTDS 5		BTDS 10		BTDS 20	
ECG parameter	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean Change	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change
	N= 3710	NN= 1578	N= 496	NN= 476	N= 353	NN= 326	N= 1297	NN= 1212	N= 448	NN= 415	N= 210	NN= 203	N= 639	NN= 594
Heart rate (bpm)	69.8	0.4	69.0	2.1	72.1	-0.6	69.9	-0.4	70.3	0.3	68.4	-1.3	70.1	-0.6
QT (msec)	386.6	0.6	387.3	-4.8	383.5	3.6	386.3	3.2	386.2	0.3	388.0	3.9	385.9	4.9
QTcB (msec)	413.4	1.8	411.6	1.1	416.7	2.4	413.5	2.1	414.4	1.3	410.7	0.4	413.9	3.2
QTcF (msec)	404.0	1.4	403.2	-1.0	405.0	2.8	404.0	2.5	404.4	1.0	402.9	1.6	404.1	3.8

(References: Appendix 11, Tables 6.1.1 and 6.1.2).
N=number of subjects with a baseline.
NN=number of subjects with a baseline and postbaseline value.
Note: The baseline value is the value at screening. The mean changes were calculated based on the number of subjects who had ECGs at both baseline and the end of the open-label run-in or double-blind period.

Reference: Sponsor provided Table 133 from page 341 of ISS

Table 7.4.4.2. Number (%) of Subjects with QT/QTc Interval Values >500 msec During the Open-Label Run-In and Double-Blind Periods of the Enriched Chronic Pain Studies (Group A2)

	Number (%) of subjects with QT/QTc interval values >500 msec						
	Open-label run-in period	Double-blind period					
ECG parameter	BTDS (N =1578)	Placebo (N=476)	OxyIR (N=326)	Total BTDS (N=1212)	BTDS 5 (N=415)	BTDS 10 (N=203)	BTDS 20 (N=594)
QTcB	5 (0.3)	1 (0.2)	2 (0.6)	8 (0.7)	1 (0.2)	0	7 (1.2)
QTcF	3 (0.2)	0	1 (0.3)	4 (0.3)	0	0	4 (0.7)

Reference: Sponsor provided Table 138 from page 344 of ISS

7.4.5 Special Safety Studies/Clinical Trials

The applicant conducted two studies (BP98-0202 and BP97-1001) to evaluate the effect of coadministration of prochlorperazine and midazolam with BuTrans on vital signs and respiratory depression.

Study BP98-0202
This was a single-dose study in 36 healthy young subjects to evaluate the effects of BTDS 10 plus prochlorperazine (Compazine) 25 mg suppository and of fentanyl transdermal (Duragesic) 2.5 mg plus prochlorperazine on respiratory depression and vital signs.

Results
The mean age of the 36 subjects was 31 years. There were no deaths or serious adverse events. Only two subjects, Subject 36 in the Fentanyl group and Subject 21 in the placebo group developed respiratory rates less than 12 breaths per minute. Both subjects had respiratory rates of 10 breaths per minute. There did not appear to be a significant effect on vital signs or oxygen saturation.

Impression
Although this study did not demonstrate an effect from coadministration of prochlorperazine 25 mg suppository and BTDS 10 on oxygen saturation or vital signs, there were several limitations to the study. The study was conducted in young healthy individuals but the intended population is likely to be elderly with multiple comorbidities. Pneumotachography was not performed. The maximum dose of BTDS was not studied.

Study BP97-1001
This was a single-dose study to evaluate the effects of BTDS 10 plus midazolam 1 mg and of fentanyl transdermal patch 2.5 mg plus midazolam on respiratory depression and vital signs in healthy young subjects. There also was a placebo patch treatment arm that received 1 mg IV midazolam.

Results
The mean age for the 10 subjects in the BTDS 10 treatment arm was 32. There were no deaths or serious adverse events. There was a slight decrease in pulse, blood pressure and respiratory rate similar in both the BTDS 10 and fentanyl groups when administered midazolam 1 mg IV. Oxygen saturation less than 94% occurred more often in the BTDS 10 than Fentanyl groups compared to placebo group with the BTDS 10 having the most.

Impression
This study demonstrates a mild effect of coadministration of BTDS with midazolam compared to placebo but comparable to fentanyl on vital signs and oxygen saturation. Limitations of the study that prevent generalization to the intended population include:

(1) use of a young healthy population; (2) low BTDS dose and (3) no use of pneumotachography.

Patch Adhesiveness

The applicant studied patch adhesion in two Phase 1 studies (BP96-00803 and BP96-0702). In study BP96-0083, 24 subjects were evaluated twice a day over a 7-day treatment period to assess 3 BTDS sizes for patch adhesion (Table 7.6.1). No patches fell off but there was more buckling with increase in system size. In study BP96-0702, 24 subjects applied three different size BTDS patches or placebo systems over a 7-day treatment period. Four small-sized systems fell off and none of the medium or large-sized systems. Taping was required for one subject with a small-sized system, 5 subjects with medium-sized systems, and three subjects with a large-sized system. Buckling was more frequent in the medium and large-sized system than small.

Table 7.6.1: Summary of BTDS Wear Observations for Different Size BTDS 10 (N=24)

Observation	System[a]	Day 1 AM/PM	Day 2 AM/PM	Day 3 AM/PM	Day 4 AM/PM	Day 5 AM/PM	Day 6 AM/PM	Day 7 AM/PM	Day 8 AM/PM
System fell off.	Small	0/0	1/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	1/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
System required taping.	Small	0/0	0/1	0/3	0/0	0/0	0/0	3/6	0/—
	BTDS 10	0/0	1/1	1/3	0/0	2/2	2/2	1/1	0/—
	Large	0/0	0/2	0/3	0/0	1/3	1/2	5/13	0/—
System shifted.	Small	0/0	1/1	0/0	0/0	2/2	2/2	2/0	0/—
	BTDS 10	0/0	1/1	0/1	5/5	8/8	7/6	1/1	0/—
	Large	0/0	2/2	2/2	2/3	3/3	2/3	4/2	0/—
System changed shape.	Small	0/0	0/0	0/0	0/0	0/0	0/0	1/1	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/1	1/0	0/—
Reservoir lifted from skin.	Small	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	0/0	0/0	0/0	1/1	1/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
Medication reservoir shifted.	Small	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
System buckled.	Small	0/3	3/3	4/4	2/4	4/5	4/3	2/2	0/—
	BTDS 10	0/0	2/2	2/2	2/3	4/4	4/4	0/0	0/—
	Large	0/1	3/5	7/11	16/17	20/20	20/19	1/0	0/—
Edge curled.	Small	0/3	2/2	2/2	1/1	1/2	1/1	0/2	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/1	0/1	0/0	0/—
	Large	0/1	1/1	1/1	0/0	1/3	1/1	4/9	1/—
System changed color.	Small	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
System became transparent.	Small	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
Presence of odor.	Small	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	BTDS 10	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
	Large	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/—
Aesthetically pleasing.[b]	Small	24/24	23/23	23/23	23/23	23/23	23/23	23/23	23/—
	BTDS 10	23/24	24/24	24/24	24/24	24/23	24/24	24/23	23/—
	Large	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/—

(Cross-references: Table 14.2.3.1; Appendix 16.2.20.)
[a]Small and large placebo TDSs and medium-sized BTDS 10.
[b]Number of subjects who answered no for this variable only.

Reference: Sponsor provided Table 2A from page 6 of CSR BP96-0803

In the clinical development program the applicant reported that only one patch fell off in a subject who was perspiring while mowing his lawn and the patch would not stay on with taping.

Study BUP3024

The applicant queried subjects in this pivotal study whether the previous patch was "removed early due to adhesion problems." Approximately 11% of subjects reported a problem with the patch adhesion, occurring more often with larger patches (Table 7.6.2 and Table 7.6.3).

Table 7.6.2: Patch Adhesion During the Run-in Period – BUP3024

20.1 Patch Adhesion in the Run-in Period - BUP3024

	Total BTDS (N=2802)	BTDS 5 (N=779)	BTDS 10 (N=1302)	BTDS 20 (N=721)
Was there a problem with the patch adhesion?				
N (Number of Patches)	2802	779	1302	721
Yes	313 (11.2)	45 (5.8)	161 (12.4)	107 (14.8)
No	2489 (88.8)	734 (94.2)	1141 (87.6)	614 (85.2)

Note: Unit of summarization reflected in table header and summary statistics is patch. Denominator for percentages is number of patches.

Reference: Sponsor provided Table 20.1 from page 801 of ISE

Table 7.6.3: Patch Adhesion During the Double-blind Period – BUP3024

20.2 Patch Adhesion in the Double-blind Phase - BUP3024

	Total Placebo (N=3149)	Placebo TDS 10 (N=1579)	Placebo TDS 20 (N=1570)	Total BTDS (N=2777)	BTDS 10 (N=1366)	BTDS 20 (N=1411)
Was there a problem with the patch adhesion?						
N (Number of Patches)	3149	1579	1570	2777	1366	1411
Yes	269 (8.5)	122 (7.7)	147 (9.4)	297 (10.7)	109 (8.0)	188 (13.3)
No	2880 (91.5)	1457 (92.3)	1423 (90.6)	2480 (89.3)	1257 (92.0)	1223 (86.7)

Note: Unit of summarization reflected in table header and summary statistics is patch. Denominator for percentages is number of patches.

Reference: Sponsor provided Table 20.2 from page 802 of ISE

7.4.6 Immunogenicity

This product does not raise concerns regarding immunogenicity.

7.5 Other Safety Explorations

None

7.5.1 Dose Dependency for Adverse Events

The rate of discontinuations due to adverse events was dose related for some of the studies.

7.5.2 Time Dependency for Adverse Events

The incidence of nausea, constipation and application site erythema and application site pruritus were highest in the first 30 days. However, for application site erythema and application site pruritus the incidence continued to increase over time.

7.5.3 Drug-Demographic Interactions

There was no significant gender effect observed for Butrans with respect to the incidence of adverse events. There was no significant gender effect observed for Butrans pharmacokinetics.

Of the total number of subjects in chronic pain clinical trials (5,415), Butrans was administered to 1377 patients aged 65 years and older. Of those, 457 patients were 75 years of age and older. In the clinical program, the incidences of selected opioid-related AEs were higher in older subjects. In a single-dose study of healthy elderly and healthy young subjects treated with Butrans 10 mcg/h, the pharmacokinetics and safety outcomes were similar. In a separate dose-escalation safety study, the pharmacokinetics in the healthy elderly and hypertensive elderly subjects taking thiazide diuretics were similar to those in the healthy young adults. In the elderly groups evaluated, adverse event rates were similar to or lower than rates in healthy young adult subjects, except for constipation and urinary retention, which were more common in the elderly. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use.

7.5.4 Drug-Disease Interactions

Start patients with mild to moderate hepatic impairment with the Butrans 5 mcg/h dose. Thereafter, individually titrate the dose to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescriber. Butrans has not been evaluated in patients with severe hepatic impairment and should be administered with caution.

Since the pharmacokinetics of buprenorphine is not altered during the course of renal failure, Butrans use in patients with renal insufficiency, including dialysis patients, is possible

The potential for QT prolongation should be taken into account when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. For patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (eg, quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (eg, sotalol, amiodarone, dofetilide) consider the risk of adding Butrans treatment.

7.5.5 Drug-Drug Interactions

The reader is referred to Section 4.2 for information on drug-drug interactions

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

No studies done

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical trials in humans have been conducted assessing the effects of BTDS on reproduction, pregnancy or lactation.

During the clinical development program of BTDS, five subjects during the first trimester of their pregnancy were exposed to BTDS. The outcomes were as follows:

- Subject 15005 (BUP3024) BTDS exposure 24 days: normal healthy infant
- Subject 83012 (BUP3024) BTDS exposure 24 days: outcome not reported
- Subject 83011 (BUP3024) BTDS exposure 56 days: outcome not reported
- Subject 44002 (BUP3015) BTDS exposure 126 days: placental abruption; preterm C-section for nonviable female (no autopsy done)
- Subject 1234 (BUP1011) BTDS exposure 27 days: C-section at week 32 due to HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count). Premature baby girl intubated on ventilator x 3 days; hospitalized for 5 weeks prior to discharge home in good condition.

The applicant reported 13 postmarketing reports of pregnancies associated with the use of all buprenorphine formulations through 30-April-2009. There was one case of spontaneous abortion considered unrelated to buprenorphine, five healthy infants (1 requiring C-section, 1 with preterm bleeding), 1 ongoing pregnancy and no information provided on the remaining cases.

No definitive conclusions regarding the safety of BTDS during pregnancy can be made from the limited number of cases of pregnancy. BTDS should be labeled as a Pregnancy Category C drug as is buprenorphine.

7.6.3 Pediatrics and Assessment of Effects on Growth

The requirement for pediatric studies was deferred.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
The applicant used the preferred terms within the Standardized MedDRA Query (SMQ) Abuse, Dependence and Withdrawal to identify subjects with overdose. There were no cases of accidental or intentional overdose reported. There was one case (Subject 51012 study BUP3015) of respiratory depression, previously discussed in Section 7.3.2, occurring in a subject who was using a heating pad and concomitant benzodiazepines.

Although no cases of overdose were recorded during the development program the potential exists as with any opioid. In fact the large residual amount of buprenorphine remaining after use may result in overdose if the patch is abused.

Drug Abuse
Eleven (11) subjects were coded with an adverse event to "drug abuse." Of these 11 subjects, it was observed that 3 abused cannabis, 2 abused cocaine, 3 abused OxyIR, 2 abused Vicodin, and 1 abused Percocet/Soma. One subject who drowned tested positive for cocaine. As with all opioids the potential for abuse with a fatal outcome exists.

Withdrawal
A total of 17 subjects in the BTDS clinical development program were reported to have drug withdrawal syndrome including: 15 of 6042 (0.25%) BTDS-treated subjects and 2 of 1085 (0.18%) placebo-treated subjects. The applicant reports that withdrawal syndrome was never reported as an SAE but my search of the ISS dataset identified one subject (Subject 75019 Study BUP3019) coded as "Drug withdrawal syndrome" and described in section 7.3.2. This subject was hospitalized for withdrawal symptoms nine days after discontinuing treatment with BTDS 20 following a 5-month exposure. As with all opioids abrupt discontinuation of BTDS can result in withdrawal. The label adequately addresses the issue of potential withdrawal:

> When the patient no longer requires therapy with BuTrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically dependent patient; consider introduction of an appropriate immediate-release

opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The applicant reviewed the worldwide postmarketing experience for transdermal formulations of buprenorpine. BTDS, first approved 16-Jul-2003, is marketed in 11 countries by Purdue and associated companies as BuTrans, ResTiva, and Norspan. Another buprenorphine patch (Transtec) available as a 3- to 4-day patch in 35, 52.5, and 70 mcg/h strengths is marketed by Gruenenthal. The cumulative patient exposure for BTDS 5, 10 and 20 mcg/h from 16-Jul-2003 to 31-Jul-2008 was calculated by the applicant as approximately (b) (4) patient treatment days and the cumulative exposure for the Transtec buprenorphine patch, first approved in June 2000, was approximately (b) (4) patient treatment days.

The following analysis of the postmarket experience is obtained from the applicant's submission. The number of cases received through 30-Apr-2009 identified in the drug safety database (ARGUS) were as follows:

- 2,097 cases that involved BuTrans, Norspan, and all other buprenorphine formulations (excluding Transtec) reported 5,308 adverse events, of which 4,305 (81%) were considered non-serious.
- 829 cases that involved Transtec reported 2,177 adverse events, of which 871 (40%) were considered non-serious.

There were 46 deaths involving any formulation of buprenorphine:

- 11 due to drug or multi-drug abuse
- 2 due to cancer
- 12 elderly subjects with unspecified causes
- 9 from heart failure, cardiovascular disease, CVA, infections, multi-organ failure
- 8 end-stage cancer deaths
- 2 overdose in patients concomitantly treated with morphine
- 1 intentional suicide
- 1 pancreatitis in male with diffuse, bilateral cerebral cortical degeneration

A total of 32 cases of abuse and dependence were identified, 35 cases of overdose and 85 cases of drug withdrawal. There were 218 cases of application site reactions of which 178 cases involved BuTrans, Norspan and unknown formulations of transdermal buprenorphine.

Table 8.1 lists the most common adverse events and Table 8.2 lists the most frequently reported serious adverse events associated with BuTrans, Norspan, and all other buprenorphine formulations (excluding Transtec).

Table 8.1: Most Frequently Reported Postmarketing Adverse Events Through 30-Apr-2009 Associated with the Use of BuTrans, Norspan, and All Other Buprenorphine Formuations, Excluding Transtec

Preferred Term	No. of Cases
Application site erythema	442
Application site pruritus	355
Nausea	223
Application site rash	167
Application site reaction	159
Pruritus	116
Dizziness	114
Vomiting	110
Application site irritation	106
Somnolence	100
Skin reaction	90
Application site vesicles	88
Drug ineffective	88
Erythema	80
Hyperhidrosis	71

Reference: Table 5, page 737 of ISS

Table 8.2: Most Frequently Reported Postmarketing Serious Adverse Events Associated with the Use of All Buprenorphine Formulations (Excluding Transtec) Through 30-Apr-2009

Preferred Term	No. of Cases
Drug abuser [a]	60
Substance abuse [a]	53
Nausea	27
Somnolence	22
Confusional state	21
Vomiting	20
Dyspnoea	18
Withdrawal syndrome	16
Hallucination	15
Coma	14
Drug abuse [a]	14
Multiple drug overdose	13
Accidental exposure	12
Overdose	12
Hyperhidrosis	12
Drug withdrawal syndrome	11

(a) The majority of the reports of drug abuse and substance abuse were received via the RADARS System.

Reference: Table 6, page 738 of ISS

As expected for an opioid and consistent with the experience from the BTDS development program the most common adverse events were application site reactions, nausea, vomiting, somnolence and dizziness. The most common serious adverse events were related to drug abuse followed by nausea and somnolence.

Adverse Events of Special Interest
QT Prolongation
A query of the worldwide drug safety database through 30-Apr-2009 for postmarketing reports involving the MedDRA SMQ for QT prolongation in patients treated with any buprenorphinen formulation resulted in 33 cases.
Cardiac/Anngina
This subject's entire report is copied below:
GBR-2003-0000705 involved a 48-year-old male with a history of tobacco use and alcoholism who developed angina pectoris with ST elevation approximately 12 days after starting treatment with Transtec 35 mcg/h. Coronary angiography was negative. Transtec treatment wad discontinued and the symptoms and ST elevation resolved. The patient was rechallenged 2-3 weeks later with ½ buprenorphine patch and the angina pectoris and (slight) ST elevation recurred.

Elevated Liver Function Tests
There were 30 cases of drug-related hepatic disorders: 15 cases associated with transdermal buprenorphine formulations and 15 cases with nontransdermal formulations. Fourteen of the cases associated with nontransdermal formulations were due to hepatitis. The remaining case occurred in an overdose where the buprenorphine plasma level was more than 50-fold above therapeutic level. The applicant reports that with the exception of 1 case of jaundice, which contained limited information, all of the transdermal buprenorphine cases had alternate potential etiologies for the hepatic abnormalities including metastatic cancer and concomitant medications known to cause LFT abnormalities.

Neutropenia
A query of the worldwide drug safety database through 30-Apr-2009 for postmarketing reports involving any buprenorphine formulation for "ANC decreased", using the preferred terms from the Leucopenia SMQ (broad search), did not identify any cases.

Conclusion
The worldwide postmarket safety experience for buprenorphine is consistent with the safety profile of other opioids. The risk of abuse and overdose exists as with other opioids. There was no apparent signal for neutropenia. Elevated LFTs were noted but as is the case with the BTDS database it is unclear whether they were related to buprenorphine. From the BTDS development program it is already known that buprenorphine can mildly prolong the QT interval. The clinical significance of one subject reported to have developed ST elevation and angina with Transtec 35 mcg/h is unknown given the vast experience of opioids and buprenorphine.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

The labeling review is still ongoing by the Division. A Boxed Warning consistent with other opioids had been added to the label.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

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 A LEVIN
03/09/2010

ROBERT B SHIBUYA
03/09/2010

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 8, 2010

From: Mónica Fiszman, M.D., Ph.D.
CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Matt Sullivan
Regulatory Project Manager
Division of Division of Anesthesia, Analgesia and Rheumatology Products

Subject: QT-IRT Consult to NDA 21-306

This memo responds to your consult to us to analyze cardiac safety data submitted to this NDA, sponsored by Purdue Pharma. The QT-IRT received and reviewed the following materials:

- Your consult
- NDA 21-306 (original submission)
- Our review to TQT study report BUP1011 (23 Dec 2009)

QT-IRT Comments for Division

We reviewed the ECG data and adverse events related to QT prolongation for buprenorphine transdermal system. Data analyzed show a modest QT prolonging effect of BTDS at the highest therapeutic dose studied (20 mg). AEs and SAEs analyses suggest that BTDS has a minimal arrhythmogenic potential, if any, at the doses studied. Our conclusions are based on the following findings:

- In none of the groups analyzed mean changes from baseline in QTc were over 5.7 ms. This highest effect was seen in the BTDS 20 arm.
- There was a low incidence rate of AEs and SAEs related to E14 ICH Guidance even at the highest dose tested. The 'cardiac' AE clearly more seen on-drug was dizziness but was not necessarily linked to QT prolongation.

- MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration and arrhythmias did not detect any signal for AERS PTs of interest that may be associated with QT prolongation.

BACKGROUND

Purdue Pharma L.P. (Purdue) has developed the BuTrans™ [buprenorphine transdermal system (BTDS)] in 3 dosage strengths, 5 mcg/h, 10 mcg/h, and 20 mcg/h, to provide continuous systemic delivery of buprenorphine over a period of 7 days in patients with moderate to severe pain requiring continuous, around-the-clock opioid treatment for an extended period of time.

In November 13 2009 a TQT study report consult was submitted to the QT-IRT for review. The review concluded that buprenorphine prolongs QTcF at the supratherapeutic (40 mg). The present consult was submitted to the team to analyze cardiac safety data for NDA 21-306. ECG data and adverse events related to QT prolongation were analyzed.

CLINICAL STUDIES

Source: ISS- module 5, section 5.3.5.3; 2 Sept 2009
The Integrated Summary of Safety includes data from 35 studies completed by Purdue Pharma L.P. (PPLP) under IND 50,273 between July 1996 and March 2009 (the cut-off date for data inclusion from these studies is 05-Mar-2009). In these 35 completed studies, a total of 6,042 subjects were treated with BTDS, 5415 of the 6042 (89.6%) were treated in clinical studies of chronic pain, the intended indication. In double-blind periods, 2130 of the 5415 were exposed to BTDS, 995 received placebo, and 633 received other active controls (Oxy/APAP, OxyIR, HCD/APAP). Of the 3758 subjects who were exposed to double-blind treatment, 1568 (42%) received BTDS in an open-label extension period, which lasted at least 6 months.

Table 1-List of completed BTDS Clinical Studies Included and Integrated in the ISS

Clinical Studies (17 Studies)
Chronic Pain (15 Studies)
Completed Studies Included in NDA 21-306
BP96-0101, BP96-0102, BP96-0103 [a], BP96-0604, BP98-1201, BP99-0203
Completed Studies Not Available for Inclusion in NDA 21-306
BUP3002 (core and extension), BUP3011 (core and extension), BUP3012 (core and extension), BUP3014 (core and extension), BUP3015 (core and extension), BUP3018, BUP3019 (core and extension), BUP3024, BUP3201 (core and extension [BUP3202 in UK])
Nonchronic Pain (2 Studies)
Completed Studies Included in NDA 21-306
BP96-0104
Completed Studies Not Available for Inclusion in NDA 21-306
BUP2003
Clinical pharmacology studies (18 Studies)
Completed Studies Included in NDA 21-306
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1202, BP98-1204, BP99-0204
Completed Studies Not Available for Inclusion in NDA 21-306
BUP1002, BUP1009, BUP1011

[a] An open-label long-term safety study which enrolled subjects from studies BP96-0101, BP96-0102, BP96-0604.

Source: ISS, Table 1, page 32

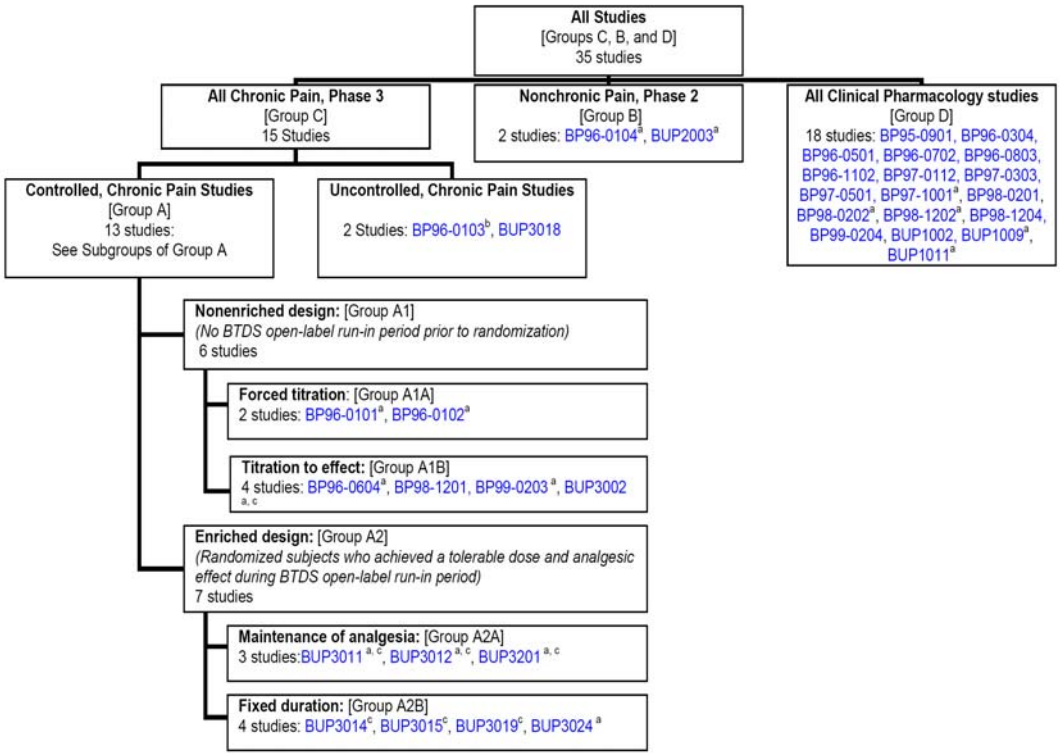
The 35 completed clinical studies included in the analyses are summarized below by study phase and design:

- Fifteen (15) controlled and uncontrolled, chronic pain, phase 3 studies
  - Thirteen (13) controlled, double-blind, multiple-dose phase 3 studies in subjects with chronic pain
    - Seven (7) of these 13 studies (BUP3002, BUP3011, BUP3012, BUP3014, BUP3015, BUP3019, BUP3201) had open-label extension periods
    - Subjects from 3 of the 13 studies (BP96-0101, BP96-0102, BP96-0604) were allowed to enroll in an open-label extension study (BP96-0103)
  - Two (2) uncontrolled studies in subjects with chronic pain
    - One (1) uncontrolled, open-label long-term phase 3 study (BP96-0103) enrolled subjects from 3 of the 13 controlled studies (BP96-0101, BP96-0102, BP96-0604)
    - One (1) uncontrolled, multiple-dose, double-blind phase 3 conversion study (BUP3018)
- Two (2) placebo-controlled, double-blind, single- and multiple-dose phase 2 studies (BP96-0104, BUP2003) in subjects with nonchronic pain (post-operative)
- Eighteen (18) controlled and uncontrolled, single- and multiple-dose clinical pharmacology studies.

Group C consists of all studies conducted in subjects with chronic pain and includes 13 controlled chronic pain studies, 1 uncontrolled study in which subjects were converted from Vicodin to BTDS and one open-label extension study in subjects with chronic pain (Figure 1 and

Table 1). The subjects in the studies of chronic pain (Group C), the intended indication, represent the majority of the BTDS-treated subjects in the safety population (90%; 5415 of 6042 subjects).

Figure 1- Overview of Analysis Groups and Designations



Source: ISS, Figure 1, page 40

[a] *Placebo-controlled studies.*

[b] *Subjects from studies BP96-0101, BP96-0102, BP96-0604 entered study BP96-0103.*

[c] *7 studies with extension periods were BUP3002, BUP3011, BUP3012, BUP3014, BUP3015, BUP3019, and BUP3201.*

Table 2- Number of Subjects Exposed to BTDS in the BTDS Clinical Development Program

Analysis group	Description of safety analysis group	Number of BTDS subjects
Completed clinical development program	**All studies - Groups C, B, D**	**6042**
Group C	Chronic pain studies	5415
Group B	Nonchronic pain studies	107
Group D	Clinical pharmacology studies	520

(Reference: ISS Appendix 11, Tables 1.1.3, 1.1.5, and 1.1.6).

Source: Summary of Clinical Safety, page 53, Table 4.

ECG analysis

ECG measurements consisted of heart rate, PR interval, QRS interval, RR interval, and QT interval, as well as corrected QT measurements using both Bazett's (QT/√RR) and Fridericia's (QT/3√RR) formulas (denoted QTcB and QTcF, respectively). In addition, morphological and rhythm abnormalities were evaluated.

For each ECG measurement, screening (baseline) values were calculated by averaging all ECG measurements obtained prior to the start of any treatment. Similarly, an average of all ECG tracings obtained at a specific post-screening visit was produced to obtain a single ECG measurement per visit. In addition, an overall average during double-blind exposure was calculated as the average of all available visit values or visit averaged values. The changes from screening to all post-screening visits and the overall average were calculated based on these averaged values. Analyses of ECG data include the presentation of summary statistics for each ECG measurement and for the change from screening in each ECG measurement at the following time-points: end of open-label run-in period; double-blind weeks 2, 4, and 12; end of double-blind period; and end of BTDS exposure.

For ECG analyses, the baseline was limited to screening evaluations.

Group A is composed of the non-enriched chronic pain studies (Group A1) and the enriched chronic pain studies (Group A2). Table 3 and Table 5 show ECG findings from Group A2.

Table 3-Mean Baseline ECG Values and Mean Changes from Baseline to the End of Open-Label Run-In Period and to the End of the Double-Blind Period of the Enriched, Chronic Pain Studies (Group A2)

	Open-label run-in period		Double-blind period											
	BTDS		Placebo		OxyIR		Total BTDS		BTDS 5		BTDS 10		BTDS 20	
ECG parameter	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean Change	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change
	N= 3710	NN= 1578	N= 496	NN= 476	N= 353	NN= 326	N= 1297	NN= 1212	N= 448	NN= 415	N= 210	NN= 203	N= 639	NN= 594
Heart rate (bpm)	69.8	0.4	69.0	2.1	72.1	-0.6	69.9	-0.4	70.3	0.3	68.4	-1.3	70.1	-0.6
QT (msec)	386.6	0.6	387.3	-4.8	383.5	3.6	386.3	3.2	386.2	0.3	388.0	3.9	385.9	4.9
QTcB (msec)	413.4	1.8	411.6	1.1	416.7	2.4	413.5	2.1	414.4	1.3	410.7	0.4	413.9	3.2
QTcF (msec)	404.0	1.4	403.2	-1.0	405.0	2.8	404.0	2.5	404.4	1.0	402.9	1.6	404.1	3.8

(References: Appendix 11, Tables 6.1.1 and 6.1.2).
N=number of subjects with a baseline.
NN=number of subjects with a baseline and postbaseline value.
Note: The baseline value is the value at screening. The mean changes were calculated based on the number of subjects who had ECGs at both baseline and the end of the open-label run-in or double-blind period.

Source: ISS, Table 136, page 341

Reviewer's comments: There were no changes from baseline in HR in BTDS treated groups. Slight changes from baseline in QTcF (3.8 ms BTDS 20) were seen compared to placebo. Those increases over baseline were slightly higher than those seen in the OxyIR arm.

Table 4 Summarizes the subjects with QTcB/QTcF interval values ≤500 ms at baseline and >500 ms during the open-label run-in and double-blind periods of the enriched, controlled, chronic pain studies (Group A2)

Table 4-Number (%) of Subjects with QT/QTc Interval Values >500 ms During the Open-Label Run-In and Double-Blind Periods of the Enriched Chronic Pain Studies (Group A2)

	Number (%) of subjects with QT/QTc interval values >500 msec						
	Open-label run-in period	Double-blind period					
ECG parameter	BTDS (N =1578)	Placebo (N=476)	OxylR (N=326)	Total BTDS (N=1212)	BTDS 5 (N=415)	BTDS 10 (N=203)	BTDS 20 (N=594)
QTcB	5 (0.3)	1 (0.2)	2 (0.6)	8 (0.7)	1 (0.2)	0	7 (1.2)
QTcF	3 (0.2)	0	1 (0.3)	4 (0.3)	0	0	4 (0.7)

(References: Appendix 11, Tables 6.3.1 and 6.3.2).
N=is the number of subjects who had at least 1 screening ECG and at least 1 ECG during the open-label run-in or double-blind period.

Source: ISS, Table 138, page 344

Reviewer's comments: In group A2 there were 4 subjects with QTcF >500 ms. All belonged to the BTDS 20 arm. Eight subjects had a QTcB >500 ms in the BTDS arm and one in the placebo arm.

Table 5- Summary of Subjects with Changes from Baseline of QTc > 30 ms but <= 60 ms and > 60 ms During Double-blind Population: Randomized Safety – Enriched, Controlled Studies (Group A2)

Change (msec)/ ECG Parameter/ Period	Placebo (N=496)			Oxy IR (N=353)			Total BTDS (N=1297)			BTDS 5 (N=448)			BTDS 10 (N=210)			BTDS 20 (N=639)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
>30 - <=60 msec																		
QTc, Bazett (msec)																		
Week 2	190	27	(14.2)	39	7	(17.9)	310	45	(14.5)	98	15	(15.3)	82	8	(9.8)	130	22	(16.9)
Week 4	328	48	(14.6)	282	45	(16.0)	961	158	(16.4)	331	54	(16.3)	145	15	(10.3)	485	89	(18.4)
Week 12	215	22	(10.2)	240	38	(15.8)	744	108	(14.5)	258	38	(14.7)	98	11	(11.2)	388	59	(15.2)
Overall	476	94	(19.7)	326	81	(24.8)	1212	282	(23.3)	415	99	(23.9)	203	31	(15.3)	594	152	(25.6)
QTc, Fridericia (msec)																		
Week 2	190	7	(3.7)	39	4	(10.3)	310	29	(9.4)	98	10	(10.2)	82	4	(4.9)	130	15	(11.5)
Week 4	328	18	(5.5)	282	21	(7.4)	961	114	(11.9)	331	38	(11.5)	145	13	(9.0)	485	63	(13.0)
Week 12	215	8	(3.7)	240	23	(9.6)	744	76	(10.2)	258	22	(8.5)	98	7	(7.1)	388	47	(12.1)
Overall	476	35	(7.4)	326	50	(15.3)	1212	196	(16.2)	415	68	(16.4)	203	21	(10.3)	594	107	(18.0)
>60 msec																		
QTc, Bazett (msec)																		
Week 2	190	0	(0.0)	39	0	(0.0)	310	0	(0.0)	98	0	(0.0)	82	0	(0.0)	130	0	(0.0)
Week 4	328	2	(0.6)	282	2	(0.7)	961	11	(1.1)	331	4	(1.2)	145	1	(0.7)	485	6	(1.2)
Week 12	215	3	(1.4)	240	2	(0.8)	744	7	(0.9)	258	3	(1.2)	98	0	(0.0)	388	4	(1.0)
Overall	476	5	(1.1)	326	4	(1.2)	1212	17	(1.4)	415	7	(1.7)	203	1	(0.5)	594	9	(1.5)
QTc, Fridericia (msec)																		
Week 2	190	0	(0.0)	39	0	(0.0)	310	0	(0.0)	98	0	(0.0)	82	0	(0.0)	130	0	(0.0)
Week 4	328	0	(0.0)	282	1	(0.4)	961	5	(0.5)	331	1	(0.3)	145	0	(0.0)	485	4	(0.8)
Week 12	215	0	(0.0)	240	0	(0.0)	744	2	(0.3)	258	1	(0.4)	98	0	(0.0)	388	1	(0.3)
Overall	476	0	(0.0)	326	1	(0.3)	1212	7	(0.6)	415	2	(0.5)	203	0	(0.0)	594	5	(0.8)

Note: Baseline is the average across all dates with ECG readings taken before the first dose, after averaging multiple tracings on a given date. N (denominator) is the number of subjects with ECG data both at baseline and during double-blind, and n is the number of subjects with at least one change (single tracing during double-blind minus baseline) in the specified range. ECG data were collected at week 2 in study BUP3012 only. ECGs were not collected for BUP3201.

Source: ISS, Table 6.2.2, page 6509

Reviewer's comments: Outliers data revealed a higher incidence in changes from baseline in QTcF and QTcB >30 ms in the BTDS arms compared to placebo.

The percentage of subjects with changes from baseline in QTcF >60 ms is nominally higher in the BTDS 5 and 20 arm than in the placebo arm, but it is neither statistically significant nor show any dose –response.

Group A2B is composed of the 4 enriched, fixed duration studies that were randomized, multiple-dose, double-blind, double-dummy, placebo/active-controlled, phase 3 studies in which the safety and efficacy of BTDS were evaluated in subjects with chronic back pain (2 studies) or chronic OA pain (2 studies). The study populations consisted of opioid-naive subjects in study BUP3024 and opioid-experienced subjects in the other 3 studies. Opioid-naive subjects were defined as those subjects not considered to be physically dependent on opioids at the time of study entry (as judged by study investigator). Subjects in these studies received BTDS during an open-label run-in period, prior to randomization into the double-blind period.

Table 6- QTcF Mean Changes from Baseline During Double-Blind Period in Group A2B - Randomized Safety Population

	QTcF mean changes in msec (SD) from baseline, by treatment				
Study	**BTDS 5**	**BTDS 10/20**	**BTDS 20**	**OxyIR 40 mg**	**Placebo**
BUP3014	+ 0.2 (11.71) (n=45)		+ 1.0 (11.24) (n=48)		
BUP3015	+ 1.0 (11.80) (n=195)		+ 4.5 (11.52) (n=202)	+ 2.4 (9.95) (n=209)	
BUP3019	+ 0.7 (11.77) (n=131)		+ 5.7 (13.00) (n=139)	+ 1.6 (11.57) (n=117)	
BUP3024		+ 2.7 (14.64) (n=240)			-1.0 (13.96) (n=268)

(References: Clinical Study Reports for BUP3014, BUP3015, BUP3019, BUP3024)
Note: Changes are from baseline at screening (in msecs) to the overall average of all double-blind values.

Source: ISS, Table 137, page 342

Reviewer's comments: In group A2B, mean changes from baseline in QTcF ranged from 1 to 5.7 ms (BTDS 20 mg). Very modest changes in mean QTcF from baseline were observed in the group treated with 5-mg BTDS and no changes were seen in the placebo group.

Table 7- Summary of Subjects with Changes from Baseline of QTc > 30 ms but <= 60 ms and > 60 ms. During Double-blind Population: Randomized Safety – Enriched, Fixed Duration Studies (Group A2B)

Change (msec)/ ECG Parameter/ Period	Placebo (N=283)			Oxy IR (N=353)			Total BTDS (N=1077)			BTDS 5 (N=404)			BTDS 10 (N=120)			BTDS 20 (N=553)		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
>30 - <=60 msec																		
QTc, Bazett (msec)																		
Week 2	35	6	(17.1)	39	7	(17.9)	147	22	(15.0)	54	7	(13.0)	19	1	(5.3)	74	14	(18.9)
Week 4	229	28	(12.2)	282	45	(16.0)	843	152	(18.0)	309	54	(17.5)	95	13	(13.7)	439	85	(19.4)
Week 12	192	17	(8.9)	240	38	(15.8)	715	107	(15.0)	258	38	(14.7)	82	11	(13.4)	375	58	(15.5)
Overall	268	49	(18.3)	326	81	(24.8)	1000	253	(25.3)	371	91	(24.5)	116	21	(18.1)	513	141	(27.5)
QTc, Fridericia (msec)																		
Week 2	35	3	(8.6)	39	4	(10.3)	147	12	(8.2)	54	4	(7.4)	19	0	(0.0)	74	8	(10.8)
Week 4	229	10	(4.4)	282	21	(7.4)	843	107	(12.7)	309	38	(12.3)	95	9	(9.5)	439	60	(13.7)
Week 12	192	6	(3.1)	240	23	(9.6)	715	75	(10.5)	258	22	(8.5)	82	7	(8.5)	375	46	(12.3)
Overall	268	20	(7.5)	326	50	(15.3)	1000	173	(17.3)	371	62	(16.7)	116	13	(11.2)	513	98	(19.1)
>60 msec																		
QTc, Bazett (msec)																		
Week 2	35	0	(0.0)	39	0	(0.0)	147	0	(0.0)	54	0	(0.0)	19	0	(0.0)	74	0	(0.0)
Week 4	229	2	(0.9)	282	2	(0.7)	843	11	(1.3)	309	4	(1.3)	95	1	(1.1)	439	6	(1.4)
Week 12	192	1	(0.5)	240	2	(0.8)	715	7	(1.0)	258	3	(1.2)	82	0	(0.0)	375	4	(1.1)
Overall	268	3	(1.1)	326	4	(1.2)	1000	17	(1.7)	371	7	(1.9)	116	1	(0.9)	513	9	(1.8)
QTc, Fridericia (msec)																		
Week 2	35	0	(0.0)	39	0	(0.0)	147	0	(0.0)	54	0	(0.0)	19	0	(0.0)	74	0	(0.0)
Week 4	229	0	(0.0)	282	1	(0.4)	843	5	(0.6)	309	1	(0.3)	95	0	(0.0)	439	4	(0.9)
Week 12	192	0	(0.0)	240	0	(0.0)	715	2	(0.3)	258	1	(0.4)	82	0	(0.0)	375	1	(0.3)
Overall	268	0	(0.0)	326	1	(0.3)	1000	7	(0.7)	371	2	(0.5)	116	0	(0.0)	513	5	(1.0)

Note: Baseline is the average across all dates with ECG readings taken before the first dose, after averaging multiple tracings on a given date. N (denominator) is the number of subjects with ECG data both at baseline and during double-blind, and n is the number of subjects with at least one change (single tracing during double-blind minus baseline) in the specified range. ECG data were collected at week 2 in study BUP3012 only.

Source: ISS, Table 6.2.4, page 6511

Reviewer's comments: Outliers data in study A2B revealed that in all BTDS arms the incidence of changes from baseline in QTcF >30 ms or >60 ms is higher than in the placebo group but it is neither statistically significant nor show any dose –response.

Adverse Events

-Adverse Events/Cardiovascular

Table 8. Incidence of Adverse Events During Double-blind Population: Randomized Safety – Enriched and Non-Enriched controlled studies (Group A)

MedDRA System Organ Class/ Preferred Term	Placebo (N=995) n (%)	Oxy/ APAP (N=150) n (%)	OxyIR (N=353) n (%)	HCD/ APAP (N=130) n (%)	Total BTDS (N=2130) n (%)
Subjects with at least one adverse event	532 (53.5)	129 (86.0)	255 (72.2)	95 (73.1)	1453 (68.2)
Cardiac disorders	18 (1.8)	4 (2.7)	5 (1.4)	6 (4.6)	42 (2.0)
Palpitations	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.5)
Tachycardia	1 (0.1)	1 (0.7)	1 (0.3)	3 (2.3)	8 (0.4)
Angina pectoris	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)	3 (0.1)
Atrial fibrillation	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Cardiac failure congestive	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Acute myocardial infarction	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Bradycardia	1 (0.1)	0 (0.0)	1 (0.3)	1 (0.8)	2 (0.1)
Cardiac flutter	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Atrioventricular block first degree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Bradyarrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Bundle branch block left	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Conduction disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Sinus bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (<0.1)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Cardiac disorders					
Atrial flutter	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorder	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Extrasystoles	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Silent myocardial infarction	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Sinus tachycardia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Wandering pacemaker	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Electrocardiogram T wave abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Electrocardiogram abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Electrocardiogram QT prolonged	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram T wave inversion	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	55 (5.5)	52 (34.7)	15 (4.2)	12 (9.2)	253 (11.9)
Syncope	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	3 (0.1)
Presyncope	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: ISS, Table 4.2.1.4, page 1781

Reviewer's comments: Incidence rate for syncope and presyncope were balanced with placebo in Group A. On the contrary, a double incidence rate for dizziness was seen in the BTDS arm compared to the placebo arm.

-Narratives

ICH E14 Subject Narratives for all BTDS-treated Subjects in all studies (Groups C, B and D). *From listed subjects, Table 3, ISS Appendix 1, page 437.*

Study BP96-0103, Patient 3310 (syncope): This 44-year-old black female entered the open-label extension study with ongoing pain syndromes due to osteoarthritis. The patient's medical history included: asthma, minor stroke, angina, hypertension, gastric ulcers/irritable bowel, reflux, gastritis, cholecystectomy, hysterectomy, cystitis, muscle spasms, osteoarthritis, fibromyalgia, diabetes, potassium deficiency, anxiety, and depression (unspecified dates). Concomitant medications taken during the study included: fosinopril, for hypertension; cyclobenzaprine for muscle spasms; etodolac, for osteoarthritis; insulin (regular), for diabetes; insulin, for diabetes; and Lasix, 40 mg for hypertension.

Patient was 14 days on BTDS 5 and then was up titrated to BTDS 10. In the 10th day on BTDS 10 mg had a syncopal episode. When recovered the subject continued on medication. The event was considered as moderate to severe. Other adverse events reported for this patient included: dry mouth, difficulty swallowing, itchiness at edges of patch, and drowsiness.

Reviewer's comments: It is possibly related to study drug. This patient was treating her diabetes with insulin, glucose levels are not reported.

Study BP96-0103, Patient 3315 (syncope-dizziness) 56-year-old white female entered the open-label extension and that same day experienced nausea, trembling/shakiness and was faint the same day that she started the extension period with 5 mg BTDS . Drug was interrupted and when reapplied the subject developed same episode as before. Other adverse events reported for this patient included: headaches, hyperactivity, insomnia, migraines, redness and burning and anxiety attacks. The event was mild.
Concomitant medications taken during the study included: simvastatin, for hypercholesterolemia; nefazodone, for depression; nizatidine, for gastric upset; and etodolac, 500 mg, for osteoarthritis.

Reviewer's comments: probably related to study medication since subject developed a similar episode after re-challenge. Since the subject reported several AEs consistent with the adverse-event profile of opioid analgesics, the syncopal episode may not be linked to QT-prolongation.

Study BP96-0101, Patient 6020, BTDS 20 (syncope) This 50-year-old white male had a medical history of hypertension; Reiter's syndrome; OA; degenerative joint disease - right hip; and Cushing's syndrome. Patient was on drug for 14 days, lower doses (5 and 10 mg BTDS). The event, drowsiness and constipation developed the same that was up-titrated to 20 mg. While re-challenge with BTDS 5 subject developed syncopal episode.

Reviewer's comment: The event is possibly related to study drug. Since the subject reported several AEs consistent with the adverse-event profile of opioid analgesics, the syncopal episode may not be linked to QT-prolongation.

Study BP96-0103, Patient 20304 - 76-year-old white female (death, Respiratory failure, Atrial fibrillation, Cardiac enlargement, Rapid ventricular response, Pulmonary edema, and [Pulmonary] bilateral infiltrates)
The patient's past medical and surgical history included: balloon angioplasty, hypertension, water retention, angina, carotid artery disease, gastroesophageal reflux disease (GERD), chronic depression, muscle aches, back pain, osteoarthritis, constipation, and polymyalgia rheumatica. Relevant baseline physical exam findings included bigeminal rhythm. After being 120 days on drug (BTDS 5 mg) the patient fell and was admitted to the emergency room with a lumbar fracture. The subject was subsequently admitted to the hospital after experiencing shortness of breath, and cardiogenic shock from an acute myocardial infarction. The patient was managed by cardio-pulmonary assist. While hospitalized an EKG and chest x-ray were performed, which noted acute myocardial infarction, atrial fibrillation, cardiac enlargement, rapid ventricular response, pulmonary edema, and [pulmonary] bilateral infiltrates, which were considered by the investigator to be severe and not related to study drug. One month later patient was discontinued

from study due to AEs and 4 days later patient experienced respiratory failure which lead to death.
The patient was taking the following medications from onset of study to onset of events: lansoprazole, propoxyphene/acetaminophen, furosemide, metoprolol, prednisone, nifedipine, docusate/senna, ticlopidine, calcium carbonate, diazepam, azathioprine and naproxen.

Reviewer's comments: It is important to note that the subject was on propoxyphene. The MI is probably not related to study medication and the rapid ventricular response could be part of this co-morbid state. The death is unrelated to study drug.

Study BP96-0103, Patient 22302 - 70-year old white male (stroke, syncopal episode/related to ventricular asystole, Heart block/ventricular asystole, cardiac arrhythmia, seizure).
Subject was previously enrolled in another BTDS study and no AEs were reported. Patient developed stroke and seizure 150 days after starting study drug. At the time of the event patient was on BTDS 20 mg. After the stroke the patient is being diagnosed of right vertebral artery stenosis of one arterial vertebra. Two hundred and fifty days later patient had a syncopal episode (related to ventricular asystole), heart block (ventricular asystole), and cardiac arrhythmia, which led to hospitalization, were considered by the investigator to be severe. At that time patient was on BTDS.
The patient's past medical and surgical history included: coronary artery bypass graft, abdominal aortic aneurysm repair/graft, transurethral resection of prostate excision basal cell cancer. Patient had a medical history of HTN, hypothyroidism, hypercholesterolemia.
The patient was taking the following medications from onset of study to onset of events: baby aspirin, dicyclomine, chlorzoxazone, isosorbide, clonazepam, lactulose, metoprolol, levothyroxine, nitroglycerin, fluvastatin and naproxen.

Reviewer's comments: The stroke episode is not related to study medication and probably linked to confounding co-morbidities (HTN, hypercholesterolemia, vascular disease). The syncopal episode may be related to heart block and ventricular asystole. Given the subject history of CV disease and time course of the event it is unlikely to be linked to study drug.

Study BP96-0604, Patient 6612, BTDS 60 –year- old white female (syncope): The patient's medical and surgical history included: migraines, sciatica, allergic rhinitis, Lyme disease, arthritis, cholecystectomy, herpes zoster, depression, non-insulin-dependent diabetes mellitus, cervical discectomy C5-6 and C6-7, hyperlipidemia, and vasopressor syncope.
Patients had vomiting while taking BTDS 10 for 16 days. One day after vomiting patient was uptitrated to BTDS 20. The event (nausea and heartburn) took place two days after up titration to 20 mg BTDS and required hospitalization. EKG during hospitalization did not reveal a cardiovascular cause. The patient was taking the following medications from onset of study to onset of event: propranolol, salsalate, and sertraline.

Reviewer's comments: These events are linked to study medication but probably are not of cardiac origin.

Study BUP3002S, Subject 0061: (Cardiac-respiratory arrest-Death). See below under **deaths while on study drug.**

Study BUP3002, Site 2179, Subject 74 (syncope) This 96 year-old white female entered the study with musculoskeletal pain of the right shoulder. The subject's medical history was significant for pneumonia treated with levofloxacin 500 mg QD and oxygen 1-3 L nasal canula continuous; congestive heart failure treated with furosemide 20 mg QPM and furosemide 40 mg QAM; complete AV block; degenerative joint disease/chronic tendonitis; Parkinson's-like syndrome; carcinoma of the breast; insomnia; and agitation treated with valproic acid 1 tablet QD. Subject had a syncopal episode same day of first dose of BTDS 5, moderate in severity. Concomitant medications included Vicodin, Di-gesic, zolpidem, Robitussin CM, and salbutamol.

Reviewer's comments: The temporal relationship suggests a drug effect. However, the case is confounded by co-morbidities and concomitant medications.

Study BUP3012S, Subject 36007 (syncope)
This is a 66-year-old, Caucasian female with left knee pain due to osteoarthritis, Patients was on study medication for 10 days with low doses of BTDS. Two days after she was up titrated to 20 mg BTDS subject had confusion, nausea and delirium. The event was mild to moderate and was possible related to study drug. The study drug was reduced to 10 mg BTDS and the dizziness resolved. When the subject began the extension phase, had another syncopal episode after 90 days on study drug. Cardiac telemetry was initiated to rule out arrhythmia and the subject was sent to ICU. Workup in the hospital revealed a left lateral intraventricular cerebral hemorrhage. The subject's past medical and surgical history included: migraine headaches, endometriosis, hysterectomy, appendectomy, osteoarthritis right knee, anemia, bladder tack cystopexy, sensitivity codeine-nausea, allergy penicillin-rash, breast cancer right breast, lumpectomy right breast, myopia, lens implants both eyes, scar tissue removal right breast, angina, hypercholesteremia, allergy levofloxacin, gastroesophageal reflux disease, left hip pain and hypertension.
The subject was taking the following medications at onset of study: tamoxifen, aspirin/ calcium carbonate/ alumina-magnesia, niacin, glucosamine/ chondroitin, mentholated aloe vera, and omeprazole.
The syncopal episode, seizure, right hip fracture, and left lateral intraventricular hemorrhage were considered to be serious adverse events, severe in intensity

Reviewer's comments: This subject developed two syncopal episodes. The first episode probably is related to study drug. The second episode was confounded with co-morbidities (left lateral intraventricular cerebral hemorrhage).

Study BUP3012S, Subject 27004 (syncope). A 64-year-old Caucasian male with a past medical history of asthma was enrolled for treatment of OA. The subject was treated with open-label BTDS for 5 days., ranzomized to placebo TDS for 7 days and then entered the open-label extension. At the open-label extension phase subject was taking fluticasone propionate, pirbuterol and rofecoxib. The same day that was placed on BTDS 5 the subject experienced vomiting, fainting, shortness of breath and dizziness mild to severe in intensity. Drug was discontinued and subject recovered from the episode.

Reviewer's comments: This mild to severe event was probably drug-related since it took place right after starting medication and subject recovered after discontinuation of study medication. No relevant medical history besides asthma.

Study BUP3015S, Subject 38027, 79-year-old Caucasian male (seizure disorder)
Subject has a relevant past medical history of hypertension and hypercholesterolemia (20 years) emphysema (14 yeas) CAD (6 years), with left ventricular dysfunction and obesity. The subject was on drug for a year before the event took place.
The subject began experiencing shaking, confusion, yawning and an episode of incontinence, was hospitalized Blood tests revealed a WBC count of 7,700 with 6% bands and 87% segs. Nonfasting blood glucose was 150. A CXR showed mild pulmonary vascular congestion. There was mild elevation of his BNP at 255 but no clinical evidence of heart failure on exam. ECG showed a paced rhythm without ischemic changes. A carotid Doppler was unremarkable with only mild plaque in the carotid arteries. A CT scan of his brain showed mild atrophy. An electroencephalogram was abnormal, compatible with toxic-metabolic insult versus deep seated midline lesions.
The subject was taking the following medications from onset of extension phase to onset of event: simvastatin, Lasix® (furosemide), potassium, Zantac® (ranitidine), Ditropan® (oxybutynin), metoprolol, and lisinopril.

Reviewer's comments: This event is probably linked to a morbid CNS state rather than to study drug.

BUP 3015, Subject 48008. Fatigue, Dizziness, Constipation, Nausea, Sleepiness,
A 73-year-old Caucasian male had a past history of HTN (24 years), hyperkalemia, COPD, pacemaker placement, T2DM, Atrial Fibrillation and CHF (1 year). Subject was on BTDS 10 for one day and had a prolonged QTc wave, considered to be mild and resolved the same day. Three days later subject was up titrated to BTDS 20. Four days later had nausea and vomiting. Another QTc prolongation was seen at the end-of study visit.
The subject was taking the following medications from onset of study to onset of events: levothyroxine, metoprolol, potassium chloride, tadalafil, aspirin, amiodarone, latanoprost, timolol and allopurinol.

Reviewer's comments: Subject reported nausea and vomiting that could be related to study drug. Regarding the QTc prolongation event, it could be linked to study drug however, it resolved without discontinuing study drug and at the time of the event the subject was taking several concomitant medications (levothyroxine and amiodarone) that can prolong QTc and hypokalemia related to vomiting. Another QTc prolongation took place while off drug.

Study BUP3015S, Subject 46002 (Acute Cardiac Death) See below **deaths while on study drug.**

Study BUP3015S, Subject 49009 (Chest Pain, Loss of Consciousness, Shortness of Breath)
A 56-year-old Caucasian male with medical history of epileptic seizures (7 years), heart stent placement (4 years)

Subject was on BTDS 10 for three days and then was up titrated to BTDS 20. One they after up titration the subject began experiencing drowsiness, considered mild.
The subject was taking the following medications from onset of extension phase to onset of events: carbamazepine, ranitidine, rabeprazole, vitamin B, multivitamin, simvastatin, and yohimbine.
Another AE took place ten days after finishing a 10-day amoxicillin course for an upper respiratory infection the subject experienced loss of consciousness, chest pain, and shortness of breath. At that time the subject had completed the double-blind phase and was on a treatment extension phase with open-label BTDS 10 (nausea and vomiting occurred while on BTDS 20 and subject was down titrated to BTDS 10). The event required hospitalization and was considered serious of moderate to severe intensity. The subject reported having increasing chest pain and pressure over the past 2 to 3 months without shortness of breath. ECG in the emergency room was read as junctional rhythm, other wise normal, but investigator disagree and stated that subject appeared to have a normal sinus rhythm. Cardiac enzymes, troponin and prothrombin time partial were normal. A slight hypokalemia was observed (3.4 mmol/L –normal 3.5-5.0). During the hospitalization, the subject also received enoxaparin; ranitidine; carbamazepine; simvastatin; potassium chloride; morphine; acetaminophen; nitroglycerin; and aspirin. One day after hospitalization the subject experienced angina and resolved after nitroglycerin. Subject continued for five more months with BTDS.

Reviewer's comments: The initial drowsiness that took place right after up titrating to BTDS 20 could be related to study medication, since the subject recovered right after decreasing the dose. The subject had a history of seizures and had a stent placed. The subject reported having several episodes that according to the description resemble angina. Therefore all the events that required hospitalization, i.e., loss of consciousness, chest pain, and shortness of breath are probably explained by the subject's preexisting conditions, i.e., responded to nitroglycerin administration. This event is probably not related to study drug.

Study BUP3019, Subject 33002 (Syncope) 53-year-old, Caucasian female with a recently diagnosed HTN and diabetes and intermittent vertigo.
The subject was taking the following medications at onset of study: methocarbamol, fluoxetine, acetaminophen with codeine No. 3, buspirone, glucosamine, acetaminophen/ isometheptene/ dichloralphenazone, fluticasone, albuterol, naproxen, calcium, hydroclorothiazide, diphenhydramine, piroxicam, omega 3, and multivitamin.
The subject began the screening period, and ECG results indicated septal MI V1, V2, (V3), and T wave flat. Nine days after, the subject began treatment for HTN, amlodipine/ benazepril. The same day the subject had an abnormal EKG (no results provided), which was considered mild, treated with a one-time dose of nitroglycerin, and normalized that day. The subject began treatment in the run-in period with open-label BTDS 10, and was provided ibuprofen or acetaminophen for use as sponsor-provided supplemental analgesia. That same day, ECG results indicated septal MI V1, V2, (V3), and T wave flat. Three days after, study drug was increased to BTDS 20. After three days of being on BTDS 20 the subject experienced syncope, which was considered mild in severity and resolved that same day.

Reviewer's comments: The subject had an abnormal ECG at screening and a recently diagnosed hypertension and was under new HTN medication, all confounding conditions. Still the syncopal episode could be an independent episode and related to the recent up titration with BTDS.

Study BUP3019S, Subject 42010 (QT Interval): 55-year-old, Caucasian female whose relevant past medical and surgical history included: asthma (50 years), hypothyroidism (21 years), hypertension (9 years), systolic ejection murmur (6 years), postmenopausal (2 years).
The subject was taking the following medications at onset of the open-label extension phase: fluticasone/ salmeterol, triamterene, levothyroxine, tocopherol (vitamin E), verapamil, and calcium chewables.
The subject was enrolled in the screening period (14-Jun-2004 to 21-Jun-2004), enrolled in opioid taper period (21-Jun-2004 to 29-Jun-2004), enrolled in run-in period and treated with open-label BTDS (29-Jun-2004 to 15-Jul-2004) and was randomized to BTDS (15-Jul-2004 to 07-Oct-2004) prior to entering the open-label extension phase.
On 07-Oct-2004, the subject entered the extension phase of the study and began treatment with open-label BTDS 5, increased to BTDS 10 on 10-Oct-2004, and then increased to BTDS 20 on 14-Oct-2004. On 24-Feb-2005, the subject was reported have a high QT interval, which was considered moderate in severity, and possibly related to study drug. That same day, the subject discontinued from the study and BTDS 20 due to a high QT interval, and the event was considered resolved.

ECG results:

Date	Time	QTc (Fridericia's) (milliseconds)	QTc (Bazett's) (milliseconds)	QT interval (milliseconds)
14-Jun-2004	16:45	478	496	446
14-Jun-2004	16:56	475	488	449
29-Jun-2004	16:37	449	461	427
29-Jun-2004	16:47	450	478	399
12-Aug-2004	15:55	525	521	533
12-Aug-2004	16:05	540	536	547
12-Aug-2004	16:15	525	521	534
12-Aug-2004	16:25	502	495	514
07-Oct-2004	15:45	468	470	465
07-Oct-2004	15:55	467	468	464
07-Oct-2004	16:05	472	473	469
07-Oct-2004	16:18	508	511	503
24-Feb-2005	15:51	514	519	505
24-Feb-2005	16:02	500	502	496
24-Feb-2005	16:12	486	482	495
24-Feb-2005	16:27	515	521	502

Reviewer's comments: Subject had a high baseline in the screening period and there was an increase in QTcF when was on study drug that resolved after discontinuing medication.

Study BUP3024, Subject 0020020 (syncope) 52-year-old, Asian / Indian male with no relevant past medical history. The subject was taking the following medications at the onset of the study: ibuprofen and benoxaprofen. One day after increasing the dose to BTDS 10 the subject began experiencing headache, lightheadedness, and syncope, all considered moderate and definitely related to study drug, and palpitations, considered moderate and probably related to study drug.

That same day the subject discontinued BTDS 10 due to syncope and the day after the headache, palpitations, and syncope resolved.

Reviewers' comments: This is probably related to study drug, syncope resolved after discontinuing study drug.

Study BUP3024, Subject 0039019 (Hypotension) 66-year-old, white female. The subject's relevant past medical and surgical history included: lower extremity edema (43 years), acid reflux (4 years), and hyperlipidemia (1 year). The subject was taking the following medications at the onset of the study: naproxen, omeprazole, triamterene/ hydrochlorothiazide, potassium, ezetimibe, and atorvastatin .
The subject entered the open-label run-in period and began treatment with BTDS 5. Two days later, she experienced hypotension (blood pressure value not given), considered severe. That same day, the subject discontinued BTDS 5 due to hypotension, the hypotension resolved

Reviewer's comments: This is probably related to study drug, hypotension resolved after discontinuing study drug.

Study BUP3024, Subject 0026009 (fainting spell-30 seconds) 51-year-old, white male; relevant past medical and surgical history recurrent migraine headaches. The subject was taking vitamin C. The subject entered the open-label run-in period and began treatment with BTDS 5. Four days later, the subject had a fainting spell that lasted for 30 seconds. The event was considered severe.

Reviewer's comments: Probably related to study drug, probably not related to QT prolongation.

Study BUP3024, Subject 0025001 (dizziness-QT prolong) 72-year-old, Asian male. The subject's relevant past medical and surgical history included: stable hypertension, angina, stable atrial fibrillation, coronary artery bypass graft, type 2 diabetes mellitus, and hyperlipidemia. The subject was taking the following medications at the onset of the study: ibuprofen, acetaminophen, atenolol, nitroglycerin skin patch, nitroglycerin, warfarin, lisinopril, simvastatin, aspirin, metformin, vitamin C, omega-3, 6, 9, antioxidant vitamins, herbal supplement, carrot juice, and multivitamin.
The subject entered the open-label run-in period and began treatment with BTDS 5. One day later, the subject began experiencing cold sweats, constipation, dizziness, and loss of appetite, all considered mild and definitely related to study drug, and nausea, considered moderate and definitely related to study drug. That same day, the subject discontinued BTDS 5 due to cold sweat, constipation, dizziness, loss of appetite, and nausea and one day later the cold sweats resolved. Four days later the constipation resolved but subject began experiencing a prolonged QT interval. That same day, the subject discontinued the study and completed end of study visit procedures. At the time of the end of study visit procedures, the prolonged QT was ongoing.

Subject: BUP3024/3556/1213A/0025001

Visit	Electrocardiogram Date	Electrocardiogram Time	QT interval (msec)	QTc (Bazett's) (msec)	QTc (Fridericia's) (msec)
Screening	31-Jul-2007	12:56	548	458	487
Screening	31-Jul-2007	13:04	554	463	492
Screening	31-Jul-2007	13:04	551	460.5	489.5
Visit 3	13-Aug-2007	16:45	600	519	545
Visit 3	13-Aug-2007	17:01	612	524	552
Visit 3	13-Aug-2007	17:01	606	521.5	548.5

Reviewer's comments: Subject had a QTcF interval prolonged at baseline. At the time of visit 3 the subject has discontinued BTDS 5 for 4 days. The QT prolonging effect could be related to study drug; however, the QT prolongation was ongoing after discontinuation of study drug.

Study BP96-0104, Patient 0079, BTDS 10 (ventricular tachycardia, respiratory failure, death)
90-year-old white female, undergoing knee surgery.
The patient's past medical and surgical history included: hypertension, cerebrovascular accident with right lower extremity weakness and minimal aphasia, chronic atrial fibrillation, soft systolic murmur. Baseline ECG findings recorded 9 days before the event noted coarse atrial fibrillation with a ventricular response of 63 and probable left ventricular hypertrophy with ST-T abnormalities.
The patient was taking the following medications from onset of study (post-surgery) to onset of event: morphine, atropine, cefazolin, docusate, metoprolol, ranitidine, nifedipine SL, bacitracin, and polymixin.
The patient began treatment with BTDS 10. That same day, the patient was started on hydrochlorothiazide, enoxaparin SC, famotidine IV, and furosemide. One day later, the patient experienced mild agitation, considered by the investigator not to be related to study-drug, that was treated with lorazepam 2 mg IV. One day later the patient experienced ventricular tachycardia and cardiac arrest, which were all judged by the investigator to be life threatening, serious adverse events, and severe in intensity. The patient was cardioverted back to atrial fibrillation and intubated. All the events resolved on the same day of onset, except for the respiratory failure. The patient was discontinued from study drug. A Swan-Ganz catheter was placed, which revealed evidence of congestive heart failure, with a pulmonary artery pressure of 60/18 and a capillary wedge pressure of 23. In addition, the patient was reported to have post-op anemia, post-op fever, and moderate acute oliguric renal failure. The post-op fever resolved the same day of onset. The acute renal failure was considered not related to study drug by the investigator. That same day, the postbaseline ECG findings included: atrial fibrillation with a ventricular response of 79 and diffuse ST-T abnormalities. Multiple CXRs post-cardiac arrest were suggestive of either atelectasis or left lower lobe infiltrate. One day after catetherization, an M-mode and 2-D echocardiogram revealed an ejection fraction of 25%. There was mild concentric left ventricular hypertrophy with diffuse hypokinesis, moderate pulmonary hypertension, decreased left ventricular compliance, mild mitral and tricuspid regurgitation and minimal aortic insufficiency. Post-cardiac arrest cardiac enzymes were consistent with a myocardial infarction. The patient was transfused several units of blood for her anemia.
After the cardiac arrest, medications given to the patient included: lidocaine IV, furosemide IV, albuterol via nebulizer, magnesium hydroxide/ cascara, potassium, metolazone, metoprolol, torsemide, lorazepam IV, dopamine IV, cefazolin IV, ceftriaxone IV, cefotaxime IV, and

acetaminophen. After 2 days total exposure to BTDS 10, and 5 days post-removal of patch, the patient died due to heart failure secondary to atrial fibrillation, respiratory failure, congestive heart failure, and acute renal failure. No autopsy was performed.

Reviewer's comments: This elderly subject underwent knee surgery and was taking morphine. Had a relevant medical history of HTN, cerebrovascular accident and chronic AF. Baseline ECGs confirmed AF and ST elevation. The ischemic episode can confound the ventricular tachycardia and cardiac arrest episodes that took place 2 days after receiving the first dose of BTDS 10. In addition, the subject had a low LVEF and pulmonary hypertension. The event is linked to an MI since cardiac enzymes were elevated after the cardiac arrest episode. The death is not temporally linked to study drug, as drug had been discontinued for 5 days. Cause of death was probably preexisting morbid conditions.

Study BP96-0104, Patient 0095 (paroxysmal supraventricular tachycardia) 83-year-old white male after undergoing right knee arthroplasty surgery.
The patient's past medical and surgical history included: apical infarct noted on thallium, remote myocardial infarction, hypertension, chronic left bundle branch block, heart murmur, coronary artery disease, and preoperative hyponatremia. Baseline ECG findings noted first degree AV block and left bundle branch block.
The patient was taking the following medications from onset of study (post-surgery) to onset of event: morphine, atropine, cefazolin, bacitracin, polymixin, lisinopril, and enoxaparin.
Five hours after taking ht first dose of BTDS 5 the patient had a mild syncope, 15 hours after this first dose had a paroxysmal supraventricular tachycardia that was treated with digoxin and resolved. Study drug was discontinued the same day.

Reviewers' comments: Based on timing of the events both, syncope and supraventricular tachycardia could be linked to study drug. Concomitant medications such as atropine may exacerbate supraventricular tachy-arrhythmias.

Study BP96-0501, Subject 0007 (syncope and shortness of breath)
This 33-year-old, Hispanic female, healthy volunteer entered the single dose, open-label, randomized, 4-treament, 4-period crossover, analytically blinded, PKPD study on 17-Jan-1997. Subjects received (BTDS 10 placed either at the midaxillary line, upper outer arm, upper chest, or upper back); each treatment was followed by a 10-day washout period.
The subject began treatment on 17-Jan-1997 and applied the BTDS 10 to the upper chest, after the 10-day washout period, on 03-Feb-1997; the subject applied the second BTDS 10 to the upper back.
On 04-Feb-1997, the subject experienced a syncope episode and shortness of breath; the duration of both events was 25 minutes and were considered by the investigator to be moderate in severity and probably related to study drug.

Reviewer's comments: This event is probably related to study drug.

-Deaths

A list of subjects who died at any point during the course of the completed studies and in the ongoing study, BUP3025, is presented in Table 9.
Eighteen (18) deaths occurred in the BTDS clinical program; 17 in all completed studies – Groups C, B, and D - and 1 in the ongoing chronic pain study (BUP3025). No deaths occurred in the clinical pharmacology studies (Group D). Two (2) of the 18 deaths occurred greater than 30 days after discontinuation of study drug; one (1) subject died during the screening period and never received study drug.

Table 9- Deaths in the BTDS Clinical Program, by Treatment at AE onset, and Cause of Death (Group C, B and D)

Study [a]/site/ subject	Age/ race/sex [b]	Cause of death (investigator term)	Last dose prior to adverse event onset	Exposure/days from discontinuation to death [c]	Relationship to study drug	Relevant medical history and/or adverse events
Deaths in BTDS treatment groups: Vascular/Cardiovascular						
BUP3011-0128A-0047005	70/W/M	Acute Myocardial Infarction (MI)	BTDS 20	24 / 2	No	Known coronary artery disease (CAD) and severe left ventricular dilation (EF25%)
BUP3002-0000Z-0000016	86/W/F	Acute MI	BTDS 10	14 / 3	No	Known CAD and congestive heart failure (CHF)
BUP3002-0000Z-0000118	91/W/F	Increased CHF	BTDS 10	43 / 6	No	Known CHF
BUP3015-0522A-0046002	74/W/M	Acute cardiac death	BTDS 20	416 / NA (receiving BTDS)	No	Known hypertriglyceridemia and cardiac conduction defect ; interim inferior MI
BUP3025-1413A-0093019 (study ongoing)	59/W/M	Hypertensive atherosclerotic cardiovascular disease	BTDS 20	16/ NA (receiving BTDS)	No	(+) tobacco, hypertension (HTN), hypercholesterolemia
BUP3002-0000Z-0000106	73/W/F	Bradycardia	BTDS 10	154 / 44	No	CHF, diabetes mellitus (DM) with neuropathy; interim sepsis and metabolic encephalopathy
BUP3002-0000Z-0000005	89/W/F	Cerebrovascular accident (CVA)	BTDS 20	21 / 9	No	CHF, HTN, hypercholesterolemia
BUP3002-0000Z-0000142	89/W/F	Cerebrovascular disease	BTDS 20	105 / 18	No	Known cerebrovascular disease with residual symptoms
BUP3019-0573A-0032004	64/W/F	Pulmonary embolism (PE)	BTDS 20	324 / 13	No	Past medical history (PMH) PE; warfarin discontinued during study.
Deaths in BTDS treatment groups: Cardiorespiratory						
BP960104-0000Z-0000079	90/W/F	Respiratory Failure	BTDS 10	2 / 5	No	PMH CVA; post-operative, with fever and renal failure
BUP3002-0000Z-0000061	77/W/F	Cardiac-Resp Arrest	BTDS 20	190 / NA (event during BTDS-treatment)	No	Known exertional dyspnea, HTN, Parkinson's
BP960102-0000Z-0020209 (BP960103-0000Z-0020304) [d]	76/W/F	Respiratory failure	BTDS 5	587 / 4	No	Known carotid artery disease s/p angioplasty
Deaths in BTDS treatment groups: Other						
BUP3201-0000Z-0000040	76/W/F	Failure to Thrive	BTDS 20	56/ 11	Yes	Other AEs include CHF

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Study [a]/site/ subject	Age/ race/sex [b]	Cause of death (investigator term)	Last dose prior to adverse event onset	Exposure/days from discontinuation to death [c]	Relationship to study drug	Relevant medical history and/or adverse events
BUP3015-0403A-0005043	25/W/F	Drowning, arrhythmia cocaine toxicity	BTDS 10	4 / NA	No	
BUP3018-0250A-0009019	64/W/M	Creutzfeldt -Jakob Disease	BTDS 20	6 / 20	No	Brain biopsy revealed Creutzfeldt-Jakob spongiform changes.
Deaths in non-BTDS treatment groups						
BP981201-0000Z-0003016	74/W/M	Heart attack, kidney failure, strangulated hernia, stroke	HCD/ APAP	22 / 35	Not specified	Known CHF, HTN
BUP3002-0000Z-0000011	78/W/M	Bilateral pneumonia, staph bacteremia	Placebo	12 / 3	No	PMH CHF, aspiration pneumonia and MRSA
BP960101-0000Z-0001139	71/W/M	NA	NA	Death during screening period		NA

(Reference: ISS Appendix 11, Table 4.5.1), and narratives in CSRs for BUP3011, BUP3002, BUP3015S, BUP3025, BUP3002S, BUP3019S, BP960104, BP960102, BUP3201S, BUP3015, BUP3018, BP981201, BP96-0101).

[a] Suffix "S" after study number denotes extension period.

[b] Age in years; W=White, F=Female, M=Male.

[c] Total days of exposure to drug, days from drug discontinuation to death.

[d] Subject ID switched from BP960102-0000Z-0020209 to BP960103-0000Z-20304 between controlled study BP96-0102 and extension study BP96-0103.

NA = Not available.

Source: Summary of Clinical Safety, page 74, Table 16

Four deaths occurred while subject on study drug.

Study BUP 3015, subject 5043. A 25-year old white female on treatment for 4 days with BTDS 10 mg, cause of death was cocaine cardiotoxicity and arrhythmia leading to drowning; not related.

Reviewer's comments: Not related to study medication.

Study BUP3002S, subject 0061- A 77-year old white female) on treatment for approximately 190 days, was on 5mg BTDS, cause of death was cardiac respiratory arrest (hospitalized with an acute myocardial infarction), had Parkinson's disease and HTN.

Reviewer's comments: probably not related to study medication.

Ongoing study BUP3025, subject #0093019-A 59-year white opioid-naive male with smoking history (45 pack a year), HTN and hypercholesterolemia received 5 mg BTDS for 3 days, 10mg BTDS for 12 days. He was found dead the day he took his first 20-mg dose. The cause of death was listed as hypertensive atherosclerotic cardiovascular disease, deemed not related to study medication.

Reviewer's comments: The subject had been on study drug for 15 days prior to the event and the transdermal patch was reportedly on the patient when he died and tested positive for buprenorphine. However, buprenorphine was not detected on toxicology testing (per forensic pathology report). The link to study drug could be controversial in this case.

Study BUP3015S, Subject 46002- A 74-year-old Caucasian male with a relevant medical history of tobacco use (for 24 years) HTN (12 years) hypertriglyceridemia. Screening ECGs results were first degree AV block and intraventricular conduction defect. The subject was also taking the following medications from onset of extension phase to onset of events: acetaminophen, candesartan/ hydrochlorothiazide, budesonide, dorzolamide/timolol, acetaminophen/diphenhydramine, aspirin/sodium bicarbonate/citric acid, and psyllium fiber. During the study (1 year after starting study medication) the subject was diagnosed with sigmoid colon cancer without evidence of metastasis which was resected. A nuclear stress test showed an ejection fraction of 46% and evidence of an inferior wall infarct without evidence of ischemia. Fourteen months after starting study drug subject experienced cardiac death. The subject remained on BTDS 20 up to the time of death. The acute cardiac event was ruled by the investigator as not linked to study drug and attributed to underlying atherosclerotic disease.

Reviewer' comments: Although the subject was on study drug at the time of the event there were confounding comorbidities (baseline conduction systems disease, MI with mild LV dysfunction) that can be also be linked to the cause of death.

MGPS Data mining Analysis

We performed an MGPS data mining analysis of AERS for Preferred Terms (PTs) related to changes in ECG intervals duration including PR, QRS and QT events and arrhythmias (please refer to the footnote below Table 10 for details on the PTs selected for analysis).
We detected no signals for Torsade and QT prolongation.

For other AERS PTs of interest that may be associated with QT prolongation, including T-wave abnormal, T-wave inversion, cardiac arrest and convulsion the signal scores were associated with EBGM values between 1 and 2 and EB05 values below 1. Similar results were seen with several bradycardia PTs with EB05 values slightly higher than 1.

Table 10-Data mining analysis

Generic name	Level 1	Level 2	PT	HLT	HLGT	SOC	N	EBGM	EB05	EB95	PRR
Buprenorphine	Oripavine Derivatives	Nerv	Bradycardia	Rate and rhythm disorders NEC	Cardiac arrhythmias	Card	25	1.61	1.15	2.21	1.68
Buprenorphine	Oripavine Derivatives	Nerv	Bradycardia foetal	Rate and rhythm disorders NEC	Cardiac arrhythmias	Card	4	2.64	1.15	5.42	21.1
Buprenorphine	Oripavine Derivatives	Nerv	Bradycardia neonatal	Rate and rhythm disorders NEC	Cardiac arrhythmias	Card	2	1.35	0.441	3.38	16.6
Buprenorphine	Oripavine Derivatives	Nerv	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	Cardiac arrhythmias	Card	31	1.34	0.993	1.78	1.48
Buprenorphine	Oripavine Derivatives	Nerv	Convulsion	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	54	1.05	0.836	1.30	1.32
Buprenorphine	Oripavine Derivatives	Nerv	Electrocardiogram T wave abnormal	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	1	1.02	0.238	3.15	3.16
Buprenorphine	Oripavine Derivatives	Nerv	Electrocardiogram T wave inversion	ECG investigations	Cardiac and vascular investigations (excl enzyme tests)	Inv	2	1.32	0.430	3.29	2.38
Buprenorphine	Oripavine Derivatives	Nerv	Sudden death	Death and sudden death	Fatal outcomes	Genrl	5	1.25	0.593	2.38	1.44

Notes	
ID:	2263
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	02/03/2010 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	02/14/2010 16:07:58 EST
User:	Monica Fiszman
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 02/03/2010 00:00:00 loaded on 2010-02-12 07:47:02.0
Dimension: 2 Selection Criteria: Generic name(Buprenorphine) + PT(Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Bifascicular block, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Cardiac arrest, Convulsion, Electrocardiogram Q waves, Electrocardiogram QRS complex prolonged, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electrocardiogram QT shortened, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave amplitude increased, Electrocardiogram T wave biphasic, Electrocardiogram T wave inversion, Electrocardiogram U wave inversion, Electrocardiogram U-wave abnormality, Electrocardiogram U-wave biphasic, Electrocardiogram abnormal, Electrocardiogram ambulatory abnormal, Electrocardiogram repolarisation abnormality, Hypokalaemia, Hypomagnesaemia, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Bifascicular block, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Cardiac arrest, Convulsion, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Hypokalaemia, Hypomagnesaemia, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia) Where: EBGM > 1.0	

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/

MONICA L FISZMAN
03/08/2010

NORMAN L STOCKBRIDGE
03/08/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	21-306
Brand Name	BuTrans
Generic Name	Buprenorphine
Sponsor	Purdue Pharma
Indication	Treatment of patients with pain requiring continuous opioid anaglesia
Dosage Form	Transdermal patch
Drug Class	Opioid analgesic
Therapeutic Dosing Regimen	5, 10, and 20-mg worn continuously for 7 days
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	Nov 11, 2009, SDN 089
Clinical Division	DAARP / HFD 170

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In this phase 1, randomized, placebo- and positive-controlled, parallel group, dose-escalating study, 132 healthy subjects were evenly and randomly divided into three groups stratified by gender: placebo, moxifloxacin (positive control), and Buprenorphine Transdermal System (BTDS) [included therapeutic (BTDS 10 mg) and supratherapeutic (2 x BTDS 20 mg) doses]. Subjects were evaluated on 2 baseline days (Days -2 and -1) and 2 treatment days (Day 6 and Day 13), with 13 time points on each day and 4 ECGs around each time point. The overall summary of findings is presented in Table 1.

The study failed to exclude a 10 ms increase in QT for both therapeutic and supratherapeutic dose levels. The upper 90% CI only was 10.9 ms at 13 hours postdose for BTDS 10 mg; however, the mean ΔΔQTc was less than 6 ms at all other timepoints. It is unlikely to be related to buprenorphine concentrations or its metabolites because the exposure is constant across the sampling times. The therapeutic dose of BTDS 10 mg is therefore considered to have no clinically meaningful effect on QT. For the 40-mg dose, the maximum mean ΔΔQTcF was 11 ms (upper 90%CI: 15 ms) at 2 hours postdose and exceeded the 10-ms threshold at 6 additional timepoints. This dose level provides a 2-fold exposure margin over the 20-mg dose, which is sufficient to cover the increased exposure for patients with severe renal impairment.

No significant relationship between buprenorphine concentrations and QTcI prolongation was identified. This finding is most likely because of the limited number of PK samples

collected at 1, 13, and 23.5 hours postdose and the limited range of concentrations within each subject.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BTDS (10 mg and 40 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Day	Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
6	BTDS 10 mg	13	7.2	(3.4, 10.9)
	Moxifloxacin 400 mg*	3	14.5	(10.4, 18.7)
13	BTDS 40 mg	2	10.6	(6.0, 15.3)
	Moxifloxacin 400 mg*	3	14.5	(10.4, 18.7)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment exceeded 5 ms.

1.2 ADDITIONAL QT-IRT COMMENTS

- Another consult for this NDA was submitted to the team to analyze cardiac safety data. ECG data and adverse events related to QT prolongation from clinical studies submitted to this NDA will be analyzed. This analysis will contribute with more updated clinical information than the one available for this consult.
- The numbers in the proposed label have been changed to sponsor's time-matched placebo corrected change from baseline analysis from sponsor's CSR Table 14.4.18.1 on page 511 instead of sponsor's average change from baseline analysis.
- There was a significant relationship between moxifloxacin concentrations and QTcI prolongation consistent with previous studies predicting a ΔΔQTcI of 11.6 ms (90% CI: 8.8-14.3 ms) at the geometric mean Cmax of 1820 ng/mL (1 hour postdose) following a single dose of 400 mg moxifloxacin. The reason for the exposure-response predictions being lower than those in Table 1 is most likely due to the PK sampling at 1, 13, and 23.5 hours postdose which is not optimal to capture the maximum moxifloxacin concentrations which occur 2-4 hours postdose.

2 PROPOSED LABEL

The sponsor proposed the following labeling under section 5 WARNINGS and section 12 Clinical Pharmacology of the label, and we have edited the label to reflect our concerns regarding BuTrans and QT prolongation. These recommendations are suggestions for labeling only and are open to modification pending further discussion with the review division. We defer all final labeling decisions to the review division.

5.6 Congenital or Acquired QT Prolongation

(b) (4)

12.2. Pharmacodynamics

3 BACKGROUND

3.1 MARKET APPROVAL STATUS

Buprenorphine is currently available in the U.S. in injectable and sublingual formulations. The Buprenorphine Transdermal System (BTDS) has been approved for use in Europe.

3.2 PRECLINICAL INFORMATION

From Katchman et al., 2002 JPET 303:688-694

Experimental assessment in stably transfected HEK 293 cells expressing high levels of the human HERG K^+ channel for the risk of buprenorphine on QT prolongation has shown that the IC_{50} for buprenorphine is in the range of 1-10 μM.

Reviewer's comment: Buprenorphine inhibits the hERG current with low affinity; the IC_{50} is ≥1000-times higher than the therapeutic Cmax exposure.

3.3 PREVIOUS CLINICAL EXPERIENCE

Summary of Cardiovascular Effects (IB, Edition 4, August 2002, page 49)

"Blood pressure: In the Phase 3 adequate and well-controlled studies, there were no clinically meaningful changes from baseline to end of study in mean systolic and diastolic blood pressure. The incidence of hypotension was ≤2% in the BTDS treatment

groups in the titration-to effect and forced-titration studies. Only 1 patient (<1%) in the BTDS group had both low and decreased systolic and diastolic blood pressure. This patient had a history of hypertension and hypothyroidism, and was receiving several different antihypertensive medications. There were no adverse events directly related to low or decreased blood pressure in these studies.

"There were no changes in mean systolic and diastolic blood pressure that met the criteria for orthostatic hypotension, defined as a decrease of ≥30 mm Hg in systolic blood pressure and of ≥15 mm Hg in diastolic blood pressure, when changing from recumbent to standing position.

"The effect of BTDS on blood pressure appears similar to that reported with another formulation of buprenorphine, Buprenex®, which has been associated with a 1% to 5% incidence of hypotension during clinical trials.

"Electrocardiograms: ECGs were evaluated in the Phase 1 and 2 clinical studies. Of the 627 patients evaluated, 5 subjects/patients (<1%) developed treatment-emergent ECG changes from baseline to the end of study. Included were 2 subjects receiving BTDS 10 who developed first-degree AV block (1 also with isolated PVCs); 1 subject receiving BTDS 10 with an inverted/flat T wave; 1 patient receiving BTDS 10 with minor, nonspecific ST-T wave changes (repeat ECG was normal); and 1 patient receiving BTDS 5 with ST-T wave abnormalities and more pronounced, asymmetric T-wave inversions inferiorly and anterolaterally, consistent with myocardial ischemia. ECG findings were associated with symptoms of respiratory failure in this patient, who had a history of cardiovascular disease at entry to the study. The patient recovered following these events.

"Pulse Rate: Throughout the clinical development program, there were no clinically meaningful changes from baseline to end of study in mean pulse rates. Changes in pulse rates among individuals were not considered clinically meaningful.

From Integrated Safety Summary:

"The Phase II/III BTDS clinical efficacy and safety program consists of 11 studies with 1708 unique BTDS-treated subjects: 338 from the titration-to-effect studies, 588 from the maintenance-of-analgesia studies, 312 from the forced-titration studies, 171 from an open-label safety study and 299 from other studies. The most common adverse events in BTDS-treated patients are events commonly reported with the use of opioids. Adverse events reported at an incidence of >10% in BTDS-treated subjects during the titration-to-effect studies were headache, constipation, nausea, vomiting, dizziness, somnolence, and pruritus at site. The incidence of opioid-related adverse events reported for BTDS-treated subjects was generally greater than placebo-treated.

"A total of 3 of 2168 (0.13%) BTDS-treated subjects died in the completed Phase I, II and III clinical studies; all were considered not related or improbably related to BTDS. No deaths were reported in any subject treated with a comparator (oxy/apap n =150, hcd/apap n =120 and placebo n =531; Phase II and III studies). Deaths in BTDS-treated subjects enrolled in the completed studies are summarized in Table 2

Table 2: Deaths in BTDS-treated subjects (completed Phase I, II and III studies)

Study	Invest	Pt	Age	Sex	Verbatim term	Preferred term (COSTART)	AE start (day)	Total BTDS exposure (days)	Last BTDS dose	Causality	Severity	Study drug Action	Outcome
BP96-0104	1215	79	90	F	Respiratory Failure	APNEA	1	1	BTDS 10	Not related	Severe	Med Discon.	Death
BP96-0103	1627	20304	76	F	Respiratory Failure	APNEA	+4	525	BTDS 5	Not related	Severe	None	Death
Clin0001	104	154	66	M	Myocardial Infarction	MYOCARDIAL INFARCTION	+1	30	BTDS 10	Improbable	Severe	None	Death

+ indicates number of days after last TDS removed that the event occurred

Source: Table 5.5.3.1.1

"A total of 9 subjects have died in the ongoing clinical studies (as of 15-Mar-04); all had causality assessed as not related to study-drug. Deaths in BTDS-treated subjects enrolled in the ongoing studies are summarized in Table 3.

Table 3: Deaths in BTDS-treated Subjects (Ongoing Studies up to 15-Mar-04)

Study	Invest	Pt	Age	Sex	Verbatim term	Preferred term (COSTART)	AE start (day)	Total BTDS exposure (days)	Last BTDS dose	Causality	Severity	Study drug Action	Outcome
BUP3002	2184	005	89	F	CVA	CEREBROVASCULAR ACCIDENT	+9	20	BTDS 20	Not related	Severe	None	Death
BUP3002	2179	016	86	F	Acute MI	MYOCARDIAL INFARCTION	13	13	BTDS 10	Not related	Severe	Med Discon.	Death
BUP3002	2179	118	91	F	Increased CHF	CONGESTIVE HEART FAILURE	35	35	BTDS 10	Not related	Severe	None	Death
BUP3002s	2186	061	77	F	Cardiac and respiratory arrest	CARDIAC ARREST	193	193	BTDS 20	Not related	Severe	None	Death
BUP3002s	2184	142	89	F	Cerebrovascular Disease	CEREBROVASCULAR DISEASE NOS	+18	129	BTDS 20	Not related	Severe	None	Death
BUP3002s	2247	106	73	F	Bradycardia	BRADYCARDIA NOS	+46	173	BTDS 10	Not related	Severe	None	Death
BUP3002s	2179	119	84	F	Nausea/vomiting, dehydration	NAUSEA/VOMITING, DEHYDRATION	+19	98	BTDS 10	Not related	Moderate	None	Death
BUP3201s	1807	40	76	F	Failure to thrive	CACHEXIA	39	43	BTDS 20	Improbable	Severe	Med Discon.	Death
BUP3018	2631	9019	64	M	Creutzfeldt-Jakob Disease	CREUTZFELDT-JAKOB DISEASE	5	5	**	Not related	Severe	Med Discon.	Death

+ indicates number of days after last TDS removed that the event occurred
** treatment blinded; subject was randomized to BTDS 10 or BTDS 20

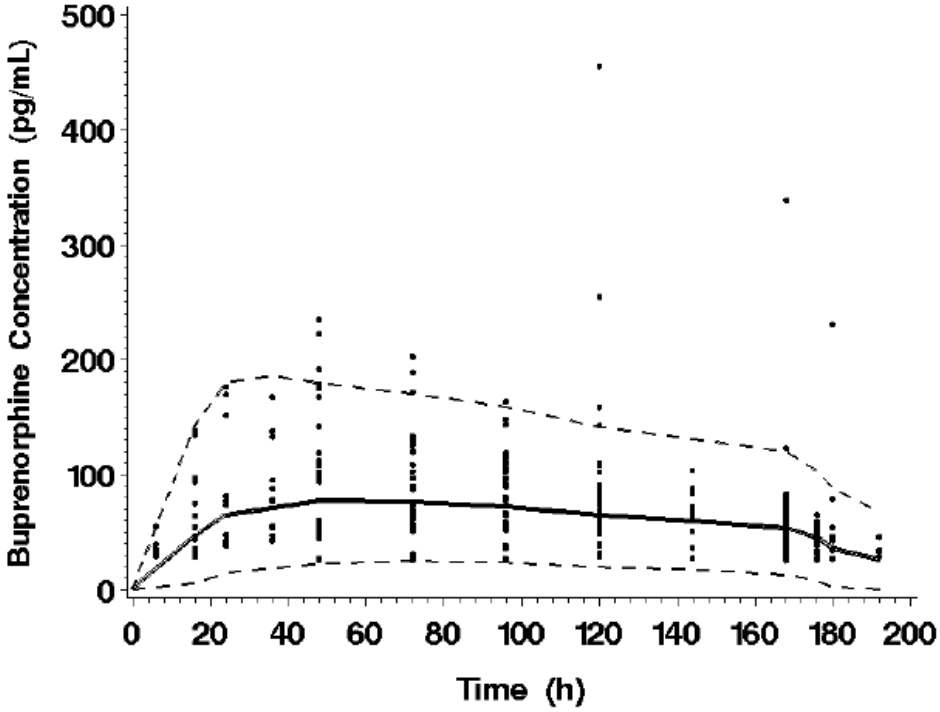
Source: Table 5.5.3.1.2

Reviewer's comments: In Phase 1 and 2 studies (up to August 2002) ECG abnormalities were reported with low frequency (<1%). No QTc prolongation was reported. Safety data as of 2004 revealed no syncope, seizures or ventricular arrhythmias. Twelve deaths were reported in patients receiving buprenorphine, all ruled by the investigators as not related or improbably related to study drug. No further information is available to establish/confirm cause of deaths.

Another consult for this NDA was submitted to the QT-IRT to analyze cardiac safety data submitted to the NDA. This analysis will contribute with more updated clinical information than the one available for this consult.

3.4 CLINICAL PHARMACOLOGY

The observed buprenophine concentration-time course following single 5-mg dose is shown below together with the population mean and 5th and 95th prediction interval.



Source: Figure 6 in Sponsor's Clinical Pharmalogy Summary on page 20

Appendix 6.1 summarizes the key features of buprenorphine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted a thorough QT study for review and the ECGs were submitted to the ECG warehouse. The QT-IRT did not review the study protocol.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Double-blind, Placebo- and Positive-Controlled, Parallel Group, Dose Escalating Study to Evaluate the Effect of Buprenorphine Delivered by the Buprenorphine Transdermal System (BTDS) at 10- and 40-mg Dose Levels on QT Intervals in Healthy Adult Volunteers

4.2.2 Protocol Number

BUP1011

4.2.3 Study Dates

02 Jul 2004 – 16 Dec 2004

4.2.4 Objectives

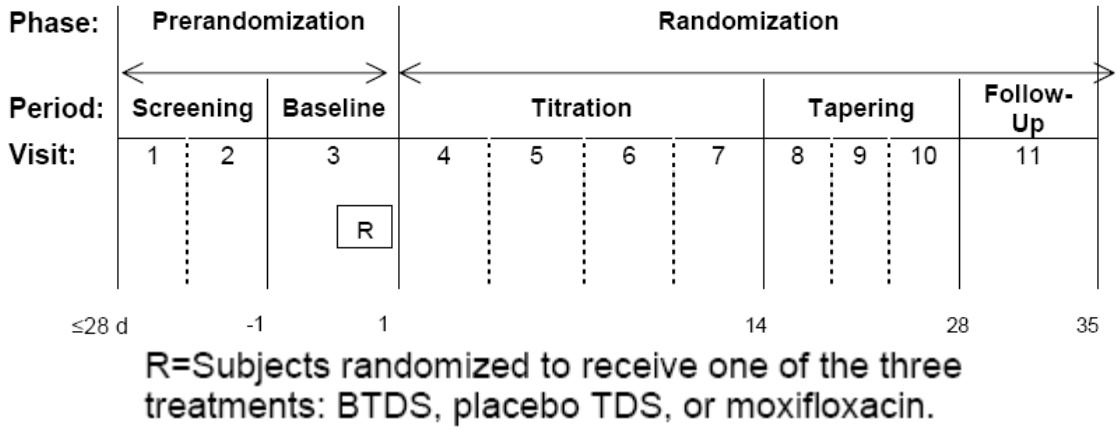
Primary: to evaluate the effect of 40-mg buprenorphine (supratherapeutic), delivered by BTDS, on QT intervals.

Secondary: to evaluate the effect of 10-mg buprenorphine (therapeutic), delivered by BTDS, on QT intervals, and to characterize the safety of BTDS dose escalation up to 40 mg in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 3-arm, placebo- and positive-controlled, parallel-design with dose-escalating from 5 to 40 mg.



4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was performed with the assignment to placebo and BTDS double blinded. Moxifloxacin treatment was open-label to subjects, the Investigator, and staff members at the study site. However, any personnel involved in the assessment of the digital ECG were blinded to all 3 treatments.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Group 1: BTDS (double-blind), BTDS 5 mg for 3 days, then BTDS 10 mg for 3 days, then BTDS 20 mg for 3 days, then 2 x BTDS 20 mg for 4 days

Group 2: Placebo TDS (double-blind)

Group 3: 400-mg oral moxifloxacin tablet on Day 6 and 13 (positive control, open-label)

4.2.6.2 Sponsor's Justification for Doses

"The BTDS dose levels evaluated were 10 mg (BTDS 10) and 40 mg (2 x BTDS 20) of buprenorphine. These dose levels were chosen based on the facts that the intended therapeutic doses for BTDS are 5, 10, and 20 mg and that titration is usually necessary for the 10 and 20 mg doses to be tolerated by opioid-naïve patients. Thus 2 x BTDS 20 is a supratherapeutic dose. Dose levels above 40 mg were not evaluated because of the lengthy titration and tapering times that would be needed, resulting in extended exposure to the subjects and likely an increased dropout rate."

Reviewer's Comment: The selected BTDS dose levels of 10 and 40 mg are adequate. The supra-therapeutic dose of 40 mg was tested in this study which is 2-fold higher than the therapeutic dose of 20 mg, produces 5.6-fold higher exposures compared to 10-mg, and covers the worst case clinical exposure scenario of 1.2-fold higher mean concentrations for patients with severe renal impairment.

4.2.6.3 Instructions with Regard to Meals

Doses will be administered without food. Meals are to be consumed and doses taken at the same time on each occasion.

Reviewer's Comment: Instructions with regard to meals are not important because transdermal route of administration.

4.2.6.4 ECG and PK Assessments

Table 4: ECG and PK Assessments.

Study Day	-2 - -1	6	13	14 - 28
Intervention	No treatment (Baseline)	10 mg	40 mg	Dose tapering
12-Lead ECGs	Record ECGs[###]	Record ECGs[###]	Record ECGs[###]	None recorded
PK Samples for drug	None collected	Collected[***]	Collected[***]	None collected

[###]0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 7, 10, 13, 18, and 23.5 h postdose
[***]1, 13, and 23.5 h postdose

Reviewer's Comment: The ECG and PK assessments are adequate to capture the QT effect at steady-state buprenorphine (and metabolite) concentrations since no distinct peak is expected for this route of administration. The sampling is however not optimal to capture the Cmax of moxifloxacin which occurs 2-4 hours postdose.

4.2.6.5 Baseline

The sponsor used the time-averaged baselines over both pre-treatment days (Day -2 and Day -1) in their primary analyses. They also considered time-matched baselines in their exploratory analyses.

Reviewer's comment: For a parallel study, we recommend using time-matched baseline for the analysis. This reviewer's independent analysis results based on time-matched baseline (using Day -1) are presented in Section 5.2.

4.2.7 ECG Collection

Digital ECG recordings were used for QT/QTc evaluations. Mortara H-12 digital recorder was used to record data. There were four 24-h recording periods: during screening at visit 2, baseline on Day -1, Day 6, and Day 13. Lead II was used as the default lead. A cardiologist blinded to all three treatments provided over-read for the digital information.

Standard 12-Lead ECGs will be obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 132 subjects (64 males and 68 females, 12 to 64 year old, 19 to 33 BMI) were randomized. Table 5 summarizes the disposition of the 132 subjects.

Table 5: Subject Disposition and Reasons for Discontinuation: Randomized Population

	Treatment Groups			
Category	Placebo (N=44)	Moxifloxacin (N=44)	BTDS (N=44)	Combined Total (N=132)
Completed, n (%)	44 (100)	41 (93)	41 (93)	126 (95)
Discontinued, n (%)	0	3 (7)	3 (7)	6 (5)
Reason for discontinuation	n (%)	n (%)	n (%)	n (%)
Adverse event[a]	0	1 (2)	2 (5)	3 (2)
Subject's choice	0	2 (5)	1 (2)	3 (2)
Lost to follow-up	0	0	0	0
Protocol violation	0	0	0	0
Administrative	0	0	0	0

[a] Documented on an adverse event case report form. These could include clinical or laboratory adverse events and changes in ECGs or vital signs (see Section 12 for additional details on these subjects).
Cross reference: Table 14.1.1 and Appendix 16.2.1.

Source: Sponsor's CSR Table 6 on Page 51.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary variable for comparison was the average difference between the mean of non-missing replicate QTcI at each time point on baseline vs. Day 13. A significant difference between moxifloxacin and placebo, using a 90% confidence interval, was necessary to demonstrate adequate sensitivity for the study. BTDS was also compared to placebo. For these analyses, ANCOVA was used, with the baseline QTcI averaged over both pretreatment days as a covariate, and with sex and treatment as effects. The full analysis population for ECG was used. The QTcI was calculated by using linear regressions of QT on RR pre-treatment values. The sponsor's results for the study drug and assay sensitivity are presented in Table 6 and Table 7, respectively. The sponsor also

performed exploratory analysis using time-matched baselines for each study time point. The results are presented in Table 8. In this analysis, the largest upper bound of the 90%CI supratherapeutic BTDS dose (2 x BTDS 20) group was 15.5 ms, exceeding the 10-ms threshold in the ICH E14 guideline.

Table 6: Statistical Analysis of Average QTc Interval Change from Baseline (ms) for BTDS and Placebo

Type of QTc	Visit* (Study Day)	Group	LS Means of QTc change	Comparison	Difference of LS Means	90% CI	*P* value
QTci	Visit 5 (Day 6)	BTDS	-1.06	BTDS vs Placebo	0.39	(-1.8, 2.6)	0.770
		Placebo	-1.46				
	Visit 7 (Day 13)	BTDS	4.20	BTDS vs Placebo	5.91	(3.4, 8.4)	0.000
		Placebo	-1.71				
QTcb	Visit 5 (Day 6)	BTDS	-0.37	BTDS vs Placebo	-0.13	(-2.9, 2.6)	0.936
		Placebo	-0.24				
	Visit 7 (Day 13)	BTDS	6.31	BTDS vs Placebo	7.16	(4.2, 10.1)	0.000
		Placebo	-0.86				
QTcf	Visit 5 (Day 6)	BTDS	-1.04	BTDS vs Placebo	1.29	(-1.4, 4.0)	0.427
		Placebo	-2.33				
	Visit 7 (Day 13)	BTDS	4.13	BTDS vs Placebo	6.01	(3.2, 8.8)	0.001
		Placebo	-1.88				

Cross reference: Table 14.4.7.1.
QTci=QT individual correction; QTcb=QT Bazett's correction; QTcf=QT Fridericia's correction.
* For BTDS treatment group, dose at Visit 5 was BTDS 10 (10 mg), dose at Visit 7 was 2 x BTDS 20 (40 mg).
For the above analyses, ANCOVA was used with baseline as covariate and with sex and treatment as effects.
Source: Sponsor's CSR Table 14 on Page 70.

Table 7: Statistical Analysis of Average QTc Interval Change from Baseline (ms) for Moxifloxacin and Placebo

Type of QTc	Visit* (Study Day)	Group	LS Means of QTc change	Comparison	Difference of LS Means	90% CI	*P* value
QTci	Visit 5 (Day 6)	Moxifloxacin	6.26	Moxifloxacin vs Placebo	7.64	(5.4, 9.9)	0.000
		Placebo	-1.38				
	Visit 7 (Day 13)	Moxifloxacin	4.17	Moxifloxacin vs Placebo	5.86	(3.3, 8.4)	0.000
		Placebo	-1.69				
QTcb	Visit 5 (Day 6)	Moxifloxacin	8.13	Moxifloxacin vs Placebo	8.23	(5.5, 10.9)	0.000
		Placebo	-0.09				
	Visit 7 (Day 13)	Moxifloxacin	6.55	Moxifloxacin vs Placebo	7.40	(4.3, 10.5)	0.000
		Placebo	-.084				
QTcf	Visit 5 (Day 6)	Moxifloxacin	4.74	Moxifloxacin vs Placebo	6.86	(4.2, 9.6)	0.000
		Placebo	-2.12				
	Visit 7 (Day 13)	Moxifloxacin	2.83	Moxifloxacin vs Placebo	4.68	(1.9, 7.4)	0.006
		Placebo	-1.85				

Cross reference: Table 14.4.7.2.
QTci=QT individual correction; QTcb=QT Bazett's correction; QTcf=QT Fridericia's correction.
* For moxifloxacin treatment group, doses at visit 5 and 7 were 400 mg.
For the above analyses, ANCOVA was used with baseline as covariate and with sex and treatment as effects.

Source: Sponsor's CSR Table 15 on Page 71.

Table 8: Upper Bounds of 90% CI for Placebo-Corrected, Time-Matched Change from Baseline QTcI (ms) for Moxifloxacin and BTDS

Time Point (h)	Moxifloxacin Day 6	Moxifloxacin Day 13	BTDS 10 Day 6	2 x BTDS 20 Day 13
0	5.1	4.4	2.2	10.4
0.5	5.1	5.0	2.1	10.4
1.0	14.6	**15.5**	3.9	10.4
1.5	13.4	11.9	4.3	10.4
2	15.5	14.0	7.6	**13.3**
2.5	16.8	13.1	3.2	8.1
3	**17.0**	14.8	3.0	11.2
4	13.8	14.2	5.8	12.0
7	9.5	6.7	3.7	9.1
10	8.2	7.9	2.0	9.7
13	10.4	8.7	**10.0**	8.4
18	9.9	6.9	3.7	7.8
23.5	11.8	7.2	5.2	9.4

Source: Sponsor's CSR Table 16 on Page 74.

4.2.8.2.2 Categorical Analysis

The sponsor's outlier analysis of ECG data included QTcI ≥500 ms and with changes in QTcI (compared to baseline) ≥30 ms and ≥60 ms. No subjects had a QTcI≥500 ms. Comparisons of all QT and QTc values with baseline are presented in Table 9.

Table 9: Number and Percentages of Subjects with QT/QTc Maximum Prolongation ≥30 ms, ≥60 ms

		Placebo			Moxifloxacin			BTDS		
Type of QT	Visit* (Study Day)	N	≥30 & <60 n (%)	≥60 n (%)	N	≥30 & <60 n (%)	≥60 n (%)	N	≥30 & <60 n (%)	≥60 n (%)
QT	Visit 5 (Day 6)	44	18 (40.9)	2 (4.5)	43	22 (51.2)	7 (16.3)	44	19 (42.3)	3 (6.8)
	Visit 7 (Day 13)	44	13 (29.5)	6 (13.6)	41	25 (61.0)	2 (4.9)	44	15 (34.1)	7 (15.9)
QTci	Visit 5 (Day 6)	44	5 (11.4)	0	43	6 (14.0)	0	44	2 (4.5)	0
	Visit 7 (Day 13)	44	1 (2.3)	0	41	5 (12.2)	0	44	3 (6.8)	0
QTcb	Visit 5 (Day 6)	44	8 (18.2)	0	43	14 (31.8)	1 (2.3)	44	4 (9.1)	0
	Visit 7 (Day 13)	44	9 (20.5)	0	41	19 (43.2)	0	44	12 (27.3)	0
QTcf	Visit 5 (Day 6)	44	4 (9.1)	0	43	11 (25.0)	0	44	5 (11.4)	0
	Visit 7 (Day 13)	44	2 (4.5)	0	41	9 (20.5)	0	44	7 (15.9)	0

Cross reference: Table 14.4.9.4 and Appendix 16.2.10.2

QTci=QT individual correction; QTcb=QT Bazett's correction; QTcf=QT Fridericia's correction.

* For BTDS treatment group, dose at Visit 5 was BTDS 10 (10 mg), dose at Visit 7 was 2 x BTDS 20 (40 mg).

Source: Sponsor's CSR Table 17 on Page 76.

4.2.8.3 Safety Analysis

Adverse events were more frequently reported in subjects receiving BTDS (98%) than placebo (70%). Gastrointestinal and central nervous system disorders were most common: nausea, constipation, vomiting, headache, and dizziness were reported in more than a third of subjects in the BTDS group, consistent with the adverse-event profile of opioid analgesics. In both the BTDS and placebo groups, pruritus at the application site was also frequently reported. No adverse events were considered severe and, the majority, were reported as mild.

Overall, the incidence of adverse events considered by the Investigator to be possibly, probably, or definitely related to study drug was greater in subjects who received BTDS than in those who received placebo. Incidence of nausea judged by the investigator to be possibly related to treatment was higher in the BTDS group (59%) than the placebo group (9%). A total of 1 subject (treated with moxifloxacin) was reported to have a serious adverse event – an induced abortion requiring hospitalization.

A total of three subjects experienced adverse events that resulted in discontinuation. Two subjects in the BTDS group discontinued: one for urinary retention and another for vomiting.

No deaths were reported during the study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Blood samples were drawn after 2 to 3 days of BTDS application to characterize steady-state plasma concentrations of buprenorphine and metabolites. The plasma concentrations of buprenorphine, nor-buprenorphine, buprenorphine-3-glucuronide, and nor-buprenorphine-glucuronide, and moxifloxacin are presented Figure 1 and summarized in Table 10 for subjects receiving BTDS and moxifloxacin.

The concentration of buprenorphine increased in a dose-dependent fashion, and the concentration of its metabolites increased with increasing doses of buprenorphine, as expected, with the exception of buprenorphine-3-glucuronide, which was not present in sufficient quantities to yield meaningful results. The metabolite present in greatest quantities was nor-buprenorphine-glucuronide.

Table 10. Summary Statistics of Plasma Concentrations for BTDS Treatment Group.

Buprenorphine (pg/mL)

	BTDS 10mg			BTDS 20mg	BTDS 40mg		
Summary Statistics	49-hr	61-hr	72-hr	72-hr	73-hr	85-hr	96-hr
n	44	44	44	44	44	44	44
Mean	136.23	131.53	162.78	355.22	829.68	708.79	712.84
SD	76.555	73.187	88.120	172.230	353.775	331.255	348.931
Median	117.53	115.56	144.89	334.45	793.63	660.41	626.00
Min	20.5	0.0	26.1	58.3	238.8	214.7	228.4
Max	305.0	262.5	388.8	774.5	1671	1790	2185

Nor-buprenorphine (pg/mL)

	BTDS 10mg			BTDS 20mg	BTDS 40mg		
Summary Statistics	49-hr	61-hr	72-hr	72-hr	73-hr	85-hr	96-hr
n	44	44	44	44	44	44	44
Mean	26.33	28.79	40.24	95.85	210.74	216.37	224.61
SD	28.263	29.039	33.572	72.596	158.659	127.715	130.953
Median	24.25	27.22	38.23	80.40	180.04	182.70	202.48
Min	0.0	0.0	0.0	0.0	20.9	30.5	51.9
Max	99.6	130.4	138.4	352.4	911.9	537.5	580.2

Buprenorphine-3-Glucuronide (pg/mL)

	BTDS 10mg			BTDS 20mg	BTDS 40mg		
Summary Statistics	49-hr	61-hr	72-hr	72-hr	73-hr	85-hr	96-hr
n	44	44	44	44	44	44	44
Mean	0.00	0.00	0.00	3.04	15.91	19.61	9.98
SD	0.000	0.000	0.000	20.161	88.148	67.410	49.772
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Max	0.0	0.0	0.0	133.7	573.9	324.3	304.6

Nor-Buprenorphine-3-Glucuronide (pg/mL)

	BTDS 10mg			BTDS 20mg	BTDS 40mg		
Summary Statistics	49-hr	61-hr	72-hr	72-hr	73-hr	85-hr	96-hr
n	44	44	44	44	44	44	44
Mean	30.95	34.13	72.49	285.90	819.23	756.16	846.68
SD	81.861	84.862	136.399	259.713	618.765	574.108	509.612
Median	0.00	0.00	0.00	244.40	699.12	622.66	731.59
Min	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Max	312.1	342.1	582.1	990.6	3587	2781	2244

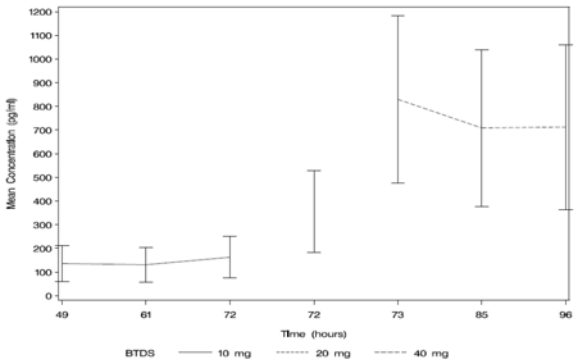
Moxifloxacin (ng/mL)

	Visit 5 (Day 6)			Visit 7 (Day 13)		
Summary Statistics	49-hr	61-hr	72-hr	73-hr	85-hr	96-hr
n	43	43	43	41	41	42
Mean	1812.3	840.19	422.81	1883.9	869.10	475.71
SD	559.911	188.372	98.600	497.321	199.954	180.419
Median	1750.0	831.00	430.00	1850.0	812.00	463.50
Min	240.0	186.0	110.0	348.0	442.0	0.0
Max	2970	1270	706.0	2940	1290	1160

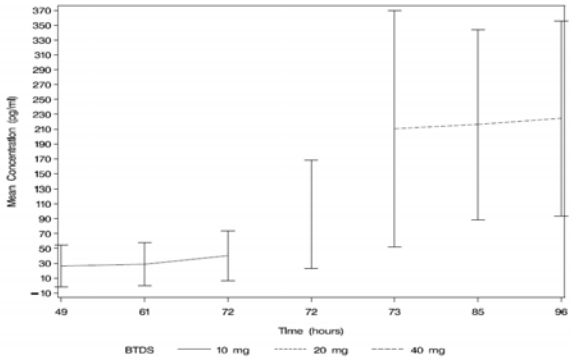
(Source: Tables 14.4.1.1 – 14.4.1.5 on pages 451-455 of BUP1011 study report)

Figure 1: Mean (± SD) Plasma Concentration-Time Profiles of Buprenorphine (Top Left), Nor-buprenorphine (Top Right), Buprenorphine-3-glucuronide (Middle Left), Nor-buprenorphine-glucuronide (Middle Right), and Moxifloxacin (Bottom Left).

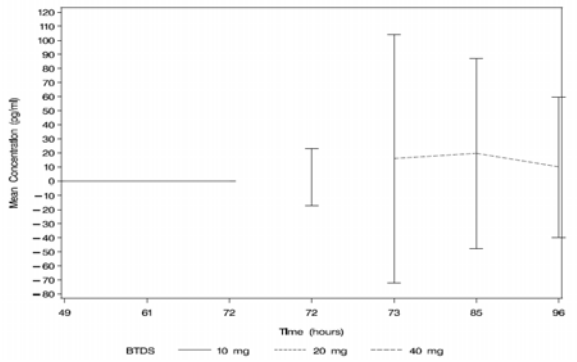
Buprenorphine (pg/mL)



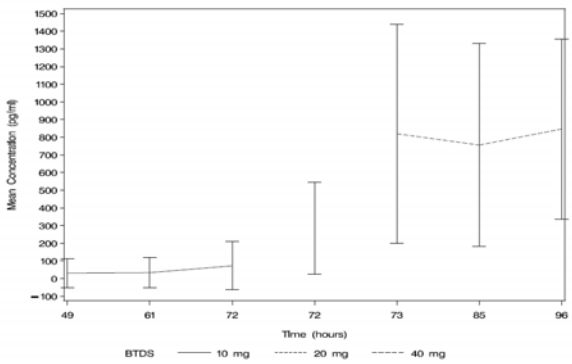
Nor-buprenorphine (pg/mL)



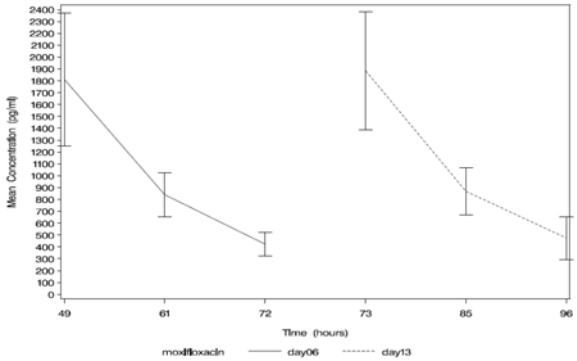
Buprenorphine-3-Glucuronide (pg/mL)



Nor-Buprenorphine-3-Glucuronide (pg/mL)



Moxifloxacin (ng/mL)



(Source: Figures 14.4.1.1 – 14.4.1.5 on pages 421-425 of BUP1011 study report)

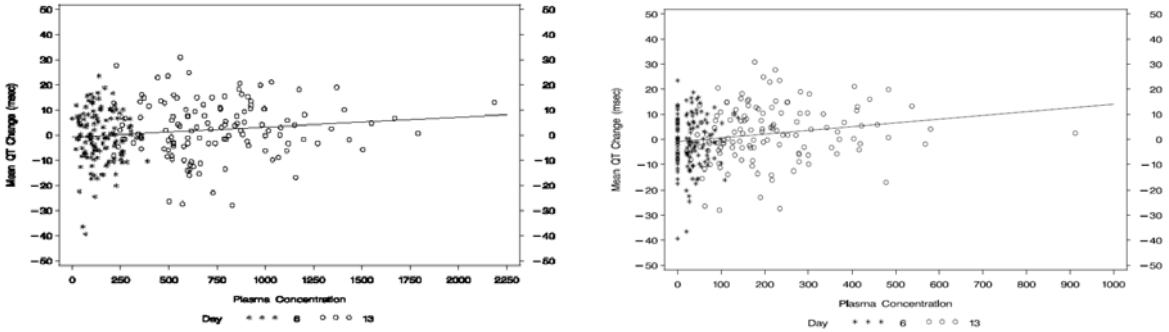
4.2.8.4.2 Exposure-Response Analysis

An exploratory statistical analysis was performed to examine a possible association between a change from baseline in QTcI and the plasma concentration of buprenorphine and nor-buprenorphine. The 3 plasma concentrations for each subject on Day 13 were averaged. A linear regression was then performed with the average change in QTcI (mean of non-missing replicate QTcI at each time point) from baseline vs. Day 13 as the dependent variable, and mean plasma concentration as the independent variable. The 90% confidence interval of the slope was calculated, and the data presented as a scatter plot with a regression line.

Increasing plasma concentrations of buprenorphine following dosing with 2 x BTDS 20 were associated with a slight increase in QTcI, as expected. Similarly, plasma concentrations of norbuprenorphine following dosing with 2 x BTDS 20 were associated with a slight increase in QTcI (see Figure 2).

Figure 2: Scatter Plot and Regression Line of Mean QTcI Change vs. Mean Plasma Buprenorphine (Left) and Nor-buprenorphine (Right) Concentration for BTDS.

Buprenorphine (pg/mL) Nor-buprenorphine (pg/mL)



(Source: Figures 14.4.4.1 – 14.4.4.2 on pages 445-446 of BUP1011 study report)

Reviewer's Comments: The sponsor should have used the 3 plasma concentrations on day 6 and 13 instead of taking the average. Furthermore, the sponsor did not conduct exposure-response analysis for moxifloxacin (see reviewer's clinical pharmacology assessment in section 5.3)

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. A good correction of QT by RR should not be affected by changes in RR intervals. We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included gender, RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 11, it appears that QTcI

had smaller absolute slopes than QTcF and therefore is a better correction method for the study data.

We also confirmed this conclusion by using the mean sum of squared slopes (MSSS) from individual regressions of QTc values versus RR as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 12, it also appears that QTcI is the best correction method. This reviewer used QTcI for the primary statistical analysis, which is also consistent with the endpoint point chosen by the sponsor.

The QT-RR interval relationship is graphically illustrated in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

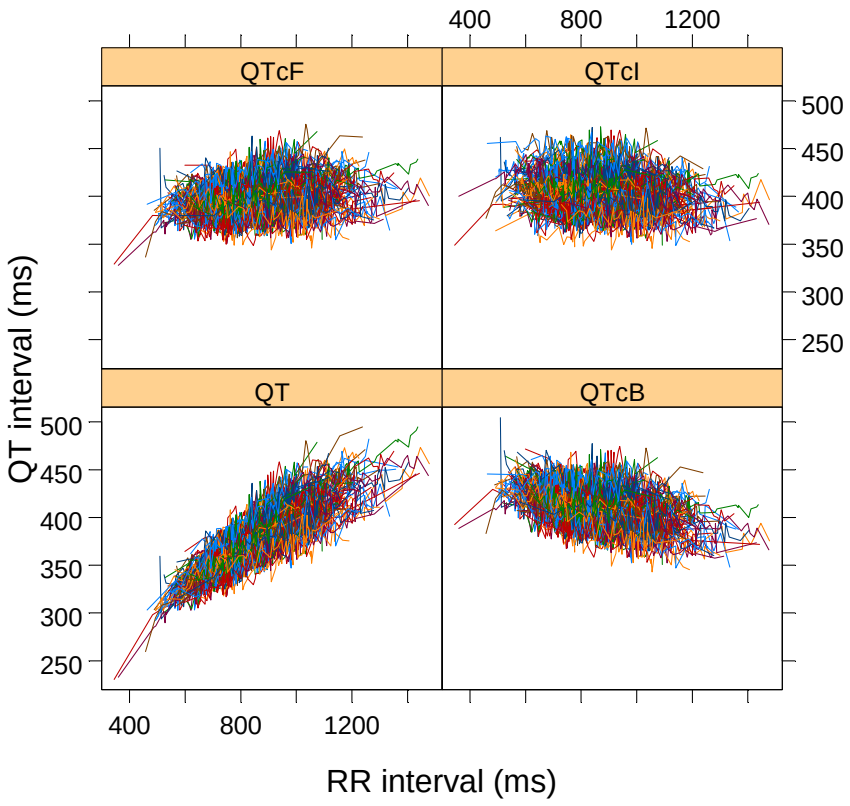
Table 11: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Group	Slope of QTcF	Slope of QTcI	p_value (difference)
BTDS	0.0394	0.0007	0.0000
Moxifloxacin 400 mg	0.0539	0.0019	0.0000
Placebo	0.0298	-0.0015	0.0000
All	0.0412	-0.0001	0.0000

Table 12: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
BTDS	44	0.0036	44	0.0027	44	0.0011
Moxifloxacin 400 mg	43	0.0021	43	0.0046	43	0.0016
Placebo	44	0.0038	44	0.0017	44	0.0009
All	87	0.0028	87	0.0036	87	0.0014

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for BTDS and Assay Sensitivity

The statistical reviewer used mixed model to evaluate the ΔQTcI effect at each of the time points. Time-matched baselines (collected at Day -1) were used in the analyses. The model also included the time-matched baseline and gender as covariates. The analysis results are presented in Table 13. The largest upper bounds of the two-sided 90% CI for the mean difference between BTDS 10 mg and placebo (on Day 6), and between BTDS 40 mg and placebo (on Day 13) were 10.9 ms and 15.3, respectively.

For the moxifloxacin group, the largest lower bounds of the unadjusted 90% confidence interval are 10.4 ms and 7.8 ms on Days 6 and 13, respectively. By considering Bonferroni multiple endpoint adjustment, the largest lower bound also exceeds 5 ms, which indicates that an at least 5-ms QTcI effect due to moxifloxacin can be detected from the study.

Table 13: Analysis Results of ΔQTcI and ΔΔQTcI

DAY=6

	Placebo	BTDS 10 mg			Moxifloxacin 400 mg		
	ΔQTcI	ΔQTcI	ΔΔQTcI		ΔQTcI	ΔΔQTcI	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	-0.8	-2.6	-1.8	(-5.6, 2.0)	0.0	0.8	(-3.1, 4.6)
1	0.7	2.1	1.4	(-2.2, 5.1)	12.2	11.5	(7.8, 15.2)
1.5	-3.8	-2.0	1.7	(-2.5, 6.0)	6.7	10.5	(6.2, 14.7)
2	-0.9	3.9	4.8	(0.0, 9.5)	10.5	11.4	(6.6, 16.2)
2.5	-0.7	-0.4	0.4	(-4.3, 5.1)	13.0	13.8	(9.0, 18.5)
3	-0.3	0.7	1.0	(-3.1, 5.1)	14.3	14.5	(10.4*, 18.7)
4	0.6	1.5	0.8	(-3.8, 5.5)	8.7	8.0	(3.4, 12.7)
7	-0.4	-0.6	-0.2	(-4.5, 4.1)	5.8	6.1	(1.8, 10.5)
10	1.9	-0.5	-2.3	(-6.6, 2.0)	6.2	4.3	(0.0, 8.6)
13	-4.2	2.9	7.2	(3.4, 10.9)	3.9	8.1	(4.3, 12.0)
18	-0.5	-0.3	0.2	(-5.3, 5.6)	6.2	6.7	(1.3, 12.1)
23.5	-1.1	0.7	1.8	(-2.2, 5.8)	7.3	8.3	(4.2, 12.4)

*The lower bound of the 90% CI is 8.4 ms after Bonferroni adjustment for 6 time points.

DAY=13

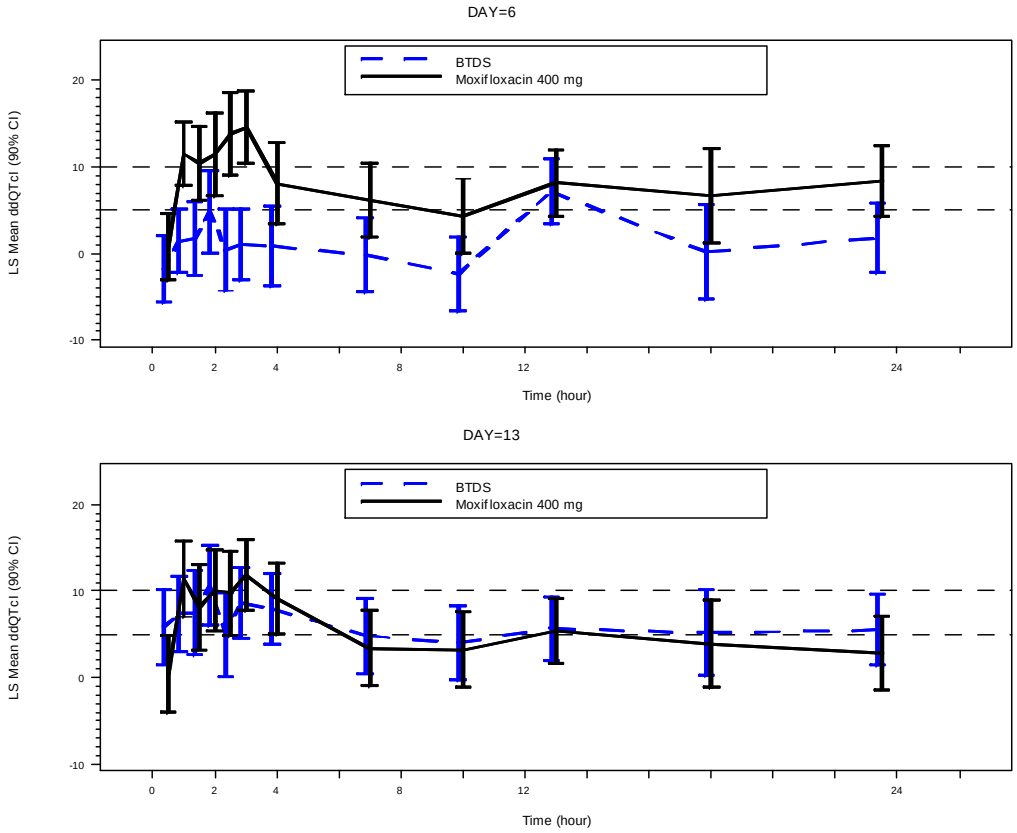
	Placebo	BTDS 40 mg			Moxifloxacin 400 mg		
	ΔQTcI	ΔQTcI	ΔΔQTcI		ΔQTcI	ΔΔQTcI	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI	LS Mean	Diff LS Mean	90% CI
0.5	-2.3	3.6	5.9	(1.5, 10.2)	-1.9	0.4	(-4.1, 4.8)
1	0.5	7.9	7.4	(3.1, 11.7)	11.9	11.4	(7.0, 15.8)
1.5	-4.7	2.8	7.5	(2.6, 12.3)	3.4	8.1	(3.2, 13.0)
2	-1.5	9.1	10.6	(6.0, 15.3)	8.5	10.1	(5.4, 14.7)
2.5	1.1	6.1	5.0	(0.2, 9.8)	10.9	9.7	(4.9, 14.6)
3	-1.5	7.1	8.6	(4.6, 12.7)	10.4	11.9	(7.8**, 16.0)
4	-1.5	6.5	8.0	(3.9, 12.0)	7.7	9.1	(5.0, 13.3)
7	0.9	5.8	4.8	(0.5, 9.1)	4.3	3.4	(-1.0, 7.8)
10	1.2	5.2	4.0	(-0.2, 8.3)	4.4	3.2	(-1.1, 7.6)
13	-3.1	2.6	5.7	(2.0, 9.4)	2.3	5.4	(1.7, 9.2)
18	-1.7	3.5	5.2	(0.2, 10.1)	2.2	3.9	(-1.2, 9.0)
23.5	0.6	6.1	5.5	(1.4, 9.6)	3.5	2.8	(-1.4, 7.0)

**The lower bound of the 90% CI is 5.9 ms after Bonferroni adjustment for 6 time points.

5.2.1.2 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 4: Mean and 90% CI ΔΔQTcI Timecourse



Note: BTDS dose reached 10 mg on Day 6 and 40 mg on Day 13.

5.2.1.3 Categorical Analysis

Table 14 and Table 15 present the categorical analysis results for the absolute QTcI and ΔQTcI, respectively. There were no subjects with QTcI above 480 ms. Nor were there any subjects with ΔQTcI above 60 ms.

Table 14: Categorical Analysis for QTcI

	Day 6			Day 13		
Treatment Group	**N**	**QTcI<=450 ms**	**450 ms <QTcI <=480 ms**	**N**	**QTcI<=450 ms**	**450 ms<QTcI <=480 ms**
Baseline (Day -1)	130	129 (33.2%)	1 (0.3%)	128	128 (32.9%)	0 (0.0%)
BTDS	44	41 (46.6%)	3 (3.4%)	44	41 (46.6%)	3 (3.4%)
Moxifloxacin 400 mg	43	37 (44.0%)	6 (7.1%)	41	37 (44.0%)	4 (4.8%)
Placebo	44	42 (47.7%)	2 (2.3%)	44	43 (48.9%)	1 (1.1%)

Table 15: Categorical Analysis of ΔQTcI

	Day 6			Day 13		
Treatment Group	**N**	**ΔQTcI <=30 ms**	**30 ms< ΔQTcI <=60 ms**	**N**	**ΔQTcI <=30 ms**	**30 ms< ΔQTcI <=60 ms**
BTDS	44	39 (44.3%)	5 (5.7%)	44	33 (37.5%)	11 (12.5%)
Moxifloxacin 400 mg	43	26 (31.0%)	17 (20.2%)	41	25 (29.8%)	16 (19.0%)
Placebo	44	38 (43.2%)	6 (6.8%)	44	40 (45.5%)	4 (4.5%)

5.2.2 PR Analysis

The same statistical analysis used for the QTcI intervals was performed for PR intervals. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the PR mean differences between BTDS 10 mg and placebo (on Day 6), and between BTDS 40 mg and placebo (on Day 13) were 15.1 ms and 11.4 ms, respectively. No subjects had a PR interval above 200 ms.

Table 16: Analysis Results of ΔPR and ΔΔPR
DAY=6

	Placebo	BTDS 10 mg		
	ΔPR	ΔPR	ΔΔPR	
Time (hrs)	**LS Mean**	**LS Mean**	**Diff LS Mean**	**90% CI**
0.5	6.5	11.6	5.1	(0.5, 9.7)
1	-0.1	8.1	8.2	(4.4, 12.1)
1.5	-5.2	0.9	6.1	(2.9, 9.2)
2	-0.6	5.3	5.9	(2.1, 9.8)
2.5	1.7	6.0	4.3	(0.9, 7.7)
3	0.4	8.1	7.7	(3.8, 11.7)
4	-3.9	4.5	8.3	(4.1, 12.6)
7	-4.4	3.9	8.4	(4.5, 12.3)
10	-5.2	5.4	10.6	(6.0, 15.1)
13	-3.8	3.5	7.3	(3.4, 11.2)
18	-2.3	1.7	4.0	(-0.6, 8.5)
23.5	-0.0	0.3	0.3	(-3.3, 3.9)

Table 16: Analysis Results of ΔPR and ΔΔPR (Continued)
DAY=13

	Placebo	BTDS 40 mg		
	ΔPR	ΔPR	ΔΔPR	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI
0.5	6.0	9.9	3.9	(-0.4, 8.3)
1	2.6	2.6	-0.0	(-3.7, 3.7)
1.5	-4.3	-3.5	0.8	(-2.8, 4.5)
2	1.8	4.1	2.3	(-1.5, 6.1)
2.5	1.0	4.3	3.3	(-0.7, 7.3)
3	-0.9	6.1	7.0	(2.6, 11.4)
4	-0.3	2.6	2.9	(-1.2, 7.0)
7	-0.7	5.7	6.4	(2.0, 10.8)
10	-2.9	1.5	4.4	(0.5, 8.3)
13	-5.4	1.8	7.1	(3.2, 11.0)
18	-0.2	1.2	1.4	(-3.7, 6.5)
23.5	-0.2	-2.2	-2.1	(-5.9, 1.7)

5.2.3 QRS Analysis

The same statistical analysis used for the QTcI intervals was performed for QRS intervals. The point estimates and the 90% confidence intervals are presented in Table 17. The largest upper limits of 90% CI for the QRS mean differences between BTDS 10 mg and placebo (on Day 6), and between BTDS 40 mg and placebo (on Day 13) were 3.8 ms and 4.4 ms, respectively. No subjects had a PR interval above 120 ms.

Table 17: Analysis Results of ΔQRS and ΔΔQRS
Day=6

	Placebo	BTDS 10 mg		
	ΔQRS	ΔQRS	ΔΔQRS	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI
0.5	1.8	1.7	-0.1	(-1.8, 1.7)
1	-0.1	0.1	0.2	(-1.6, 2.0)
1.5	-2.4	-0.6	1.8	(0.3, 3.4)
2	-0.4	-0.2	0.2	(-1.3, 1.6)
2.5	-0.7	-0.1	0.5	(-1.0, 2.0)
3	-0.1	1.3	1.4	(-0.3, 3.1)
4	-0.4	1.4	1.8	(0.2, 3.3)
7	-0.5	1.4	1.9	(0.1, 3.7)
10	-0.6	1.5	2.0	(0.3, 3.8)
13	-0.7	0.5	1.2	(-0.6, 3.0)
18	0.2	-0.4	-0.6	(-2.5, 1.2)
23.5	0.3	0.3	0.0	(-1.8, 1.9)

DAY=13

	Placebo	BTDS 40 mg		
	ΔQRS	ΔQRS	ΔΔQRS	
Time (hrs)	LS Mean	LS Mean	Diff LS Mean	90% CI
0.5	3.8	3.7	-0.1	(-1.8, 1.7)
1	2.4	2.8	0.4	(-1.4, 2.2)
1.5	-0.4	-0.5	-0.1	(-1.8, 1.7)
2	0.2	0.4	0.2	(-1.5, 1.8)
2.5	-1.1	-0.2	0.9	(-0.7, 2.6)
3	-0.5	2.0	2.5	(0.6, 4.4)
4	1.2	2.0	0.8	(-0.9, 2.6)
7	1.0	2.0	0.9	(-1.0, 2.9)
10	0.7	1.5	0.8	(-1.0, 2.6)
13	0.1	-0.4	-0.4	(-2.1, 1.3)
18	0.7	1.3	0.6	(-1.2, 2.5)
23.5	0.7	2.3	1.6	(-0.2, 3.3)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 Buprenorphine Concentration-QTcI Analysis

The relationship between ΔΔQTcI and buprenorphine concentrations was investigated by linear mixed-effects modeling. The concentration-time profiles of the metabolites nor-buprenorphine and nor-buprenorphine-glucuronide where similar to the parent compound buprenorphine and therefore not further explored for the reviewer's exposure-response analysis.

The following linear models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear model with no intercept.

Table **18** summarizes the results of the buprenorphine concentration - QTcI analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best. The predicted ΔΔQTcI at mean peak buprenorphine concentration can be found in

Table 19. It is noted that the slope of the buprenorphine concentration-ΔΔQTcI is non-significant with a p-value of 0.6. This finding is most likely because of the limited number of PK samples collected at 1, 13, and 23.5 hours postdose and the limited fluctuations in the concentrations.

Table 18: Exposure-Response Analysis of Buprenorphine associated ΔΔQTcI Prolongation.

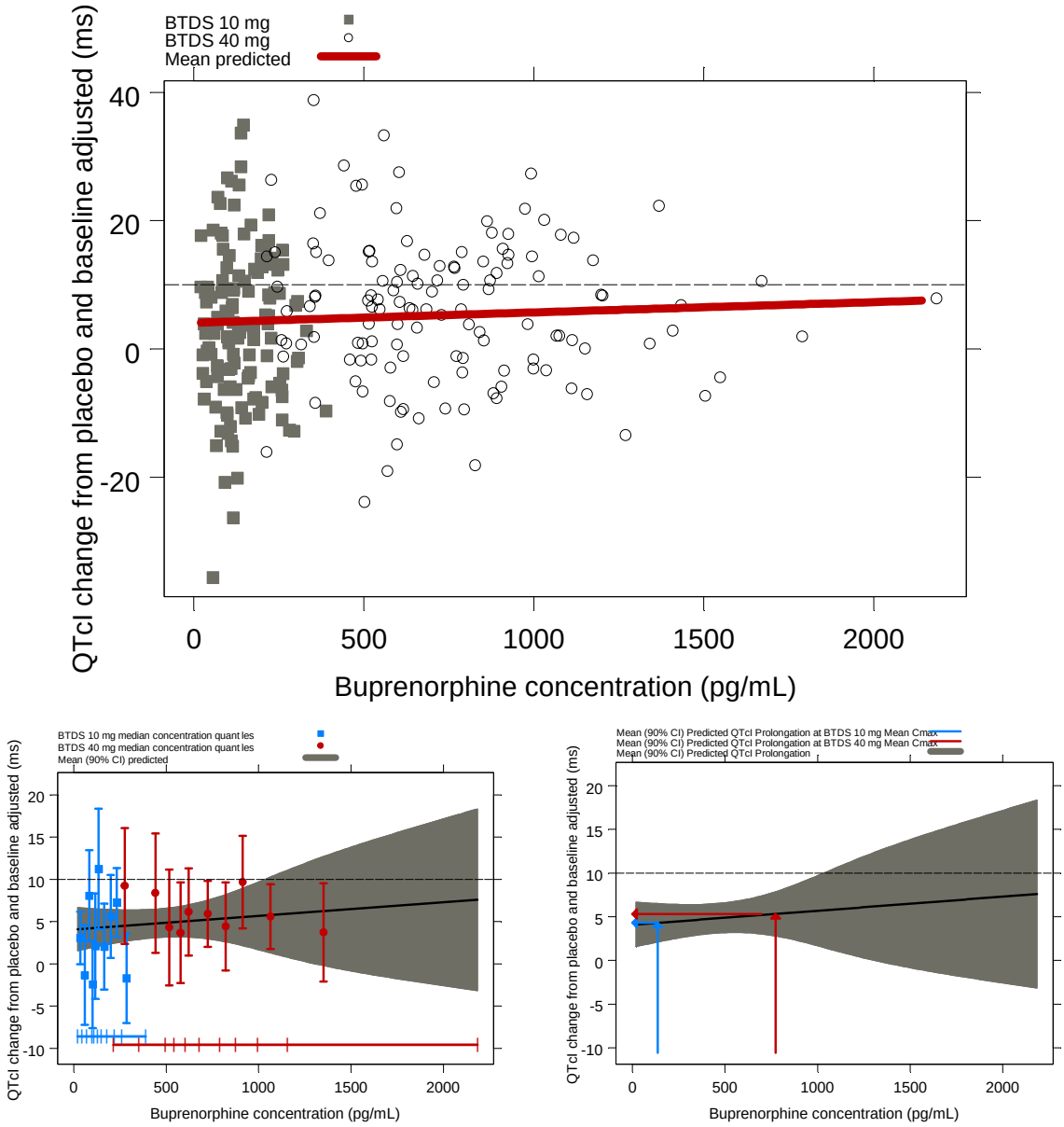
	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔΔQTcI = Intercept + slope * Buprenorphine Concentration		
Intercept (ms)	4.08 (1.46; 6.69) 0.0123	6.01
Slope (ms per pg/mL)	0.00161 (-0.00327; 0.00648) 0.5551	0
Residual Variability (ms)	10.45	--
Model 2: ΔΔQTcI = slope * Buprenorphine Concentration (No Intercept)		
Slope (ms per pg/mL)	0.00796 (0.00498; 0.0109) 0.0002	6.83
Residual Variability (ms)	11.34	--

Table 19: Predicted Change of ΔΔQTcI Interval at Mean Peak Buprenorphine Concentration using Model 1.

Dose Group	Predicted change in ΔΔQTcI interval (ms)	
	Mean	90% Confidence Interval
BTDS 10 mg		
Mean C_{max} (138 pg/mL)	4.3	(2.09; 6.51)
BTDS 40 mg		
Mean C_{max} (774 pg/mL)	5.32	(2.78; 7.86)

The relationship between buprenorphine concentrations and ΔΔQTcI is visualized in Figure 5 where the raw data is shown on top together with the population predictions. The goodness-of-fit is illustrated in the bottom left graph of Figure 5 showing the observed median-quantile concentrations and associated mean ΔΔQTcI (90% CI) together with the mean (90% CI) predicted ΔΔ QTcI (black line with shaded grey area). The mean (90% CI) predicted ΔΔ QTcI at mean C_{max} is shown in the bottom right graph of Figure 5.

Figure 5. ΔΔ QTcI vs. Buprenorphine Concentration. Observed Data (Top), Concentration Quantile Plot (Bottom Left), and Predicted ΔΔQTcI at Mean C_{max} (Bottom Right).



5.3.1 Moxifloxacin Concentration-QTcI Analysis

The relationship between ΔΔQTcI and moxifloxacin concentrations was investigated by linear mixed-effects modeling.

The following three linear models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear/ model with mean intercept fixed to 0 (with variability);
- Model 3 is a linear model with no intercept.

Table 20 summarizes the results of the moxifloxacin concentration - QTcI analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best.

Table 20: Exposure-Response Analysis of Moxifloxacin Associated ΔΔQTcI Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔΔQTcI = Intercept + slope * Moxifloxacin Concentration		
Intercept (ms)	3.56 (0.09; 7.03) 0.0916	10.19
Slope (ms per ng/mL)	0.00441 (0.00168; 0.00714) 0.0096	7.7
Residual Variability (ms)	10.34	--
Model 2: ΔΔQTcI = Intercept + slope * Moxifloxacin Concentration (Fixed Intercept)		
Intercept (ms)	0	10.75
Slope (ms per ng/mL)	0.00678 (0.0053; 0.00826) <.0001	8.01
Residual Variability (ms)	10.36	--
Model 3: ΔΔQTcI = slope * Moxifloxacin Concentration (No Intercept)		
Slope (ms per ng/mL)	0.00677 (0.0053; 0.00824) <.0001	3.91
Residual Variability (ms)	11.84	--

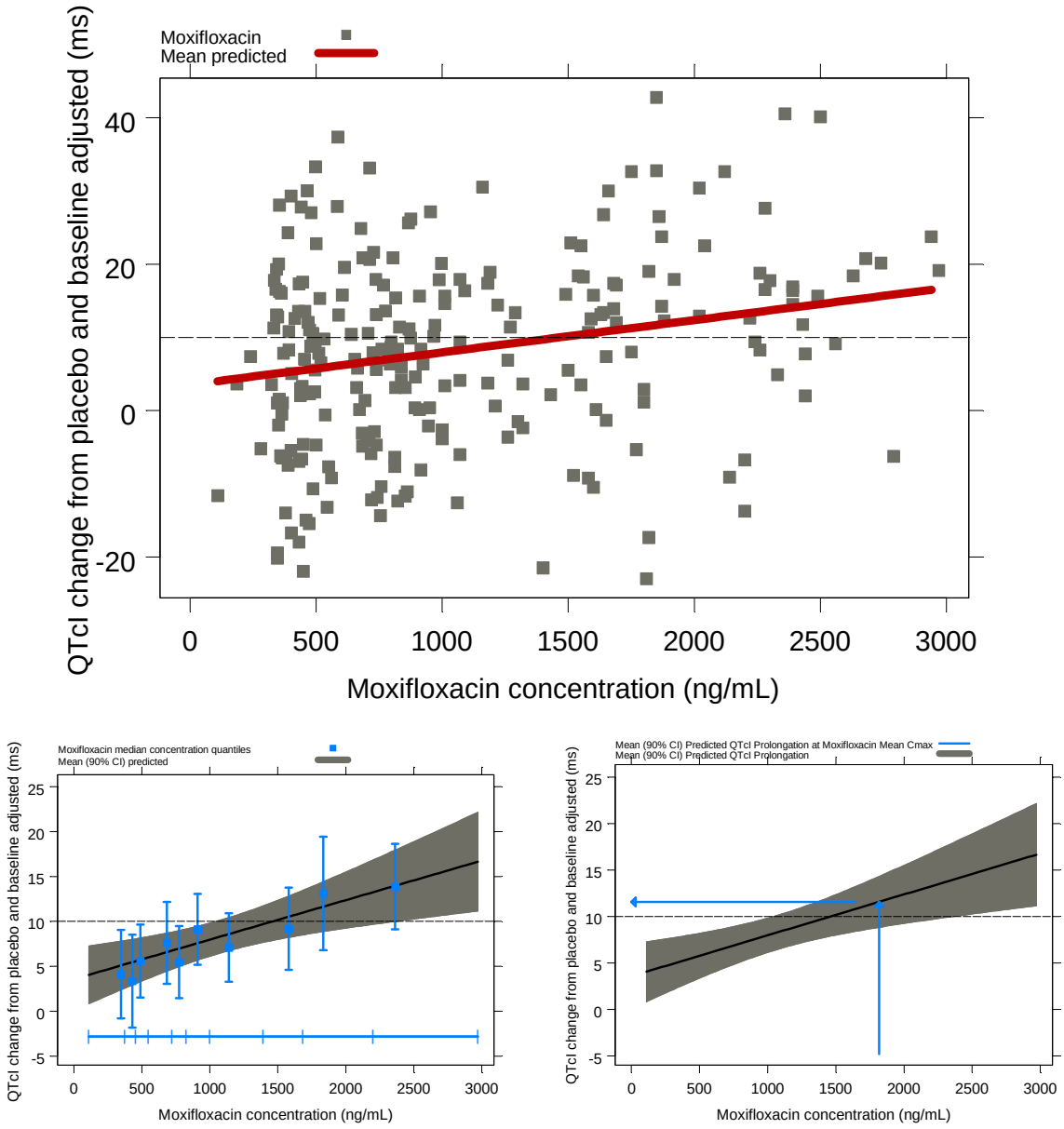
The predicted ΔΔQTcI at mean peak moxifloxacin concentration can be found in Table 21. The reason for the predictions being lower than those in Table 1 is most likely due to the PK sampling at 1, 13, and 23.5 hours postdose which is not optimal to capture the maximum moxifloxacin concentrations which occurs between 2-4 hours postdose.

Table 21: Predicted Change of ΔΔQTcI Interval at Mean Peak Moxifloxacin Concentration using Model 1.

Dose Group	Predicted change in ΔΔQTcI interval (ms)	
	Mean	90% Confidence Interval
Moxifloxacin		
Mean C_{max} (1820 ng/mL)	11.6	(8.82; 14.3)

The relationship between moxifloxacin concentrations and ΔΔQTcI is visualized in Figure 6 where the raw data is shown on top together with the population predictions. The goodness-of-fit is illustrated in the bottom left graph of Figure 6 showing the observed median-quantile concentrations and associated mean ΔΔQTcI (90% CI) together with the mean (90% CI) predicted ΔΔQTcI (black line with shaded grey area). The mean (90% CI) predicted ΔΔ QTcI at mean C_{max} is shown in the bottom right graph of Figure 6.

Figure 6. ΔΔQTcI vs. Moxifloxacin Concentration. Observed Data (Top), Concentration Quantile Plot (Bottom Left), and Predicted ΔΔQTcI at Mean C_{max} (Bottom Right).



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety Assessments

None of the events identified to be of clinical importance per the ICH E14 guideline, i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

5.4.2 ECG Acquisition and Interpretation

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 88% of the ECGs were annotated in the primary lead II with lead V2 or V5 as back up leads. According to the automated algorithm 17.3 % of ECGs were reported to have significant QT bias, this trend was similar among treatment groups. Overall ECG acquisition and interpretation in this study appears acceptable.

T-wave changes and ST segment depression were minor and similar among all treatment groups.

5.4.3 PR and QRS Interpretation

Buprenorphine does not affect PR and QRS duration. No subject had a PR over 200 ms and a QRS over 120 ms

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td colspan="2">Include maximum proposed clinical dosing regimen
BTDS 5 mcg/h, BTDS 10 mcg/h, and BTDS 20 mcg/h worn continuously for 7 days.</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">Include if studied or NOAEL dose
No maximum tolerated dose has been established for BTDS. The highest dose studied to date is BTDS 2 x 20 mcg/h patches (Study BUP1011) This dose is 2x the highest dose included in Phase 3 studies and was adequately tolerated.</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">Include most common adverse events; dose limiting adverse events
The AEs which occurred in ≥5% of subjects were: nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, pruritus and fatigue.</td></tr>
<tr><td rowspan="2">Maximum dose tested</td><td>Single Dose</td><td>Specify dose BTDS 20 mcg/h</td></tr>
<tr><td>Multiple Dose</td><td>Specify dosing interval and duration
1. Study BP99-0204: 3 sequential BTDS 5 applications each for 7 days for a total of 21 days
2. Study BP97-0303: Fixed dose escalation: BTDS 5 for 3 days, BTDS 10 for 3 days, and BTDS 20 for 7 days</td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Mean (%CV) Cmax and AUC
Study BP97-0501
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="3">Arithmetic Mean (%CV)</th></tr>
<tr><th>BTDS 5 (N = 12)</th><th>BTDS 10 (N = 12)</th><th>BTDS 20 (N = 9)</th></tr>
<tr><td>AUCt (pg·h/mL)</td><td>12647 (55)</td><td>24311 (34)</td><td>51106 (36)</td></tr>
<tr><td>AUCinf(pg·h/mL)[a]</td><td>12087 (37)</td><td>27035 (29)</td><td>54294 (36)</td></tr>
<tr><td>Cmax (pg/mL)</td><td>176 (67)</td><td>191 (34)</td><td>471 (49)</td></tr>
</table>
a: BTDS5 N = 6, BTDS 10 N=10, and BTDS 20 N=8.</td></tr>
<tr><td>Multiple Dose</td><td>Mean (%CV) Cmax and AUC
Study BP99-0204
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="3">Arithmetic Mean (%CV) (N = 27)</th></tr>
<tr><th>Week 1 (0-168 hrs)</th><th>Week 2 (168-336 hrs)</th><th>Week 3 (336-504 hrs)</th></tr>
<tr><td>AUC (pg·h/mL)</td><td>9459 (50)</td><td>11482 (41)</td><td>15827 (45)</td></tr>
<tr><td>Cmin (pg/mL)</td><td>53 (59)</td><td>58 (54)</td><td>57 (46)</td></tr>
<tr><td>Cavg (pg/mL)</td><td>56 (46)</td><td>68 (38)</td><td>94 (44)</td></tr>
</table>
Study BP97-0303
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="3">Arithmetic Mean (%CV)</th></tr>
<tr><th>Young Healthy (N = 11[a])</th><th>Elderly Healthy (N = 10)</th><th>Elderly Hypertensive (N = 11)</th></tr>
<tr><td>AUCt (pg·h/mL)</td><td>86026 (30)</td><td>78674 (31)</td><td>94022 (15)</td></tr>
<tr><td>AUCinf (pg·h/mL)</td><td>87485 (32)</td><td>81129 (31)</td><td>99087 (15)</td></tr>
<tr><td>Cmax (pg/mL)</td><td>722 (38)</td><td>562 (44)</td><td>610 (32)</td></tr>
</table>
[a]Ten subjects were evaluable for AUCinf.</td></tr>
</table>

<table>
<tr><td>Range of linear PK</td><td colspan="2">Specify dosing regimen
Single doses of BTDS 5 mcg/h, 10 mcg/h, and 20 mcg/h, worn continuously for 7 days</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Mean (%CV); specify dosing regimen
Study BP99-0204: Accumulation Index = 1.21 (AUCweek2/AUCweek1); 3 sequential 7-day BTDS 5 mcg/h applications</td></tr>
<tr><td>Metabolites</td><td colspan="2">Include listing of all metabolites and activity
Metabolites of Buprenorphine: Norbuprenorphine, buprenorphine-3β-O-glucuronide, and norbuprenorphine-3β−O-glucuronide.

In vitro receptor binding activities for the above metabolites were evaluated and the results are reported in Study BUP-P-007.

Hydroxy buprenorphine and hydroxy norbuprenorphine are known to be minor metabolites; however, their receptor binding activities are unknown.</td></tr>
<tr><td rowspan="3">Absorption</td><td>Absolute/ Relative Bioavail-ability</td><td>Mean (%CV) Cmax and AUC
Study BP97-0501
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="3">Arithmetic Mean (%CV)</th></tr>
<tr><th>BTDS 5 (N = 12)</th><th>BTDS 10 (N = 11)</th><th>BTDS 20 (N = 8)</th></tr>
<tr><td>Absolute bioavailability (F)</td><td>0.16 (43)</td><td>0.15 (44)</td><td>0.16 (35)</td></tr>
</table></td></tr>
<tr><td>Tmax</td><td>Median (range) for parent and metabolites
Study BP97-0501
<table>
<tr><th></th><th colspan="3">Arithmetic Mean (range)</th></tr>
<tr><th></th><th>BTDS 5 (N = 12)</th><th>BTDS 10 (N = 12)</th><th>BTDS 20 (N = 9)</th></tr>
<tr><td>Buprenorphine Tmax (h)</td><td>107 (48-168.75)</td><td>99 (48-168.50)</td><td>90 (48-168.75)</td></tr>
<tr><td>Norbupre-norphine Tmax (h)</td><td>116 (0-180)</td><td>126 (0-174)</td><td>141 (84-172)</td></tr>
</table></td></tr>
<tr><td>Distribution</td><td>Vd/F or Vd</td><td>Mean (%CV)
Study BP97-0112
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="2">Arithmetic Mean (%CV)</th></tr>
<tr><th>Healthy (N = 12)</th></tr>
<tr><td>Vd (SS) (L)</td><td>430 (67)</td></tr>
</table></td></tr>
<tr><td></td><td>% bound</td><td>Mean (%CV) Buprenorphine is approximately 96% bound to plasma proteins, mainly to alpha- and beta-globulin</td></tr>
</table>

<table>
<tr><td rowspan="3">Elimination</td><td>Route</td><td>Primary route; percent dose eliminated
Other routes Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. Buprenorphine primarily undergoes N-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes to buprenorphine 3-O-glucuronide. Norbuprenorphine is also glucuronidated prior to elimination. Buprenorphine is also eliminated in the feces. Following intramuscular administration of 2 mcg/kg dose of buprenorphine, approximately 70% of the dose was excreted in feces within 7 days. Approximately 27% was excreted in urine.</td></tr>
<tr><td>Terminal t½</td><td>Mean (%CV) for parent and metabolite
Study BP97-0501
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="3">Arithmetic Mean (%CV)</th></tr>
<tr><th>BTDS 5
(N = 6)</th><th>BTDS 10
(N = 10)</th><th>BTDS 20
(N = 8)</th></tr>
<tr><td>t½ (h)</td><td>17.32 (53)</td><td>26.21 (54)</td><td>34.63 (32)</td></tr>
<tr><th>Norbuprenorphine</th><th>BTDS 5
(N = 1)</th><th>BTDS 10[a]
-</th><th>BTDS 20
(N = 7)</th></tr>
<tr><td>t½ (h)</td><td>55.77(-)</td><td>-</td><td>51.82 (28)</td></tr>
</table>
a: t1/1 not estimable for all subjects in this treatment.</td></tr>
<tr><td>CL/F or CL</td><td>Mean (%CV)
Study BP97-0112
<table>
<tr><th>Buprenorphine</th><th>Arithmetic Mean (%CV)
Buprenex® 0.3 mg/mL
(IV over 10 min)
Healthy Subjects
(N = 12)</th></tr>
<tr><td>CL_{tot} (mL/min)</td><td>778 (32)</td></tr>
</table></td></tr>
</table>

Intrinsic Factors	Age	Specify mean changes in Cmax and AUC

Study BP96-0702

	Elderly Subjects (N = 12)	Young Subjects (N = 12)	Elderly/ Young Ratio (%)	90% CI
	Geometric Means			
AUCt (pg·h /mL)	17415	18791	93	72 to 120
Cmax (pg/mL)	142	159	90	69 to 116

Study BP97-0303

	Young Healthy (N = 11)	Elderly Healthy (N = 10)	Elderly Healthy/ Young Ratio (%)	90% CI
	Geometric Means			
AUCt (pg·h /mL)	82207	74122	90	72 to 113
AUCinf (pg·h /mL)	83177	76367	92	72 to 117
Cmax (pg/mL)	672	507	76	55 to 103

	Young Healthy (N = 11)	Elderly Hypertensive (N = 11)	Elderly Hypertensive/ Young Ratio (%)	90% CI
	Geometric Means			
AUCt (pg·h /mL)	82207	92956	114	90 to 141
AUCinf (pg·h /mL)	83177	97986	118	93 to 149
Cmax (pg/mL)	672	581	86	64 to 117

aTen subjects were evaluable for AUCinf

<table>
<tr>
<td>Intrinsic Factors</td>
<td>Sex</td>
<td>Specify mean changes in Cmax and AUC
No studies in the BTDS clinical development program directly assessed the pharmacokinetics of BTDS by gender.

BTDS pharmacokinetic metrics by gender in the 10 mg, single dose, 7 day patch application pooled data analysis.
<table>
<tr><th></th><th colspan="2">Arithmetic Mean (%CV)</th></tr>
<tr><th>Metric</th><th>Male</th><th>Female</th></tr>
<tr><td>N</td><td>50</td><td>40</td></tr>
<tr><td>AUC (0-168h) (pg·h /mL)</td><td>18483 (46)</td><td>17846 (47)</td></tr>
<tr><td>AUC (0-168h) (pg·h/mL/kg)</td><td>245 (48)</td><td>283 (58)</td></tr>
<tr><td>Cmax (0-168h) (pg/mL)</td><td>175 (45)</td><td>168 (43)</td></tr>
<tr><td>Cmax (0-168h) (pg/mL/kg)</td><td>2.31 (48)</td><td>2.67 (51)</td></tr>
</table>
Analysis of variance results for pharmacokinetic metrics by gender.
<table>
<tr><th>Metric</th><th>p-value</th></tr>
<tr><td>AUC</td><td>0.1232</td></tr>
<tr><td>Body Weight-Normalized AUC</td><td>0.0931</td></tr>
<tr><td>Cmax</td><td>0.1971</td></tr>
<tr><td>Body Weight-Normalized Cmax</td><td>0.0622</td></tr>
</table>
</td>
</tr>
<tr>
<td>Intrinsic Factors</td>
<td>Race</td>
<td>Specify mean changes in Cmax and AUC
No studies in the BTDS clinical development program directly assessed the pharmacokinetics of BTDS by race.

BTDS pharmacokinetic metrics by race in the 10 mg, single dose, 7 day patch application pooled data analysis.
<table>
<tr><th></th><th colspan="3">Arithmetic Mean (%CV)</th></tr>
<tr><th>Metric (0-168h)</th><th>Black</th><th>Hispanic</th><th>White</th></tr>
<tr><td>N</td><td>13</td><td>31</td><td>44</td></tr>
<tr><td>AUC (pg·h /mL)</td><td>17162 (44)</td><td>19797 (51)</td><td>17723 (41)</td></tr>
<tr><td>AUC (pg·h/mL/kg)</td><td>248 (48)</td><td>291 (58)</td><td>251 (45)</td></tr>
<tr><td>Cmax (pg/mL)</td><td>169 (38)</td><td>182 (51)</td><td>168 (39)</td></tr>
<tr><td>Cmax (pg/mL/kg)</td><td>2.42 (64)</td><td>2.67 (58)</td><td>2.38 (45)</td></tr>
</table>
Analysis of variance results for pharmacokinetic metrics by race.
<table>
<tr><th>Metric</th><th>p-value</th></tr>
<tr><td>AUC</td><td>0.2794</td></tr>
<tr><td>Body Weight-Normalized AUC</td><td>0.5984</td></tr>
<tr><td>Cmax</td><td>0.5933</td></tr>
<tr><td>Body Weight-Normalized Cmax</td><td>0.8586</td></tr>
</table>
</td>
</tr>
</table>

Intrinsic Factors	Hepatic Impairment	Specify mean changes in Cmax and AUC **Study BP97-0112**

Buprenorphine	**Arithmetic Mean (%CV)**		
Metric	**Healthy (N = 12)**	**Mild (N = 8)**	**Moderate (N = 4)**
AUCt (pg·min/mL)	342299 (23)	328554 (22)	293262 (40)
Cmax (pg/mL)	11770 (59)	6378 (60)	4640 (38)

Norbuprenorphine	**Arithmetic Mean (%CV)**		
Metric	**Healthy (N = 12)**	**Mild (N = 8)**	**Moderate (N = 2)**
AUC_t (pg·min/mL)	12723 (169)	16573 (120)	23175 (140)
Cmax (pg/mL)	75 (44)	55 (44)	45 (30)

	Mild (n=8) versus Healthy (n=12) Subjects			**Moderate (n=4[a]) versus Healthy (n=12) Subjects**		
	Ratio	**90 %CI**		**Ratio**	**90 %CI**	
Ratio Metrics	**(LS Mean)**	**Lower**	**Upper**	**(LS Mean)**	**Lower**	**Upper**
Buprenorphine						
AUCt (pg·min/mL)	0.96	0.80	1.16	0.83	0.62	1.11
Cmax (pg/mL)	0.55	0.34	0.89	0.44	0.25	0.79
Nor-buprenorphine						
AUCt (pg·min/mL)	1.20	0.33	4.33	0.73	0.07	7.72
Cmax (pg/mL)	0.74	0.53	1.04	0.63	0.35	1.14

a: For norbuprenorphine, moderate subjects N=2.

<table>
<tr>
<td>Intrinsic Factors</td>
<td>Renal Impairment</td>
<td>No studies in the BTDS clinical development program directly assessed the pharmacokinetics or safety of BTDS in renally-impaired subjects. However, in lieu of AUC and Cmax, the relationship between buprenorphine concentration and estimated creatinine clearance rates was evaluated for subjects from two BTDS phase 3 trials (studies BP96-0101 and BP96-0102) and is presented below.
<table>
<tr><th>Creatinine clearance (group)</th><th>N</th><th>Mean buprenorphine plasma concentration (%CV)</th></tr>
<tr><td>≥80 mL/minute (Normal renal function)</td><td>49</td><td>60.71 (47)</td></tr>
<tr><td>≥50 and <80 mL/minute (Mild renal impairment)</td><td>88</td><td>57.42 (58)</td></tr>
<tr><td>≥30 and <50 mL/minute (Moderate renal impairment)</td><td>61</td><td>60.77 (44)</td></tr>
<tr><td><30 mL/minute (Severe renal impairment)</td><td>13</td><td>69.94 (67)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Extrinsic Factors</td>
<td>Drug interactions</td>
<td>Include listing of studied DDI studies with mean changes in Cmax and AUC
Study BUP1009: (Ketoconazole DDI study)
<table>
<tr><th rowspan="2">Buprenorphine</th><th colspan="2">Arithmetic Mean (%CV)</th></tr>
<tr><th>BTDS 10 + Ketoconazole (N = 18)</th><th>BTDS 10 + Placebo (N = 16)</th></tr>
<tr><td>AUCt (pg·h/mL)</td><td>16355 (38)</td><td>16628 (33)</td></tr>
<tr><td>AUCinf (pg·h/mL)[a]</td><td>18239 (36)</td><td>19013 (35)</td></tr>
<tr><td>Cmax (pg/mL)</td><td>142 (38)</td><td>146 (33)</td></tr>
</table>
a: For AUCinf, BTDS+Keto N= 13 and BTDS+PBO N=9.
<table>
<tr><th></th><th>BTDS 10 + Ketoconazole (N = 18)</th><th>BTDS 10 + Placebo (N = 16)</th><th>BTDS + Ketoconazole /BTDS Ratio (%)</th><th>90% CI</th></tr>
<tr><td></td><td colspan="2">Exponentiated LSM</td><td></td><td></td></tr>
<tr><td>AUCt (pg·h/mL)</td><td>15272</td><td>15359</td><td>99</td><td>87 to 113</td></tr>
<tr><td>AUCinf [a] (pg·h/mL)</td><td>15570</td><td>17963</td><td>87</td><td>71 to 106</td></tr>
<tr><td>Cmax (pg/mL)</td><td>131</td><td>134</td><td>98</td><td>88 to 109</td></tr>
</table>
a: For AUCinf, BTDS+Keto N= 13 and BTDS+PBO N=9.
</td>
</tr>
</table>

Extrinsic Factors	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) Not applicable for transdermal drug delivery
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. A DDI study (BUP1009) with CYP3A4 inhibitor ketoconazole did not produce clinically relevant increases in mean maximum (Cmax) or total (AUC) buprenorphine exposure following BTDS with ketoconazole as compared to BTDS alone. In addition, pooled data analysis was performed to explore the relationships between pharmacokinetic and subject demographic variables across multiple Phase I studies conducted with BTDS 10 patches. No significant differences in Cmax and AUC were observed for subject demographic variables of age, body weight, gender, and race.	

6.2 TABLE OF STUDY ASSESSMENTS

Phase	Prerandomization				Randomization							
Period	Screening			Baseline	Titration				Tapering[a]			Follow-up[a]
Visit Number	1	2		3	4	5	6	7	8	9	10	11
Visit Name	FV	H-12		Baseline	BTDS 5	BTDS 10	BTDS 20	BTDS 40	T10	T5	T0	EOS
Study Days	-29 to -3	-3	-2	-1	1-3	4-6	7-9	10-13	14-16	21	28	35
Demographics	X											
Informed Consent	X											
Eligibility	X	X										
Medical History	X	X										
Vital Signs and SpO_2	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[c]	X[d]	X[d]	X
Physical Exam	X	X										X
Drug/Alcohol Screening	X	X										
Urine Cotinine	X	X										
Serology	X											
Pregnancy Test[f]	X	X										X
Lab Tests	X	X							X[g]			X
12-Lead ECG (conventional)	X				X[h]	X[h]	X[h]	X[h]	X[e]			X
ECG Telemetry			X									
24-hr H-12 ECG			X[i,j]	X[j]		X[j]		X[j]				
Randomization				X[k]								
TDS Application[l]					X	X	X	X	X	X		
Moxifloxacin						X[m]		X[m]				
PK Samples						X[n]	X[n]	X[n]				
AE	X											
Con. Med.		X										
In Study Unit		X										

[a] Subjects in the moxifloxacin group skipped the tapering period. Their End-of-Study procedures were performed on Day 14. Procedures listed in the follow-up period were conducted at End-of-Study or at early discontinuation.

[b] Vital signs and SpO_2 were measured on Day -3 at check in; Day -2 prior to Holter start; Visit 3 at -24 and -11 hrs; Visit 4 and 6 at predose, 13, 24, 37, 48, and 61 hr after TDS application; Visit 5 at predose, 13, 24, 37, 48, 49, 50, 51 and 61 hr after TDS application; and Visit 7 at predose, 13, 24, 37, 48, 61, 72, 73, 74, 75, and 85 hr after TDS application. Vital signs and SpO_2 for subjects in the moxifloxacin treatment group were measured at the same time of the day.

[c] Vital signs and SpO_2 were measured at 4, 8, 13, 24, 37, and 48 hr after the application of BTDS 10 or placebo TDS.

[d] On Day 21 prior to TDS exchange and on Day 28 after the removal of the last TDS.

[e] Prior to check-out on Day 16.

[f] Serum pregnancy test was performed on female subjects of childbearing potential.

[g] On Day 14 prior to TDS change.

[h] A conventional ECG was performed prior to each new TDS application and 24 hr after each TDS application. On Visit 5, an additional ECG was performed at 49 and 50 h after TDS application. On Visit 7, an additional ECG was obtained at 73 and 74 h after TDS application. Conventional ECGs for subjects in the moxifloxacin group were obtained at the same time of the day.

[i] Performed only on subjects who met other entry criteria.

[j] The 24-hour digital Holter recording started approximately 0.25 h prior to dosing for subjects in the moxifloxacin treatment group. Recordings performed during screening and baseline periods (Visit 2-3) and for subjects in other treatment groups started at a similar time of the day. Each recording lasted 24 h and ended at the next day. Subjects were required to rest in a supine position for at least 10 minutes at the following ECG extraction time points: at the start of the recording, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 7, 10, 13, 18, and 23.5 h after the start of recording.

[k] Performed on Day -1 after lab results were available.

[l] BTDS or placebo TDS was applied/exchanged on Day 1, 4, 7,10, 14, and 21. The last TDS was removed on Day 28 (Visit 10).

[m] A moxifloxacin tablet was administered to subjects in Group 3 at approximately 8 AM on Days 6 and 13.

[n] Blood samples were collected after vital signs and ECG at the following time points: 49, 61, and 72 h after BTDS 10 or placebo TDS application (Visit 5); 72 h after BTDS 20 or placebo TDS application (Visit 6); and 73, 85, and 96 h after the 2 x BTDS 20 (or placebo TDS) application (Visit 7). Blood samples for the moxifloxacin group were collected at the same time of day for Visit 5 and Visit 7 only.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BUPRENORPHINE TRANSDERMAL SYSTEM

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/s/

CHRISTINE E GARNETT

12/23/2009

Christoffer Tornoe was the primary clinical pharmacology reviewer.
Lihan Yan was the primary statistical reviewer.

MONICA L FISZMAN

12/23/2009

NORMAN L STOCKBRIDGE

12/23/2009

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 15, 2002

To: Bob Rappaport, M.D., Acting Director
Division of Anesthetic, Critical Care
And Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

From: Silvia Calderon, Ph.D., Team Leader
Ann-Kathryn Maust, M.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: Consultation regarding Proposed Extractability Procedure
NDA 21-306, Norspan (buprenorphine TDS)
Sponsor: Purdue Pharma L.P.
Submitted to FDA: 9/25/02

This memorandum responds to the Sponsor's questions regarding the adequacy of the protocol designed to assess the extractability of buprenorphine from Norspan patches.

The feasibility of extracting buprenorphine from used or unused patches is relevant to the characterization of the abuse potential of the proposed drug product. A formulation will have a higher abuse potential if it contains active drug that can be easily extracted and solubilized. Soluble drugs can be injected to produce a fast and intense psychoactive effect.

CONCLUSIONS AND RECOMMENDATIONS:

The Sponsor must revise the protocol to incorporate the following recommendations:

1. Specify the number and strengths of patches that will be used.

2. Measure the amount of buprenorphine extracted at 12, 18 and 24 hours under the conditions indicated in the protocol (use of various solvents at room temperature and higher temperatures). The amount of buprenorphine extracted will depend on the length of the extraction. Extractability of buprenorphine a (b) (4) as proposed by the Sponsor is not adequate.

3. In addition to using 10 ml of the various solvents, measure extractability using 50 ml of the solvents for patches with 10 mg or lower amount of drug and 100 ml of the solvents for patches with a higher content of drug.

4. Determine the effect of using unfolded pieces of patches under the conditions specified in the protocol.

5. Describe and justify assay methodology used to quantify buprenorphine.

6. In addition, the Sponsor should send a proposal indicating which component of the RMP will address the ease of extraction.

We remind the Sponsor that labeling must include appropriate warnings to prevent abuse and diversion of the patches and must not underestimate the abuse potential of the formulation. The high concentration of buprenorphine in the formulation; the ease of extraction of buprenorphine from the patches; and the fact that the amount of buprenorphine absorbed can be increased by either applying heat to the patch, by re-applying a patch to a site recently used, or by chewing of the patch are factors that may increase the abuse potential of this formulation.

The Controlled Substance Staff is available for further assistance if needed.

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/s/

Ann-Kathryn Maust
11/22/02 10:26:25 AM
MEDICAL OFFICER

Deborah Leiderman
11/22/02 05:41:15 PM
MEDICAL OFFICER

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	21-306
Sponsor	Purdue Pharma, LLP
Generic Name	Buprenorphine Transdermal System
Proprietary Name	Norspan™
Pharmacologic Class	Opioid analgesic
Proposed Indication	"Norspan™ is indicated for the management of patients with pain requiring continuous opioid analgesia"
Submission Date	January 8, 2002
Review Date	January 17, 2002
Medical Reviewer	Gerald J. Dal Pan, MD, MHS
Supervisory Medical Reviewer	Bob Rappaport, MD
Project Manager:	Sara Shepherd

1 Background

The NDA for Norspan™ was found to be Non-Approvable on September 30, 2001. On November 6, 2002, the Sponsor and the Division had an End-of-Review Meeting to discuss the clinical and biopharmaceutics issues in the Non-approvable letter. These were items 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, and 62. On January 8, 2002, the Sponsor submitted a letter detailing points of disagreement with the Division's meeting minutes. This review responds to those points of disagreement.

2 Responses to Sponsor's Points of Disagreement

Question 52

Sponsor had no points of disagreement. No Agency response required.

Question 53

Sponsor had no points of disagreement. No Agency response required.

Question 54

Sponsor's points of disagreement relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

Question 55

Sponsor's points of disagreement relate to various issues regarding the Division's determination that Studies BP96-0604 and BP99-0203 failed to demonstrate the effectiveness of the product. The Division's responses to the Sponsor's comments are as follows:

The Division acknowledges that Purdue stated that it did not believe BP99-0203 and BP96-0604 had failed to show efficacy.

The Division acknowledges that Study BP 99-0203 was incorrectly referred to as BP96-0203 in the minutes.

The Division acknowledges that Purdue maintains that the quotation from Dr. John Jenkins' letter is appropriate in the context in which it was presented by Purdue at the End-or-Review meeting. The Division maintains that Dr. Jenkins' statement quoted by Purdue in its statement of "PPLP Significant Differences" is not applicable if for no other reason than Norspan has not yet been shown to be effective. Clinically and statistically significant superiority of Norspan over placebo must be demonstrated in clinical trials before Norspan can be considered effective. Furthermore, the Division notes that Dr. Jenkins' letter was not written regarding issues related to the Norspan NDA (21-306) and thus the Sponsor should submit a copy of this letter to NDA 21-306 if it wishes to use it as a point of discussion.

The Division acknowledges that the sentence "The approaches provide good observation for patients but not for AEs" is not clear. The point of this sentence is that the analytical approaches that rely on imputation allow for favorable pain scores to be imputed for patients who drop out because of drug-related adverse events.

The Division acknowledges that Study BP99-0203 used a binary (ie, success/failure) outcome as the primary outcome while Study BP96-0604 used pain scores as the primary outcome.

The Division notes that in describing Studies BP96-0101 and BP96-0102 as "negative", it simply meant that the studies failed to show superiority of Norspan over placebo. The Division acknowledges that Purdue maintains that these studies failed to show a difference between treatment and placebo because they lacked sensitivity. The Division

has not reviewed the studies in sufficient detail to determine the reason for their being failed studies.

Question 56

Sponsor had no points of disagreement. No Agency response required.

Question 57

Sponsor had no points of disagreement. No Agency response required.

Question 58

The Division acknowledges that Purdue will see if they have ECG data in the archives at some clinical sites. The Division also acknowledges that Purdue stated that Purdue believes that preclinical information from in vitro electrophysiology studies is sufficient, but that if additional clinical studies are conducted, ECG data will be collected.

Question 59

Sponsor's points of disagreement relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

Question 60

Sponsor's points of disagreement with regard to Question 60a relate to clinical pharmacology. The clinical pharmacology staff will review this point and provide any required response.

With regard to Question 60b, the Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the human abuse liability study. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

Question 61

The Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the Risk Management issues. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

Question 62

The Division acknowledges that Purdue intends to address the issues in Question 62 in its response to Item 35.

Action Items – Item 5

The Division acknowledges Purdue's proposal to submit a response regarding Study BP99-0203. If at the time of submission, Purdue believes that further discussion of this issue is necessary, Purdue can submit a request for a meeting, which the Division will review.

Action Items – Item 6

The Division acknowledges Purdue's proposal to submit a summary of multiple analgesic trials.

Action Items – Item 9

The Division acknowledges it advised Purdue to collect ECG data in any upcoming studies.

Action Items – Item 10

The Division accepts Purdue's proposal to submit written information on the outlier analysis. The Division agrees that a teleconference on this issue is not necessary at this time.

Action Items – Item 11

The Division acknowledges that Purdue expressed its intent to request face-to-face meeting with the Division and the Controlled Substances staff to discuss further the Risk Management issues. A meeting, however, will only be scheduled once a formal request has been submitted to the Division.

3 Reviewer's Comments

The above comments should be forwarded to the Sponsor.

RECOMMENDATION – Forward comments to Sponsor.

Gerald J. Dal Pan, MD, MHS Date Medical Officer	Bob Rappaport, MD Date Deputy Director, DACCADP

CC: NDA #21-306
HFD-170: Division File
HFD-170: B. Rappaport, MD
HFD-170: G. Dal Pan, MD, MHS

HFD-170: S. Shepherd, MS

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/s/

Gerald DalPan
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1/18/02 01:47:45 PM
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Medical Officer's Review and Evaluation of Clinical Data

NDA # (serial):	**21-306 (000)**
Drug Name (generic):	**Norspan™ (buprenorphine transdermal system, BTDS)**
Sponsor:	**Purdue Pharma, LP**
Proposed Indication:	**"Norpsan™ is indicated for the management of patients with pain requiring continuous opioid analgesia"**
Type of Submission:	**Proposed Pediatric Study Request (Revised)**
Date of Submission:	**03AUG01**
Date of Receipt (CDR):	**06AUG01**
Review Date:	**25SEP01**
Material Reviewed:	**NDA 21-306 (PA) – Proposed Pediatric Study Request (Revised)**
Reviewer:	**Gerald J. Dal Pan, MD, MHS**
Project Manager:	**Sara Shepherd, MS**

1 Background

The Sponsor has submitted a New Drug Application (NDA) for Norspan™ (buprenorphine transdermal system, BTDS). The Sponsor submitted a Proposed Pediatric Study Request (PPSR) on February 20, 2001. The Agency reviewed that PPSR and was unable to issue a Written Request. Specific clinical deficiencies in that PPSR included:

- Pediatric age groups younger than 5 years old were not addressed.
- Age-appropriate formulations were not addressed
- The proposed number of patients (b) (4) was not sufficient for an adequate safety database. About 200 patients are required.
- The clinical setting, (b) (4), is one that requires analgesic agents that have rapid onset and the ability to be titrated and tapered. The 7-day transdermal formulation would thus not be appropriate in many of these cases.
- Amore comprehensive pediatric plan was required.
- A plan for determining multiple-dose pharmacokinetics in all pediatric age groups was required.
- A plan to study titration to doses higher than BTDS 5 was required.
- The Sponsor's proposed large percent difference (b) (4) in mean pharmacokinetic metrics between adults and children required justification.

This review assesses the Sponsor's response to the Agency's comments and the revised Proposed Pediatric Study Request.

2 Overview of Sponsor's Proposed Pediatric Program

The Sponsor proposes three pediatric studies, as outlined below:

(b) (4)

3 Overview of Sponsor's Proposed Studies

3.1 Study 1

Protocol #: None given.

Title: (b) (4)

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(b) (4)

4 Reviewer's Comments

1) The plan does not address children below age 2 years old. A full pediatric plan must address all pediatric age groups.

2) There is not an adequate justification for not developing a smaller patch or studying the effects of buprenorphine administered via another route in pediatric patients.

3) The entry criteria for the proposed clinical trials do not completely characterize in the intended clinical trial population, nor does the protocol clearly state how the need for continuous opioid analgesic treatment will be defined. For example, the protocol must state if children are to opioid-naïve or opioid-experienced. The protocol must state under what circumstances chronic opioid therapy is required. (b) (4)

4) The (b) (4) setting is not appropriate for Norspan. This point was acknowledged by the Sponsor in NDA 21-306 (b) (4) The Division concurs with the Sponsor's conclusion that Norspan is not indicated for (b) (4) use in adults, and sees no reason to think that Norspan will have an improved safety profile in children compared to adults. Thus, the (b) (4) setting is not appropriate for Norspan in either adults or children.

5) The (b) (4) minimum need for chronic opioid therapy is not consistent with the known pharmacokinetic profile of Norspan. The time to reach Cmax is about 120 hours (roughly five days). During the first five days of treatment with Norspan, the buprenorphine levels may be subtherapeutic, and the patient may require additional analgesics. Once a therapeutic level is reached, it can be sustained by weekly re-applications of the patch. The clinical utility of the patch lies in its ability to maintain therapeutic buprenorphine levels over weeks with weekly re-application of the patch. The pharmacokinetic profile of the patch is not suitable, however, short-term pain.

6) Titration after three days may be premature based on the known PK profile of the product. Because the product does not reach Cmax until 5 days after the first dose is applied, titration to the next level at three days is premature, and may potentially result in an overdose.

7) Dosing may be too high for the youngest (or smallest) patients, and further justification of the dosing is required.

5 Recommendations

Forward comments to Sponsor.

Gerald J. Dal Pan, MD, MHS Medical Officer	Date	Bob Rappaport, MD Deputy Division Director	Date

NDA# 21-306
Division File
HFD-170: C. McCormick, MD
HFD-170: B. Rappaport, MD
HFD-170: G. Dal Pan, MD, MHS
HFD-170: S. Shepherd, MS

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/s/

Gerald DalPan
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DIVISION DIRECTOR'S REVIEW AND BASIS FOR ACTION

DATE:	August 31, 2001
DRUG PRODUCT:	Norspan™ (buprenorphine transdermal system) 5, 10, and 20 mg
SPONSOR:	Purdue Pharma, L.P.
SUBMISSION:	NDA # 21-306
DRUG CLASS:	Opioid analgesic
PROPOSED INDICATION:	for the management of patients requiring continuous opioid analgesia
DATE RECEIVED:	November 3, 2000
REVIEWED BY:	Cynthia G. McCormick, MD Director, Division of Anesthetic, Critical Care and Addition Drug Products, ODE II, CDER, FDA

This memorandum conveys my endorsement of the review team's recommendation that Purdue Pharma, L.P.'s NDA # 21-306 Norspan (buprenorphine transdermal system should not be approved. I agree that the NDA fails to provide sufficient evidence to support the conclusion that Norspan will be safe and effective for use under the conditions recommended in its proposed labeling.

Background

This product is a modified release formulation of buprenorphine, an opioid with mixed agonist and antagonist properties, in a transdermal patch designed for q7day application. It is available in doses of 5, 10, and 20 mg per patch delivering 5, 10 and 20 mcg/hr, respectively. This formulation is designed for the patient suffering from chronic pain.

The only currently marketed formulation of buprenorphine is an IV formulation indicated for perioperative pain management. There are sublingual formulations available in Europe for the treatment of opiate addiction. These are not marketed in the United States.

Efficacy

The evidence for efficacy was provided by only two adequate and well-controlled trials. There were several trials performed in the setting of chronic pain in which the test drug failed to establish superiority over the comparator and they were considered failed by the sponsor. An active-controlled study positioned as a noniferiority trial was also submitted but because of certain unfounded assumptions was discarded as a study not capable of demonstrating efficacy.

The two adequate and well-controlled trials have been detailed by Dr. Dal Pan in his review of efficacy and Dr. Grosser in her statistical analyses. These were studies BP96-0604 and BP99-0203.

In the first Study, BP96-0604, a multiple-dose, 84-day, double-blind, placebo-controlled, double dummy, multiple dose study in back pain, patients underwent titration-to-effect and were assessed during maintenance (Days 21-84) for change from baseline in pain. The treatment arms included BTDS, placebo and Oxy/APAP. The outcomes analyzed included change in pain on average and pain right now. Using LOCF methodology the sponsor described a statistically significant difference between the groups during maintenance on both measures. In this study there was a very high rate of discontinuation early on, and the dropout rate due to adverse events was considerably higher in the active treatment groups than the placebo. As Dr. Dal Pan has pointed out, this study has several defects. First, is that the LOCF methodology, due to the significant disparity between dropouts due to AEs and dropouts due to lack of efficacy among the treatment groups, leads to a spurious conclusion. Indeed the dropouts in the active treatment groups are carrying forward an artificially high score, which may reflect the fact that doses that are effective can not be sustained due to adverse events. The other difficulty is that there is no meaningful difference in pain reduction between groups after day 60 in Norspan treated patients and placebo. The relevance of this finding, which may be ultimately attributed to tolerance, although unproven, is that for chronic treatment, a drug which does not maintain efficacy during the clinical trial is not appropriate for long term use as expected. This could be considered a treatment failure.

Study BP99-0203, a 28-day study in hip and knee pain due to osteoarthritis, had a similar study design flaw as the study described above. In addition, the study was prospectively designed to show efficacy by demonstrating a separation between treatment groups of 30% difference in pain relief, assuming a 40% placebo success rate. The study was powered accordingly but in fact demonstrated a treatment effect of only 12%. Finally the study had been prospectively designed to be able to demonstrate a statistically significant effect on pain relief in both the hip and knee joints separately. It was found that there was no statistically significant difference in patients with osteoarthritis of the hip, however.

Additional studies in the target populations, which may include various etiologies of pain or homogeneous populations such as have been submitted, should demonstrate an unequivocal, clinically meaningful and sustained effect. While these studies demonstrated analgesic effect, they did not demonstrate a meaningful effect in the target population. Additional studies should be performed to demonstrate that the drug Norspan can provide meaningful pain relief in a target population with chronic pain requiring sustained opioid treatment. The criteria upon which this target population is based should be more carefully defined in the future clinical trials.

Biopharmaceutics

The sponsor has adequately characterized the pharmacokinetic profile of Norspan™. It is highly protein-bound (96%), and it is metabolized by CYP3A4 and by glucuronidation. Pharmacodynamic drug-drug interaction studies suggest that benzodiazepines, thiazide diuretics and chlorpromazine did not augment the adverse event profile of buprenorphine.

Buprenorphine has been found to have a low transdermal bioavailability (15%) from Norspan™, but that the bioavailability could be increased to 26-55% by applying an external heat source.

Population PK analyses did not reveal any effects of age, race and gender on pharmacokinetics of buprenorphine in Norspan™.

There were several deficiencies identified in the Biopharmaceutics portion of the NDA, which should be corrected. These include:

(1) Data from the hepatic impairment study were pooled. For the purpose of writing appropriate labeling, the sponsor should analyze the data by degree of hepatic impairment into subgroups such as mild and moderate hepatic impairment.
(2) The sponsor has not adequately characterized the potential for drug interactions between CYP3A4 inhibitors and buprenorphine.
(3) An invalidated assay was used in study BP95-0901 to determine plasma buprenorphine. concentrations. The trend toward an exposure-response relationship, which was seen in this study, was not reported. It is suggested that samples from this study be reassayed and used to evaluate the data for PK/PD relationships.
(4) The sponsor will need to tighten dissolution specifications for this product.

Safety—Nonclinical

The nonclinical evaluation of acute and chronic safety of buprenorphine was performed in multiple species, mainly through transdermal exposure, but also through the oral and oral buccal mucosal route. In addition, genotoxicity and mutagenicity testing were performed in accordance with agency standards. Carcinogenicity testing was agreed to as a phase 4 commitment, as was reproductive toxicity testing.

I do not agree with the sponsor's presumption that (b) (4) the NDA requirements for nonclinical

testing. Furthermore the sponsor has no (b) (4) and none was or would have been granted. The clinical experience with the US marketed formulation limited to pain control in the perioperative stetting is largely single dose use. This information cannot be referenced by the sponsor without fulfilling the regulatory requirements of a 505(b)(2) application, nor would it suffice. The projected human exposure (dose and duration) to buprenorphine through the transdermal system (TDS) in the clinical setting of chronic pain control is expected to be greater than that for the IV formulation in acute postoperative pain control.

It is also true, when the applicant and the agency rely upon published literature in making the assessment of safety, that such information cannot be referenced by the sponsor without fulfilling the regulatory requirements of a 505(b)(2) application. In all cases where Dr. Papoian has cited published literature, it has been for background only, and in my opinion, these references were not relied upon in making a regulatory decision.

Since the sponsor filed its application through a different regulatory pathway, 505(b)(1), the requirements of the nonclinical section of the NDA must be provided by studies either performed by the sponsor or by another party who has granted right of reference to the sponsor.

When one critically examines the studies performed by the sponsor for compliance with the NDA regulations, there appear to be two basic issues to sort out. The first issue relates to adequate dosing to establish the toxicity profile of this drug for acute (7 days) and chronic (6 months to a year) treatment. There was considerable discussion about the variation in bioavailability from the patch but no final conclusion as to whether the absence of histopathologic findings across the board in all studies was a function of decreased bioavailability or low toxicity. It is of interest that most animals developed common GI side effects from chronic use, but did not experience the respiratory failure that would be expected from excessive dosing. Some animals experienced reduction in activity. The low pharmacologic toxicity calls into question the adequacy of exposure. While a transmucosal buccal absorption study appeared to deliver greater doses, there was not accompanying histopathology in these studies, since the focus of these studies was not toxicity.

In summary the low clinical toxicity might lead one to conclude that the dosing or route of dosing was not adequately explored. There is no question, however that the sponsor provided a plethora of data on the local skin toxicity of this product, however this should not be the main focus of these acute and chronic toxicity studies.

The second issue to sort out with these data is whether there is adequate detail reported in the nonclinical dermal toxicology studies to provide adequate assessment of systemic toxicity. Dr. Papoian points out that in many of the studies toxicokinetic assessment and basic histopathology was performed. Therefore, the basic systemic toxicity should have been apparent from these studies, if, again, the exposure was adequate.

The genotoxicity and mutagenicity were negative, as Dr. Papoian has detailed in his review.

In summary, the studies performed in support of this NDA may have been sufficient on their face to assess the nonclinical toxicity of buprenorphine delivered in the acute and chronic setting. However the variation in bioavailability and absence of any serious or common pharmacological toxicity suggest that dosing may not have been adequate by the transdermal route to fully test the toxicity of this drug particularly if one assumes that patients may ultimately require considerably more drug than the 20 mg dose studied in this NDA. Dosing by the oral mucosal or IV route might have provided more assurance that the toxicity profile was adequately evaluated. The fact that some degree of tolerance is expected from buprenorphine, and that the human AUCs used for comparison were based on the PK studies, the ultimate dosing in humans may be expected to be many fold higher than assumed. Therefore the sponsor will be requested to perform an additional chronic toxicity study exploring systemic toxicity at higher AUCs than were possible in the transdermal exposure studies.

While the carcinogenicity and reproductive toxicology studies (Segment I and III) were deferred as a phase 4 commitment, this should be renegotiated, taking into consideration the time needed to provide a complete response to the action letter. To date no segment II (teratogenicity study) has been performed. A "prior agreement" on the toxicology package was invoked by the sponsor at the preNDA meeting of November 18,1998, however, there is no documentation for such an agreement.

Safety—Clinical

The clinical safety database for the BTDS product included 1296 patients who received at least one dose of BTDS, a seven-day exposure. A total of 377 subjects were treated in clinical pharmacology studies, either single or multiple dose application of BTDS. There were 99 patients who received a single application of single dose BTDS in the postoperative setting. The remaining 820 patients were treated for chronic pain with multiple dose application of BTDS. A total of 220 patients were treated for ≥6 months and 132 patients were treated for ≥12 months although not all at the maximum dose.

On the surface the common adverse event profile was similar to that of any other opioid drug product. In placebo-controlled trials the incidence of >5% adverse events that were at least two-fold higher in the treatment group (any dose) with BTDS than placebo included: nausea, dizziness, somnolence, constipation, dry mouth, vomiting, asthenia, sweating, and nervousness. In the phase 3 studies such events as somnolence and dizziness were reported at a high frequency approximately 31% for each.

In phase 1 studies and in phase 2 clinical studies in opioid-nontolerant patients such as those treated for postoperative pain, there was an unacceptable incidence of hypoventilation, apnea, and decreased respiratory drive. There was one reported death associated with apnea/ respiratory failure in the postoperative pain setting. Dose related hypotension was also observed in some studies. These adverse events comprise an unacceptable risk for use in the setting of acute pain control and should be labeled accordingly. The sponsor has come to this conclusion.

Dr. Dal Pan has identified a number of clinical concerns about this drug that could not be adequately answered from the existing clinical safety database. There were two cases of treatment-emergent selective neutropenia with ANC's in the range of 240-480 cells/mm^3. In once case the patient responded to treatment with granulocyte colony stimulating factor. In the other case the findings were not discovered or followed up during the clinical trial, therefore no further information is known except that the patient has since died.

During the course of his review, Dr. Dal Pan was able to recognize and document countless examples of errors in data entry, clinically implausible laboratory values, failure to correlate adverse events with dose, failure to report complete EKGs, data and data analysis irregularities in many areas such as hepatic function studies, and others, which were so ubiquitous as to preclude an meaningful interpretation of the data. Examples are detailed in section 4.3 of Dr.Dal Pan's review. The sponsor will be expected to apply extensive quality control to the safety database, ensuring its integrity, before these results can be relied upon for a regulatory decision.

Abuse Liability

The abuse liability assessment of buprenorphine is a requirement for the NDA, even in a case in which the drug substance is already controlled (scheduled) in the Controlled Substances Act (CSA). There are numerous examples of a new formulation contributing to increased abuse by virtue of a change in the pharmacokinetic profile of the drug or a change in the target patient population leading to diversion when the difference in the distribution results in widespread availability. This may be the case with Norspan™. The proper control for buprenorphine has recently been under scrutiny due to the increasing reports of abuse and addiction from buprenorphine in the new sublingual formulation available in Europe. The Controlled Substances Staff has enumerated a number of factors that may contribute to abuse and diversion of this product. The incomplete nature of the data provided by the applicant limits the ability of the FDA to make a proper assessment of the level of control required at this time.

Some preliminary information is known which is relevant to the abuse potential of this product:

(1) The target population for Norspan™ is much broader than has been the case for the existing product on the market and the low level of abuse reported with the existing product may be a reflection of that fact.
(2) Norspan™ contains residual buprenorphine on the order of (b) (4) after one week of use
(3) The sponsor suggests (although there are no data) that reapplication of a worn patch is expected to continue to deliver buprenorphine
(4) Buprenorphine substance is up to (b) (4) extractable from a Norspan™ patch, using commonplace organic solvents.
(5) There is documented adherence failure reported by 6% of the patients who were treated with Norspan™ in clinical trials, requiring reapplication before 7 days.
(6) Buccal absorption studies performed in dogs reveals 345-375 fold increase in bioavailability over the transdermal or oral route.

These few facts alone suggest the potential for significant diversion that is unacceptable for a controlled substance. This risk should be properly addressed by reengineering the patch, rather than restricting distribution and potentially limiting access by legitimate patients.

The likely routes for abuse, based on the animal and chemistry information might be either intravenous or oral buccal mucosal use. The bioavaiablity and pharmacokinetic profile of buprenorphine through the latter route should be fully characterized in the presence of ethanol, a common accompaniment for orally or transmucosally abused drugs. The controlled substances staff has outlined a number of other likely routes for abuse, including multiple patch administration with heat.

The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine and because of failure to extend the patch to full duration of dosing, resulting in inadequate exposure and failure to acheive the actual Cmax of the product and the peak pharmacodynamic effect. Failure to use a standard comparator, such as morphine and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. This study should be repeated taking into consideration these design issues.

While I concur with the review team that withdrawal has been poorly characterized in this NDA, I have concerns about how this can be safely studied in the population under chronic opioid treatment. Any human experiment to test this further should be carefully weighed against the risks to the patient in such a study. Animal studies may have to suffice as a surrogate. There is also ample evidence from the European experience to suggest that buprenorphine is associated with physical dependence.

Some of the information obtained in the course of the abuse liability review, such as the pharmacodynamic interaction with benzodiazepines and the emergency steps to reverse respiratory failure in an overdose setting, can be properly handled with labeling.

The sponsor has submitted a risk management program in brief. There are features of this program that have merit. The details of the program will have to be further developed once the rescheduling decision has been made, the issues of the formulation have been worked out, and once the drug is positioned for approval.

Chemistry Manufacturing and Controls

There were a number of deficiencies noted upon review of the Chemistry portion of this application that relate to drug substance and drug quality. As noted in Dr. Harapanhali's review the material submitted in support of the drug substance does not provide sufficient control over impurities and their safety qualification. The noncompendial novel excipients and their impurities have not been adequately evaluated for dermal absorption and toxicity.

Controls over the manufacturing process are not sufficient to ensure consistent production of drug product. The impurities and degradation products present in the drug product have not been qualified. There are additional stability issues identified in the assay, degradants, in vitro drug release, and adhesion and release strength.

The problem of inadequate patch adhesion has important implication both on the product's efficacy but also on the potential for diversion. This requires correction.

The magnitude and number of deficiencies will preclude the approval of this product. In addition, the drug product should be formulated to minimize the potential for diversion of drug substance that can be readily extracted from the used patch. The deficiencies are detailed in the letter to the sponsor.

Nomenclature

The proprietary name Norspan™ has been found acceptable by the Office of Post Marketing Drug Risk Assessment. However, since the NDA is not deemed appropriate for approval at this time, the name will have to be resubmitted for reevaluation at the time of the complete response.

Specific deficiencies regarding the carton and container labels were conveyed to the sponsor in a discipline review letter dated July 5, 2001. These may be related again in the final action letter as specific steps to avoid medication errors.

Summary and Recommended Action

In this NDA the applicant has failed to provide adequate evidence of safety and efficacy. The controlled studies taken together fail to provide sufficient evidence that this product will be effective in the setting of chronic administration for pain.

The safety data on which the safety profile of this product was developed has been demonstrated to be unreliable and not properly analyzed for complete characterization of safety. There are significant data integrity issues that the sponsor should be corrected prior to resubmission. If it is not possible to verify the integrity of the safety database, then some or all of it will have to be generated anew.

There are additional deficiencies in the characterization of the drug's pharmacokinetic profile necessary for appropriate labeling.

Preclinical studies may be inadequately dosed to characterize the toxicity of this product.

There are significant concerns about the abuse potential of this product for which the Controlled Substances Staff recommends rescheduling, reformulation and a risk management program. Necessary information is lacking for the final determination of abuse liability.

The chemistry and manufacturing and controls of this product are not acceptable. Some of these deficiencies, such as the lack of adequate adherence may have led to inappropriate dosing in clinical trials or an inaccurate assessment of efficacy and safety.

Action: There is insufficient data upon which to approve this product. The sponsor will be sent a nonapprovable letter outlining the deficiencies along with the remedies to bring this application into a position of approvability.

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/s/

Cynthia McCormick
8/31/01 06:59:54 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

REVIEW AND EVALUATION OF CLINICAL DATA – ADDENDUM TO NDA REVIEW

NDA #	**21-306**
Sponsor	Purdue Pharma, LLP
Generic Name	Buprenorphine Transdermal System
Proprietary Name	Norspan™
Pharmacologic Class	Opioid analgesic
Proposed Indication	"Norspan™ is indicated for the management of patients with pain requiring continuous opioid analgesia"
Submission Date	November 3, 2000
Dosage forms	Transdermal system
Strengths	5 mg, 10 mg, 20 mg
Route	Transdermal
Medical Reviewer	Gerald J. Dal Pan, MD, MHS
Supervisory Medical Reviewer	Bob Rappaport, MD
Statistical Reviewer	Stella Grosser, PhD
Supervisory Statistical Reviewer	Tom Permutt, PhD
Addendum Date	August 15, 2001

ADDENDUM TO NDA REVIEW

In the early part of the review cycle for NDA 21-306 (Norspan™), a decision was made that this review division (HFD-170) would not request a routine inspection of a clinical investigation site by the Division of Scientific Investigation (DSI). The basis of this decision was that multiple investigational sites had contributed to both the safety and efficacy data. For example, thirteen investigational sites enrolled a total of 134 patients into Study BP96-00604, one of the placebo-controlled studies that the Sponsor submitted as an adequate and well-controlled study. The number of patients enrolled at each site ranged from 5 to 23, with three sites enrolling 17 patients or more, and four sites each enrolling five or six patients. While the sites enrolling more patients obviously contributed more data to the final analyses, there was no reason to believe that data at these sites was less reliable than data at sites enrolling fewer patients. In Study BP99-0203, another placebo-controlled study that the Sponsor submitted as evidence of the product's effectiveness, 24 investigational sites enrolled a total of 315 patients. In that study, the number of patients enrolled at each site ranged form four to 30, with three sites enrolling 23 patients or more, and six sites each enrolling four or six patients. The highest enrolling site in Study BP 96-0604, which enrolled 23 patients in that study, enrolled 16 patients in BP99-0203. The three highest enrolling sites in BP99-0203 (site 1741 – 30 patients, site 1995 – 29 patients, and site 2063 – 23 patients) did not participate in Study BP96-0604. Thus, no one site contributed an overwhelmingly large number of patients in both studies. For this reason, a routine inspection of a clinical site was not requested.

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/s/

Gerald DalPan
8/20/01 11:14:48 AM
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Bob Rappaport
8/20/01 06:34:09 PM
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REVIEW AND EVALUATION OF CLINICAL DATA

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Route	Transdermal
Medical Reviewer	Gerald J. Dal Pan, MD, MHS
Supervisory Medical Reviewer	Bob Rappaport, MD
Statistical Reviewer	Stella Grosser, PhD
Supervisory Statistical Reviewer	Tom Permutt, PhD
Completion Date	August 10, 2001

EXECUTIVE SUMMARY

CLINICAL REVIEW

Executive Summary

1 RECOMMENDATIONS

1.1 Recommended Action

Based on the clinical information submitted, I do not recommend approval of Norspan™ . This recommendation is based upon my conclusion that the Sponsor has failed to provide substantial evidence of efficacy of the product for its intended use, the "management of patients with pain requiring continuous opioid analgesia." Specifically, the two placebo-controlled clinical trials that form the basis of the Sponsor's effectiveness claim do not demonstrate the sustained effectiveness of the product, relative to placebo, for the management of pain. One of these two studies, Study BP96-6004, does demonstrate an analgesic activity that is superior to placebo over the first 45 to 60 days of treatment, but superiority of the product's effect compared to that of placebo is not sustained throughout the entire 84 days of the trial. The other study, Study BP99-0203, does not provide any evidence of effectiveness of the product. The recommendation is also based upon my conclusion that the extent of data discrepancies and other irregularities in the presentation of safety data in the Integrated Summary of Safety preclude any meaningful interpretation of the safety data, especially the clinical laboratory data. The effect of this deficiency is that the application has insufficient information to determine whether the drug is safe for its intended use. Without substantial evidence of efficacy and given the inadequacy of the safety data, a conclusion about the risk-to-benefit profile of this drug can not be made at this time. The risk-to-benefit profile will also need to consider the abuse liability of the drug product, a potent opioid analgesic, the majority of which remains in the patch after seven days of use and is easily extractable.

1.2 Recommended Phase IV Studies or Marketing Restrictions

No clinical Phase 4 studies are recommended.

1.3 Deficiencies and Recommended Corrective Actions

The clinical deficiencies, and the corresponding recommended corrective actions, are listed below:

1. The Sponsor has not provided substantial evidence that the drug will have its intended effect. The Sponsor should submit the results of an additional adequate and well-controlled clinical study that demonstrates the effectiveness of Norspan™ in the management of chronic pain.

2. The extent of errors and inconsistencies in the safety database and in the safety analyses preclude meaningful interpretation of the safety data. The Sponsor should submit safety data in clinical study reports and in an Integrated Summary of Safety (ISS) that is accurate and presented in a clear manner. Safety data in this context refers to the primary safety database, the tables and listings of safety data in the text of the reports and ISS, the tables and listings in appendices, and the text of the reports and of the ISS and their appendices. Adverse events were not coded consistently. The Sponsor should code all adverse events in the safety database in a consistent manner across all studies. The Intercurrent Diseases and

Conditions that were reported in some of the studies appear to be adverse events. The Sponsor should include in the analysis of adverse events an analysis of Intercurrent Diseases and Conditions, and address how not classifying these events as adverse events may impact the reported rates of adverse events. As part of this analysis, the Sponsor should review all of the events classified under Intercurrent Diseases and Conditions to insure that none meet criteria for a serious adverse event.

3. The safety analyses did not analyze the effect of BTDS dose on safety outcomes. For all safety measures, the Sponsor should include in the ISS analyses that focus on the relationship between BTDS dose at the time of a safety measure and the outcome of the safety measure.

4. The electrocardiogram data do not analyze electrocardiographic intervals. The Sponsor should include in the ISS analyses of electrocardiographic intervals (eg, PR, QRS, QT, QT_c, etc).

5. The electronic case report tabulations do not conform to the standards set forth in the guidance document ***Providing Regulatory Submissions in Electronic Format — NDAs (January 1999)***. Specifically, the guidance regarding the "General consideration for datasets" was not followed with regard to including in all relevant datasets duration of treatment, treatment assignment, sex, age, race, and text in addition to arbitrary number codes. The Sponsor should submit electronic case report tabulations that conform to this guidance document.

6. A potential problem with the design of studies BP96-0604 and BP99-0203 was the fact that during the titration period patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reach at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both. The Sponsor should address this issue, both in regards to the completed studies and in the design of a future study.

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The clinical development program consisted of 15 Phase 1 clinical pharmacology studies involving 459 subjects, 377 of whom received a single dose or multiple doses of the buprenorphine transdermal system (BTDS). These single-dose and repeated-dose studies were designed to assess dose proportionality, bioavailability, bioequivalence at various applications sites, effects of subject age, pharmacokinetics, the effect of elevated body temperature, the effect of hepatic impairment, interaction between BTDS and midazolam, apparent absorption and kinetics, interaction between BTDS and prochlorperazine, and the effect of external heat on BTDS.

A single-dose, randomized, double-blind Phase 2 study in patients with acute post-operative pain enrolled a total of 110 patients, 99 of whom received a single dose of BTDS. Because the acute post-operative setting was deemed not appropriate for a long-acting product such as BTDS, no further studies in this setting were conducted.

Five randomized, controlled, double-blind, multi-dose studies in chronic musculoskeletal pain (two in osteoarthritis and three in low back pain) were conducted. These studies enrolled a total of 1238 patients, 650 of whom received BTDS. Two of the studies (BP96-0101 and BP96-0102) were forced-titration studies, in which subjects were randomly assigned to one of three dose levels (corresponding to BTDS 5, BTDS 10, and BTDS 20), and were titrated to the assigned dose. Three other studies (BP96-0604, BP98-1201, and BP99-0203) used a titration-to-effect dosing regimen, in which patients started at the lowest dose, BTDS 5 and titrated to BTDS 10 and then to BTDS 20, based on tolerability and the amount of pain relief achieved. The latter dosing regimen was used in the trials because it was judged to be more indicative of the dosing regimen to be used in actual clinical practice. Four of the studies (BP96-0101, BP96-0102, BP96-0604, and BP99-0203) included a placebo control group, while one study (BP98-1201) was an active-control study. The controlled Phase 3 studies are summarized in the table below.

Study	Indication/ Treatment Duration	BTDS Doses	Control(s)	Total N
BP96-0101	Osteoarthritis/ 60 days	5, 10, 20 Forced Titration	Oxy/APAP Placebo	270
BP96-0102	Low back pain/ 60 days	5, 10, 20 Forced Titration	Oxy/APAP Placebo	249
BP96-0604	Back pain/ 84 days	5, 10, 20 Titration to Effect	Oxy/APAP Placebo	134
BP98-1201	Back pain/ 56 days	5, 10, 20 Titration to Effect	HCD/APAP	270
BP99-0203	Osteoarthritis/ 28 days	5, 10, 20 Titration to Effect	Placebo	315

In addition to the five controlled Phase 3 studies, an open-label Phase study (BP96-0103), which was largely an open-label extension for some of the earlier controlled Phase 3 trials, enrolled 385 patients, 215 of whom had also received BTDS is an earlier study.

The extent of exposure to BTDS in the Phase 3 program included 919 patients who received at least one dose of BTDS, 220 patients who received BTDS for at least 6 months, and 132 patients who received BTDS for at least 12 months.

At the time of NDA submission, an abuse liability study was being conducted. The final study report for this study was submitted during the review cycle.

2.2 Efficacy

Taken as a whole, the efficacy results form the controlled clinical trials do not support the effectiveness of Norspan for the treatment of chronic pain.

Two forced-titration placebo-controlled studies (Study BP96-0101, a 60-day study in patients with osteoarthritis, and Study BP96-0102, a 60-day study in patients with low-back pain) both failed to achieve their primary endpoint and were labeled as failed studies by the Sponsor. Study BP98-1201, a 56-day active-control study in patients with back pain, could not demonstrate the effectiveness of Norspan because the lack of a placebo control provided no internal assay sensitivity.

Study BP96-0604, an 84-day titration-to-effect study in patients with back pain achieved statistical significance on its primary endpoints – difference in least-squares mean change from baseline between Norspan and Placebo in a repeated measures analysis using the last observation carried forward during the Maintenance Period (Days 21-84) for both Pain on the Average and Pain Right Now. Further review of the study results, however, places these findings in a clinical context that better defines the true efficacy of the product. First, the last-observation-carried-forward methodology has a different effect on the Norspan group compared to the placebo group. Many of the Norspan-treated patients dropped out because of drug-related adverse events, and the relatively favorable efficacy results in these patients (relative to Placebo patients who dropped out) was a factor in the statistical demonstration of a superior effect of Norspan over Placebo. However, both an endpoint analysis (ie, an analysis using the last recorded observation on each randomized patient) and a completers' analysis (ie, an analysis using the last observation only on patients who completed the protocol) indicate no statistically significant difference between Norspan and Placebo. Second, using only observed data (ie, no LOCF), there is no meaningful difference in pain reduction after Day 60 between Placebo- and Norspan-treated patients. Third, the magnitude of effect of the between-group difference in LS mean change from baseline for Pain on the Average and Pain Right Now is less than was contemplated in the protocol. Nonetheless, the data do demonstrate some degree of analgesic activity of BTDS over Placebo during the first 45 to 60 days of treatment. At Day 21 and 30, this effect is statistically significant for both Pain on the Average and Pain Right now using the LOCF methodology. Thus, the Sponsor has demonstrated analgesic effectiveness of the product, but has failed to demonstrate that the effect is superior to Placebo over an 84-day period. These findings may need to be described in the labelling.

Study BP99-0203, a 28-day titration-to-effect study in patients with osteoarthritis of the hip or knee, met its primary endpoint – proportion of all patients successfully treated at Day 28. Taken as a whole, however, the efficacy findings in Study BP99-0203 do not support the effectiveness of the BTDS for the treatment of pain. First, patients were counted as "successfully" treated if their pain evaluations indicated pain relief using an LOCF methodology, regardless of the reason for discontinuation. When patients who were discontinued due to a drug-related adverse event were re-classified as treatment failures, the difference between Norspan and Placebo was no longer clinically or statistically significant. Second, the statistical significance of the Sponsor's analysis may be due, in part, to the large study sample size, which was based on the ability of each of the two study subgroups (hip and knee) to demonstrate separately a statistically significant finding. In fact, when subgroup analyses were based on site of osteoarthritis (hip versus knee), there was no beneficial effect of BTDS in patients with osteoarthritis of the hip compared to placebo (42% success rate for BTDS and 35% success rate for placebo). Third, in the Sponsor's primary efficacy analysis, the between-group difference in treatment successes is

not very large, about 12% (44% success rate in the BTDS group and 32% success rate in the placebo group). The protocol had planned for a between-treatment difference of 30%, assuming a 40% response rate in the placebo group. While the results in the placebo group are close to those contemplated in the protocol, the results in the BTDS group do not approach the intended success rate. While a 12% between-group difference may be clinically significant in some circumstances, much of the apparent increase in treatment success rate in the BTDS group, compared to the placebo group, is due in large part to the favorable treatment response of patients who could not tolerate the study drug, as noted above. Fourth, the four-week duration of the study, which included a three-week titration period and a one-week maintenance period, did not allow sufficient time on the maintenance dose to define a time course of response.

2.3 Safety

Safety data in the NDA comes from 15 clinical pharmacology studies, one Phase 2 study, five controlled Phase 3 studies, and one open-label Phase 3 study. In the clinical pharmacology studies, 377 subjects were exposed to at least one dose of BTDS. In the Phase 2 study, 99 subjects were exposed to a single dose of BTDS. In the five controlled Phase 3 studies, 650 subjects were exposed to BTDS. In the open-label study, 215 subjects were treated with BTDS, 170 of whom had never received the drug previously. Thus, a total of 820 subjects were treated in the Phase 3 studies with BTDS, and a total 919 patients were treated with in the Phase 2/3 program. In the Phase 2/3 program, 784 patients were exposed to BTDS 5, 677 were exposed to BTDS 10, and 533 were exposed to BTDS 20. In the entire clinical development program 1296 individuals were exposed to BTDS. Two-hundred-twenty patients were exposed to BTDS for at least six months, and 132 were exposed for at least one year.

In the Phase 3 studies, about 61-64% of patients were female and about 36-39% were male. The mean age of BTDS-treated patients was 55.9 years in the titration-to-effect studies and 57.3 years in the forced-titration studies. The majority of patients (87-88%) I the Phase 3 controlled studies were white. In the Phase 2 study, 71% of patients were female. The mean age was 68 years. In the open-label study, 62% of patients were female, 91% were white, and the mean age was 57.6 years. In the clinical pharmacology studies, 64%of BTDS-treated subjects were white, 21% were black, 12% were Hispanic, and 1% were Asian. Sixty-six percent were male, and the mean age was 35.0 years.

The overall rate of completion was high in the clinical pharmacology studies, about 95%. In these studies, 2% of subjects discontinued because of adverse events. Discontinuations were common in the Phase 2/3 program. In the titration-to-effect Phase 3 studies, 52% of BTDS-treated patients discontinued prematurely, 23% because treatment-related adverse events and 20% because of ineffective treatment. In the forced-titration studies, 53% of BTDS-treated discontinued, 23% because of treatment-related adverse event and 20% because of ineffective treatment. In both the forced-titration and titration-to-effect studies, discontinuations due to drug-related adverse events were more common in the BTDS- groups and in other active treatment groups compared to the placebo group. In the Phase 2 study, discontinuations due to adverse events occurred in 18% of BTDS 5-treated patients, 3% of BTDS 10-treated patients, 15% of BTDS 20-treated patients, and 9% of placebo-treated patients. In the open-label study, 67% of patients discontinued, 35% because of adverse events, and 15% because of ineffective treatment. On the whole, discontinuations due to adverse events accounted for many of the discontinuations among the BTDS-treated patients, with discontinuations due to ineffective therapy also accounting for a significant number of discontinuations.

Three deaths have been reported in BTDS-treated patients, two in the NDA studies and one in a patients receiving BTDS in a study Sponsored by Napp Pharamceuticals, an affiliated company of the Sponsor. In the NDA studies, one patient in the open-label study died of cardiac-related causes during a hospitalization for a fall. The events leading to her death occurred on Study Day 524, the patch was removed on Day 525, and death occurred four days after the patch was removed, on Day 529. This death was judged by the investigator to be unrelated to study medication. Review of this death suggests that cardiopulmonary disease was the cause of the patient's death, though the reason for the in-hospital deterioration is not clear. In addition, the reason for the fall, which prompted the hospitalization, is not clear. While the buprenorphine in the BTDS patch could have contributed to her ventilatory insufficiency, it is certainly possible that her cardiopulmonary disease was extensive, and that it would have resulted in death regardless of the presence of an opiate. The second death in the NDA studies occurred in a 90-year-old woman in the Phase 2 post-operative study. At 38 hours after study medication was started, she had symptoms of severe hypoxia and developed severe, life-threatening respiratory failure (apnea) and ventricular tachycardia followed by asystole (cardiac arrest). She required cardioversion, converted to an atrial fibrillation rhythm, and was intubated; Swan-Ganz catheterization revealed evidence of congestive heart failure. She was treated with lidocaine for ventricular tachycardia; albuterol and normal saline by nebulizer for respiratory failure; and sodium chloride and dextrose 5%/0.45 normal saline for fluid replacement. The study medication was discontinued at 39 hours. Despite assisted ventilation, intravenous lidocaine, and potassium chloride, the patient died from respiratory failure on study Day 6, 5 days after system removal. The investigator judged the cardiac arrest to be possibly related to study medication, but did not consider the apnea or the tachycardia to be related to study medication. The third death, which occurred in an ongoing non-NDA study, involved a 66-year-old man who was taking BTDS in a clinical trial for osteoarthritis. He was taking BTDS 10 when, on Day 25, he developed dyspnea, attributed to a viral infection. Five days later (Day 30) he was admitted to the hospital, where he was treated with nebulized drugs. The BTDS was removed that day. He died the following day (day 31). The discontinuation page of his CRFs stated myocardial infarction as the cause of death, while the death certificate listed the cause of death as (a) left ventricular failure, (b) atrial fibrillation, and (c) septicemia and indicated evidence of underlying ischemic heart disease. The events were judged by the investigator to be improbably related to the study medication. In review of this case, it is not clear if the primary event was pulmonary (ie, dyspnea due to a pulmonary viral infection) or cardiac (eg, dyspnea due to left ventricular failure). It is also possible that he suffered a myocardial infarction after developing a primary pulmonary process, such as a pulmonary viral infection. In the absence of more detailed information about the patient's clinical course, no firm conclusions can be made about this death

Two serious adverse events occurred in the clinical pharmacology studies. In one case, a 33-year-old woman had a syncopal episode after the second application of a BTDS patch, which occurred 10 days after the removal of the first patch. In the second case, a 37-year-old woman with a prior history of gallstones developed cholecystitis, the symptoms of which began to appear about 11 hours after removal of a BTDS 20 patch. The cholecystitis was diagnosed about three days later, and she underwent a cholecystectomy two days after that. She reportedly did well after that.

In the placebo-controlled Phase 2/3 studies, the proportion of BTDS-treated patients who developed a serious adverse event (2.0%) was similar to the proportion in the Placebo group (2.1%). The rate of patients with at least one serious adverse event was higher in the long-term open label study (BP96-0103), though this higher rate may be the result of prolonged exposure. In general, review of the SAEs in each treatment group reveals that the clinical spectrum of SAEs is comparable among the groups, and reflects events that can be expected to occur in a patient

population of this age. Review of the SAEs is notable for that fact that the use of BTDS in the post-operative setting is associated with apnea and therefore, as the Sponsor has noted, is not indicated for post-operative use. This association with apnea in post-operative patients raises the possibility that use of BTDS in patients with chronic pain may not be appropriate when these patients experience acute changes in cardiac or pulmonary function (eg, myocardial infarct, pulmonary edema, pneumonia, exacerbation of COPD, etc). Apart from the cases of apnea, the clinical spectrum of SAEs in BTDS-treated patients is similar to the clinical spectrum of SAEs in patients in the other treatment groups, including the placebo group. In general, these SAEs are typical of what might be expected in patients in this age group. Apart from the cases of apnea, the causal role of BTDS in these SAEs is not definitive, and generally can not be ascertained.

Common (≥ 2%) Adverse events leading to discontinuation of BTDS-treated patients in the titration-to-effect studies included nausea (8%), vomiting (6%), dizziness (6%), headache (5%), and somnolence (3%). Common (≥ 2%) adverse events leading to discontinuations of BTDS-treated patients in the forced-titration studies included nausea (8%), dizziness (6%), somnolence (6%), vomiting (5%), headache (3%), and constipation (2%). Adverse events leading to discontinuation in more than 1% of patients in the open-label study included nausea (10%), rash (9%), dizziness (6%), pruritus (6%), vomiting (4%), somnolence (4%), application site reaction (4%), headache (3%), constipation (3%), depression (1%), and dyspnea (1%). In the Phase 2 study, common reasons for discontinuation in BTDS-treated patients included confusion (5%), somnolence (3%), hostility (2%), and apnea (2%). The profile of adverse events leading to discontinuations in the Phase 2 study is notable for the cases of apnea, which were also serious adverse events. The Sponsor, however, has indicated that the post-operative setting of the Phase 2 study is not appropriate for use of BTDS. Apart from the cases of apnea in the Phase 2/3 studies, the spectrum of adverse events leading to discontinuation in BTDS-treated patients is consistent with common opioid-related side effects.

Of the nine BTDS-treated subjects in the clinical pharmacology studies who discontinued because of adverse events, in eight the adverse events were judged definitely or probably related to study drug. These events included vomiting, syncope, dyspnea, hypoventilation, anxiety, confusion, dizziness, and hypotension. Hypoventilation occurred in one healthy subject who experienced 2-30 second periods of apnea and whose oxygen saturations decreased to about 87%. Signs and symptoms returned to normal about 33 hours after patch removal.

Drug interruptions were those cases in which the drug was stopped, but later resumed. The incidence of adverse events that led to drug interruptions in the titration-to-effect studies ranged between 2.3% and 2.4% for the BTDS, Oxy/APAP and HCD/APAP groups, and 1.4% for the Placebo group. The incidence of individual adverse events that led to drug interruption was <1% for all such adverse events. Adverse events leading to drug interruption occurred in eight BTDS-treated patients, and included: anorexia (n=1), dyspepsia (n=1), nausea (n=2), vomiting (n=1), confusion (n=1), dizziness (n=1), insomnia (n=1), asthma (n=1), other site reaction (n=1), pruritus (n=1), and pruritis at site. The incidence of adverse events that led to drug interruptions in the forced-titration studies was 2.9% in the BTDS 5 group, 6.8% in the BTDS 10 group, 3.9% in the BTDS 20 group, and 3.7% in the Oxy/APAP group. The incidence of individual adverse events that led to drug interruption was between 1% and 2% for all such adverse events. Adverse events leading to drug interruption occurred in two BTDS 5-treated patients, and included: edema at three different sites (n=1), erythema at three different sites (n=1), and rash (n=1). Adverse events leading to drug interruption occurred in four BTDS 10-treated patients, and included: nausea (n=2), vomiting (n=2), dizziness (n=1), sweating (n=1) and erythema at site (n=1). Adverse events leading to drug interruption occurred in four BTDS 20-treated patients, and included: dizziness (n=1), vomiting (n=1), and headache (n=1). Review of these data indicates

that the incidence of adverse events that led to drug interruption was generally similar between the titration-to-effect studies and the forced-titration studies, though the rate in the BTDS 10 group (6.8%) in the forced-titration studies was higher than other rates. The adverse events leading to drug interruption are typical of opiate-related adverse reactions, except for the local reaction, which may be related to the patch itself. As in the controlled clinical trials, the adverse reactions commonly leading to drug interruption in the open-label study were those typically associated with opiate-related side effects, or those related to local site reactions. There were no adverse events leading to drug interruptions in the Phase 2 study or in the clinical pharmacology studies.

In the titration-to-effect studies, the incidence of any adverse events that led to dose reduction was 11.8% in the BTDS group, 6.2% in the HCD/APAP group, 4.7% in the Oxy/APAP group, and 1.9% in the placebo group. Among BTDS-treated patients, 22/338 (6.5%) required dose reduction due to an adverse event in the digestive system, including anorexia (n=1), constipation (n=3), dry mouth (n=3), nausea (n=17, 5%), and vomiting (n=6, 1.8%). The rates of nausea requiring dose reduction was notably higher in the BTDS group (5%) than in the HCD/APAP group (0.8%), the Oxy/APAP group (2.3%), or the placebo group (0%). Twenty-four of 338 BTDS-treated patients (7.1%) required dose reduction due to an adverse event in the nervous system, including confusion (n=1), depression (n=1), dizziness (n=7, 2.1%), insomnia (n=1), nervousness (n=1), paresthesia (n=2), somnolence (n=13, 3.9%), speech disorder (n=1), stupor (n=1), thinking abnormal (n=1), and tremor (n=1). The rate of somnolence leading to dose reduction in the BTDS group (3.9%) was higher than the corresponding rates in the HCD/APAP group (0.8%), the oxy/APAP group (2.3%), or the Placebo group (0%). In the forced-titration studies, one patient in the Oxy/APAP group, and none in the BTDS group, required dose reduction due to an adverse event. There were no adverse events leading to dose reductions in the Phase 2 study or in the clinical pharmacology studies.

Common adverse events in the Phase 3 controlled studies were, in general, those typically associated with opioid analgesics. These adverse events were also more common in BTDS-treated patients than in Placebo-treated patients, as indicated in the table below.

BTDS-Placebo Difference for All Adverse Events Occurring in More than 5% of BTDS-treated Patients in the Four Phase 3 Placebo-Controlled Trials			
Adverse Event (COSTART Term)	Any BTDS Dose	Placebo	Difference (BTDS-Placebo)
Nausea	37.5	14.0	23.5
Dizziness	35.7	14.6	21.1
Somnolence	34.5	10.4	24.1
Headache	30.8	18.2	12.6
Consipation	29.6	10.7	18.9
Dry Mouth	27.1	13.3	13.7
Pruritus	23.1	13.6	9.5
Pruritus at Site	18.2	14.9	3.3
Vomiting	16.7	3.9	12.8
Asthenia	10.4	5.2	5.2
Dyspepsia	6.9	5.5	1.3
Erythema at Site	6.9	5.2	1.7
Sweating	6.9	2.9	3.9
Diarrhea	6.7	6.2	0.5
Insomnia	6.3	4.9	1.4
Rash at Site	6.1	10.7	-4.6
Nervousness	5.7	1.3	4.4
Source: Table 3 in Sponsor Submission o f July 26, 2000			

The adverse event profile in the open-label study was similar to that in the Phase 3 controlled studies and in the clinical pharmacology studies. The spectrum of adverse events was also similar in the Phase 2 study, though the incidence of opioid-related adverse events in that study may be confounded by the co-administration of morphine patient-controlled analgesia.

Investigators characterized adverse events as mild, moderate or severe. The majority of adverse events were not severe. In the phase 3 studies, most of the adverse events whose frequency of moderate or severe events was 3% or higher are those generally associated with opioid usage. These rates were similar in the BTDS-treated patients and other active-control-treated patients, and these rates were higher than the corresponding rates in the placebo group. Adverse events whose frequency of moderate or severe events was 3% or higher in the clinical pharmacology studies included headache (13% moderate, 3% severe), nausea (13%, 2%), vomiting (9%, 1%), dizziness (7%, 1%), constipation (7%, 1%), somnolence (5%, <1%), asthenia (3%, 1%), and non-site pruritus (3%, 1%). These rates were higher than the corresponding rates among Placebo-treated subjects, whose rate of moderate or severe adverse events was low.

Investigators assessed the relationship of study drug to an adverse event as none, possibly, probably, or definitely related to study drug. For both the titration-to-effect studies and the forced-titration studies, the body systems with the highest frequencies of adverse events judged to be related (ie, either possibly, probably, or definitely) were the digestive, nervous, skin, and body as a whole systems. The same pattern was seen in the open-label study. In the Phase 2 study, the respiratory body system had a high frequency of treatment-related adverse events, in addition to the other body systems. These body systems contain nearly all of the adverse events commonly associated with opioids.

To characterize the time course of onset for common adverse events, the Sponsor used Kaplan-Meier methodology and calculation of hazard rate per day to measure the proportion of patients

with the event over time and the rate of new events over time. These analyses were performed for nausea, vomiting, dry mouth, dizziness, somnolence, constipation, and headache. The Sponsor notes that the risk of these adverse events is highest early in treatment, generally within the first 5 or 10 days of treatment.

The Sponsor's analyses of adverse events and the presentation of adverse event data did not consider BTDS dose level. Specifically, the number and frequency of adverse events was not specified by dose level. At the request of the Agency, the Sponsor provided frequency tables of adverse events by the dose at which the event occurred. For common adverse events, there was no clear trend of increase event frequency with increasing doses of BTDS. In fact, many common adverse events had a higher frequency at the BTDS 5 dose level than at any other dose level. Because patients spent variable amount of time at the different dose levels (eg, all patients wore the BTDS 5 patch for at least a few days, while many never wore the BTDS 20 patch), a simple calculation of rates may not be sufficient to analyze the relationship of dose to development of adverse events. At the request of the Agency, the Sponsor provided person-time exposure for all studies. When the number of reported adverse events at each dose level (not the number of patients with the adverse event at each dose level) was used to characterize the number of events per person-year of exposure, the data suggested that the risk is highest at the BTDS 5 level, and decreases at the two higher dose levels. This finding is consistent with the Sponsor's analysis that many of the common adverse events occur early in the course of treatment.

Clinical laboratory testing was conducted in all the clinical studies. In general, clinical laboratory testing was conducted at screening and at the end of the study. In the open-label study, clinical laboratory testing was conducted at screening, every 12 months, and at the end of the study. The Sponsor notes that no laboratory abnormality was considered a significant adverse event. The Sponsor evaluated the lab data in three ways: analysis of mean change from baseline, shift table analysis, and analyses of clinically significant abnormal values. Review of the mean changes from baseline revealed several clinically implausible values, which made further interpretation of the remaining laboratory analyses difficult. The Sponsor was asked to address these issues, and as of July 30, 2001 had not submitted a complete response to these requests. The Sponsor has noted in a July 30, 2001 submission, however, that 34 clinically implausible laboratory values were found and corrected. Although the extent of data irregularities in the laboratory database is not known, there are a sufficient number of data irregularities to preclude any meaningful interpretation of the lab data.

Analysis of hepatic function data suffers from the same limitation as the remainder of the laboratory data – data and data analysis irregularities that preclude any meaningful conclusions.

Two patients developed clinically significant neutropenia after administration of BTDS. One subject, a 23-year-old man in an ongoing IND clinical pharmacology study (not part of the NDA submission) developed an absolute neutrophil count (ANC) of 240 cells/mm^3 about two months after removing his second BTDS patch. Pre-treatment ANC was 2200 cells/mm^3, and this began to decline slowly after the entry into the study. Bone marrow analysis was reportedly normal, with no arrest in white blood cell precursors. He responded to granulocyte colony stimulating factor (G-CSF), and the event was attributed by his hematologist to "peripheral granulocytic consumption/sequestration." The causal role of BTDS is not known. In the NDA studies, one patient was identified with a post-treatment ANC of 480 cells/mm^3. Her baseline value was 4274 cells/mm^3. This low value was taken at the end of the study, and no follow-up values were available. Potentially contributory concomitant medications included allopurinol, amlodpine, and diclofenac. She died about two years later, though the cause is not known. Because this neutropenia was retrospectively discovered, it was not evaluated, and the cause is not known.

While in both cases, a causal role of BTDS can not be definitively excluded, the time course of the neutropenia in the healthy volunteer relative to BTDS exposure and the potential causal role of concomitant medications in the second case (b) (6) argue against BTDS as the sole causative agent.

Vital signs were measured in all the clinical studies. Analysis of vital sings included between-group analyses of mean changes (baseline to end of study) for all vital sings (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and body temperature). In the Phase 3 controlled studies, the mean values of all vital sings for the BTDS and placebo groups were within the normal range at baseline and at the end of the study. The same pattern was observed in the clinical pharmacology studies, and in the open-label study. In the Phase 2 Study BP96-0104, mean systolic blood pressure, diastolic blood pressure, and respiratory rate were notably lower at the end of the study, compared to screening for all treatment groups. The effect of systolic blood pressure was notably greater for the BTDS 10 and BTDS 20 groups than for the BTDS 5 or Placebo groups. The effect on diastolic blood pressure was lower than the effect on systolic blood pressure, and was least pronounced in the Placebo group, compared to the three BTDS groups. Heart rate was increased in all four treatment groups. These findings may be consistent with the post-operative setting.

In the Phase 2/3 studies, apnea was reported in two patients in the Phase 2 study. In each of these cases, other contributing factors in the post-operative setting likely played a role, though a role for BTDS can not be excluded. In the open-label study, two cases of apnea were reported, each occurring after BTDS had been stopped. In one case, a patient suffered a cardiac disease, including a myocardial infarction and pulmonary edema. In the other case, apena was attributed to a benzodiaepine overdose.

Dyspnea was reported in 9/384 (2.3%) of BTDS patients in Study BP96-0103. Of the 9 BTDS patients, 8 had one report of dyspnea and 1 had two reports. Six of the ten reports occurred at the BTDS 20 dose, 2 occurred at the BTDS 10 dose, and 2 occurred at the BTDS 5 dose. One patient (4306) required hospitalization; in the other 8 patients the event was non-serious. Study medication was discontinued for four patients. Causality was judged as possible in 3 patients, and as probable in one. In Patient 4306, the causality was judged as none.

In the clinical pharmacology studies hypoventilation was reported in 2/377 (0.5%) BTDS subjects, 1/83 (1.2%) BIV subjects, and 1/24 (4.2%) Duragesic subjects in the clinical pharmacology studies. In the two BTDS-treated subjects, five episodes were reported – one in Subject 36 (Inv 195) and four in Subject 1 (Inv 1277). None of the episodes was judged to be serious. Subject 36 was reported to have “subjective decreased respiratory drive” (investigator verbatim term), but never had a respiratory rate below 12 (see Data Listing 16.9.2.1 in the BP98-0201 Study Report). Subject 1 had several episodes of apnea and at least one episode of oxygen desaturation.

In the Phase 2 study BP96-0104, mean systolic and diastolic blood pressures were lower at the end of the study compared to screening. The Sponsor suggests that these changes in blood pressure between the pre-operative period and the post-operative period may be due to factors other than BTDS.

In the clinical pharmacology studies, hypotension was defined as a simultaneous decrease from baseline of ≥ 20 mm Hg in systolic blood pressure and ≥ 10 mm Hg in diastolic blood pressure. Among all BTDS-treated subjects, a decrease in systolic blood pressure of at least 20 mm Hg was observed in 152/564 (27%) of subjects. Such decreases in systolic blood pressure appeared dose-

related, occurring in 13% of BTDS 5 subjects, 25% of BTDS 10 subjects, and 33% of BTDS 20 subjects. The frequency of a reduction of 10 mm Hg or more is diastolic blood pressure was even more common, occurring in 322/564 (57%) of all BTDS subjects, without any clear relationship to dose. Hypotension, as defined above, appeared dose-related, occurring in 3/40 (8%) BTDS 5 subjects, 53/350 (15%) BTDS 10 subjects, and 35/127 (28%) BTDS 20 subjects. At any BTDS dose, hypotension occurred in 16/25 (64%) healthy elderly subjects compared to 66/483 (14%) healthy young subjects (see Sponsor Table 8.13.8.6.1E in the ISS). The timing of hypotension and other changes in blood pressure was examined over the first 96 hours of patch placement, and no temporal pattern could be discerned (see Table 8.13.A.7B in the ISS).

Apart from rash and other local application site reactions, which were reported as adverse events, there were no clinically significant changes in the physical examination.

There were no electrocardiograms performed during any of the Phase 3 controlled studies or during the open-label study BP96-0103. In the Phase 2 study, electrocardiograms were recorded at screening and at the end of the study. Shift table analysis of the frequency of changes from normal to abnormal revealed that shifts from either Normal to Abnormal or from Abnormal to Normal is similar for the four treatment groups (BTDS 5, BTDS 10, BTDS 20 and Placebo). Such an analysis, however, is limited by the fact that the nature of these abnormalities is not clear. Data Listing 16.2.9.4 in the BP96-0104 study report lists the ECG status (ie, Normal or Abnormal) at screening at baseline, and provides the investigator's summary of and comments on the ECG abnormalities. Review of this listing is limited by the fact that when compared to the case report forms, many of the comments are truncated, that is, the final words or phrases are missing. Thus, a full review of these ECG changes is not possible.

No significant drug-demographic interactions were identified in the safety review.

Drug-drug interactions assessed in the clinical pharmacology program included midazolam (BP97-1001), prochlorperazine (BP98-0202), and thiazide diuretics (BP97-0303). In these pharmacodynamic interaction studies, no clinically relevant drug-drug interactions were noted when buprenorphine was co-administered with midazolam, prochlorperazine, or thiazide diuretics (see Studies BP97-1001, BP98-0202, and BP97-0303).

Drug-disease interactions assessed in the development program included hepatic impairment (Study BP97-0112), hypertension (Study BP97-0303), and fever/external heat application (Studies BP98-1204 and BP99-0204). No studies of the pharmacokinetics of buprenorphine have been conducted in patients with renal impairment. The Sponsor has conducted a single study evaluating the pharmacokinetics of buprenorphine in patients with mild or moderate hepatic impairment. Results of this study indicate that similar systemic exposures (AUC) but a 50% reduction in Cmax are observed when comparing systemic buprenorphine levels from healthy subjects to those of patients with mild or moderate hepatic impairment. Systemic exposure to norbuprenorphine did not appear to be affected by mild or moderate hepatic impairment. However, this analysis is based on pooling of subjects with mild and moderate impairment. Such pooling may obscure clinically important changes in subjects with moderate hepatic impairment (see Study BP97-0112). Fever (internal heat) does not alter the pharmacokinetics of buprenorphine with BTDS applications (see Study BP96-1102). However, external heat application results in a 26-55% higher Cmax relative to application without heat (see Study BP98-1204). There were no clinically significant drug interactions in hypertensive patients receiving thiazide diuretics.

Review of the Sponsor's abuse liability data is notable for the fact that a withdrawal syndrome can occur after BTDS discontinuation. The methodologies used in the clinical trials were not sufficiently sensitive to assess the potential magnitude of this problem. BTDS may be a drug sought out by those who seek to abuse opioid analgesics, though the strict drug dispensing standards in a clinical trial setting, relative to general clinical practice, preclude an assessment of how common this problem will be. The relatively strict environment of a clinical trial, compared to actual clinical practice, precludes assessment of the abuse liability or abuse risk that may derive from the fact that the majority of the buprenorphine is still in the patch even after the patch has been worn for 7 days, and that the buprenorphine is easily extractable from the patch.

Taken as a whole, the safety data indicate that the most common adverse effects of BTDS are those typically associated with opioids, such as nausea, vomiting, dizziness, and somnolence. These side effects limit the tolerability of the drug. The high frequency of dizziness (31.2%) and somnolence (30.6%) in the Phase 3 controlled studies are an indication of the central nervous system side effects of the product, which will need to be addressed in the labelling. The use of BTDS in the post-operative is associated with apnea and therefore, as the Sponsor has noted, is not indicated for post-operative use. This association with apnea in post-operative patients strongly suggests that use of BTDS is inappropriate not only in post-operative patients but also in patients with chronic pain who are experiencing acute changes in cardiac or pulmonary function (eg, myocardial infarct, pulmonary edema, pneumonia, exacerbation of COPD, etc). This issue will need to be addressed in labelling.

2.4 Dosing

In all of the Phase 3 studies, patients were titrated from BTDS 5 to the final assigned dose or to the final effective dose. This strategy appears to have been successful. Of note, the Sponsor's analysis, while it did not directly address dose-response of adverse events, did note that the risk of common adverse events is highest in the first five to ten days of treatment.

A potential problem with the design of studies BP96-0604 and BP99-0203, which was not explored in either the Sponsor's analysis or in this review, was the fact that during the titration period patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reach at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both.

2.5 Special Populations

No clinically significant drug-demographic interactions were noted in the safety analyses, and no obvious drug-demographic interactions were noted in the efficacy analyses. Apart from the pediatric population, a wide age range of patients was included in the NDA studies to support the conclusion that no significant age effect exists for safety or efficacy. Both genders were also well represented in the clinical studies, and no clinically significant gender effects were noted. The proportion of non-white races was small in the Phase 2/3 program, and the proportion of individual racial groups was event smaller.

Other special populations studied include patients with hepatic impairment. Though the data from that study will need to be re-analyzed to look at patients with mild hepatic impairment separately

from those with moderate hepatic impairment, the preliminary conclusion is that mild or moderate hepatic impairment does not impact BTDS dosing.

Clinical Review

1 INTRODUCTION AND BACKGROUND

1.1 Proposed Indications

The Sponsor's proposed indication for Norspan is:

> "Norpsan™ is indicated for the management of patients with pain requiring continuous opioid analgesia."

Norspan™ (buprenorphine transdermal system), when applied to the skin, is designed to release continuously buprenoprphine to intact skin, and thus deliver therapeutic levels of buprenorphine for the control of moderate to severe pain.

Buprenorphine is an opioid analgesic with partial mu-opioid agonist and kappa-opioid antagonist properties. The analgesic activity of buprenorphine at low to moderate doses is 25 to 50 times that of morphine, with a longer duration of action (6 to 8 hours). Despite being more potent than morphine, buprenorphine's maximal effects are less than those of morphine, which is a full mu-opioid agonist. Relative to morphine, this pharmacological property of buprenorphine implies that its analgesic effects have a ceiling effect.

The pharmacokinetic rationale of delivering buprenorphine for the management of pain via a continuous transdermal release system is that both orally and sublingually administered buprenorphine have poor bioavailability (about 1/15 and 2/3 as potent, respectively, as parenteral buprenorphine). Parenteral buprenorphine, however, has a relatively short duration of action, about 6 to 8 hours.

An injectable form of buprenorphine (Buprenex Injectable, NDA 18-401) is the only approved buprenorphine product in the United States. Its approved indication is "Buprenex is indicated for the relief of moderate to severe pain."

1.2 Milestones in Product Development

IND 50,273 for buprenorphine transdermal system was submitted on April 4, 1996.

In January 10997, the Sponsor changed its development plan to examine a 7-day duration of wear (b) (4)

The Sponsor, Purdue Pharma, LP and the Agency met for a Pre-NDA meeting on November 18, 1998. At the time, results of clinical studies BP96-0101(osteoarthritis), BP96-0102 (low back pain), BP96-0104 (post-operative pain), and BP96-0604 (low back pain) were available. (b) (4) the study in post-operative pain was deemed irrelevant with regard to the claim of moderate to severe pain. Because studies BP96-0101 and BP96-0102 were did not meet their primary statistical endpoints, the Agency asked the Sponsor for an additional efficacy study to expand the efficacy database in chronic pain. Two additional efficacy study protocols, BP98-1201 (low back pain) and BP99-0203 (osteoarthritis) were submitted in 1999.

A cancer pain study was discussed at this pre-NDA meeting. The Sponsor then designed a cancer pain study (BP99-0101), but the Sponsor reports problems executing this plan. An alternative plan was submitted on June 7, 1999. This plan called for labeling against the use of the product in opioid-tolerant patients, the use of a surveillance program to alert of any trends toward use by oncologists, and the possible inclusion of a summary of safety experience in cancer patients outside the US. The cited rationale behind this plan was that Agency for Health Care Policy and Research (AHCPR) guidelines (Publication #94-0592, page 78, March 1994) recommended against the use of buprenorphine in cancer pain because mixed agonist/antagonists such as buprenorphine, when used in patients who are dependent on high doses of mu-agonists, could cause withdrawal effects.

At the pre-NDA meeting, the Agency requested the Sponsor to include in the NDA a justification to keep BTDS at Schedule 5. The Agency and the Sponsor also agreed that both reproductive toxicology and carcinogenicity studies could be performed post-approval, as Phase 4 commitments.

In a letter to the Sponsor on July 6, 2000, the Agency stated that the proposed format for the presentation of the descriptive statistics for the ISS and the pooled analyses for the ISE appeared to be acceptable, but noted that a complete evaluation could only be performed during review.

In a CMC/PK meeting on July 14, 2000, the Sponsor and the Agency agreed that a second pre-NDA meeting was not necessary, in view of the fact that the late timing of the meeting would not allow for appropriate modifications to the program.

The Sponsor submitted NDA 21-306 on November 3, 2000.

1.3 Foreign Marketing

The Sponsor has not marketed Norspan in any foreign country, and has no pending application for the product in any country. The product has never been withdrawn from the market in any country.

An identical formulation of BTDS 5, 10, and 20 mg is being studied in clinical trials in the United Kingdom by Napp Pharmaceuticals, an associated company of Purdue Pharma, LP, the Sponsor, under CTX 16950/0109/A (approved April 1, 1999).

The Sponsor notes that it is aware that Grunenthal GmBH has applied for marketing authorization in Europe for a 3-day buprenorphine transdermal system in 20, 30, and 40 mg dosage strengths. This product is also manufactured by (b) (4)

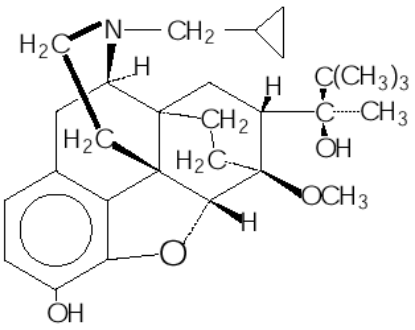
In Europe, but not in the United States, a sublingual formulation of buprenorphine is marketed for the treatment of heroin addiction.

2 FINDINGS FROM OTHER REVIEW DIVISIONS OR CONSULTS

2.1 Chemistry

The active substance in BTDS is buprenorphine($C_{29}H_{41}NO_4$; M.W. 467.6; CAS Registry No. 52485-79-7). Buprenorphine is a synthetic opioid analgesic derived from the opium alkaloid thebaine and is a partial m-opioid agonist which provides sustained analgesia. The chemical name

for buprenorphine is: 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- a-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-a-methyl-, [5a, 7a,(S)]-. The structural formula is:



The buprenorphine transdermal system (BTDS) is a square or rectangular patch with rounded corners that is designed to provided a controlled release of buprenorphine for seven days. BTDS is a matrix system in which the drug is in direct contact with the skin and is dissolved in apolymer matrix. The rate of drug release is controlled by the diffusion of buprenorphine in the adhesive matrix through the stratum corneum of the epidermis.

The Sponosr's Figure 3.4.1, reproduced below, illustrates the structure and content of the BTDS. The outermost backing layer prevents the transdermal system (TDS) from sticking to clothing. The next layer, which contains the adhesive matrix without buprenorphine, allows the TDS to stick to the skin. A separating foil prevents the buprenorphine in the buprenorphine-containing adhesive matrix from diffusing into the adhesive matrix without buprenorphine. The buprenorphine-containing adhesive matrix is in direct contact with the skin. A (b) (4) release liner protects the contact surface and is removed prior to application of the BTDS to the skin.

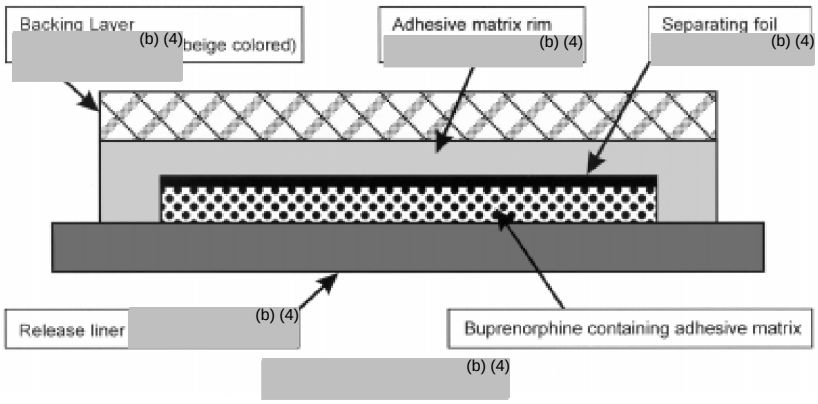


FIGURE 3.4.1.

Buprenorphine Transdermal System

The chemistry reviewer are finalizing the chemistry issues at this point, and these are not available for incorporation into the review at this time.

2.2 Pharmacotoxicology

The pharmacotoxicology of Norspan has been reviewed by Dr. Tom Papoian, Supervisory Pharmacologist in HFD-170. Dr. Papoian has concluded that the results of acute, subchronic, and chronic dermal studies in several animal species have demonstrated minimal dermal toxicity after exposure to buprenorphine-containing patches. Although some of the dermal findings, such as edema and erythema were attributed to the drug, many of the effects were also seen in animals treated with placebo patches, suggesting that the dermal effects may results as much to the patch as to the drug itself. Other signs in animals, such as reduced activity and low fecal output, could be attributed to the opioid effects. Other than skin changes, no histopathological changes were reported in any of the tissues examined. Plasma levels in animals were 4-21 times those seen in humans. Buprenorphine was found to be negative for genotoxicity.

In beagle dogs, there was marked systemic absorption of buprenorphine after buccal administration, suggesting that children who accidentally chew on a Norspan patch could absorb dangerously high amounts of buprenorphine. This marked buccal absorption may pose a significant safety issue.

Dr. Papoian has concluded that the results of non-clinical studies conducted both *in vitro* and *in vivo* indicate that BTDS (Norspan) is relatively safe for its intended clinical use. He has recommend changes to the proposed labeling. He has also noted that an agreement was reached between the Sponsor and the reviewing division that all reproductive toxicity studies and carcinogenicity studies could be conducted as Phase 4 commitments.

2.3 Clinical Pharmacology and Biopharmaceutics

The biopharamceutics and clinical pharmacology review was conducted by Dr. Suliman Al-Fayoumi of the Office of Clinical Pharmacology and Biopharmaceutics. The principal pharmacokinetic and pharmacodynamic features of BTDS are summarized in Section 3 below. Dr. Al-Fayoumi has concluded that the Human Pharamcokinetics and Bioavailability section of the NDA is acceptable, though labeling issues will have to be addressed at the appropriate time. He has noted certain comments should be forwarded to the Sponsor. First, data from the hepatic impairment study, which pooled data from mildly and moderately hepatically impaired subjects, should be re-analyzed separately for each subgroup. Second, if stored blood samples from PK/PD Study BP95-0901 are still available, they should be re-analyzed using a validated assay for buprenorphine, in order to characterize better any PK/PD relationships. Third, the Sponsor should address potential drug-drug interactions between CYP450 inhibitors and BTDS. Fourth, Dr. Al-Fayoumi has made specific recommendations for including additional time points to the proposed dissolution test, and has noted that the proposed dissolution specifications are too broad.

2.4 Controlled Substances Staff

The Controlled Substances Staff (CSS) has reviewed the abuse liability of Norspan. Review of this individual application coincides with an ongoing review within the FDA and the Department of Health and Human Services (DHHS) regarding a recommendation for the re-scheduling of the drug substance buprenorphine, which is currently in Schedule V. It is possible that the FDA and DHHS will recommend Schedule III, though the final scheduling is determined by the Drug Enforcement Agency (DEA).

At an End-of-Phase 2 Meeting in November 1998, the Agency asked the Sponsor to submit in the NDA a justification of the scheduling of Norspan in Schedule V. The Sponsor has addressed this request in Section 8.15 of the NDA. CSS has reviewed this section of the NDA; in addition, this clinical review also contains a review of the clinical sections of Section 8.15 of the NDA (see Section 8.4 of this review).

CSS has concluded that available epidemiological data suggest that buprenorphine usage will increase once the transdermal formulation is available. In countries such as France where a high-dose sublingual formulation has been available since 1996, over 100 death for buprenorphine have been reported. This experience, coupled with the experience in the US with abuse of other partial opiate agonists, raises the concern that an accessible outpatient dosage from of buprenoprhine will significantly increase buprenorphine-related misuse, abuse, and morbidity. This concern is heightened by the fact that buprenorphine is readily extractable from the BTDS matrix and most of the drug (about (b) (4) remains in the patch after seven days of use. In addition, simple manipulation such as heat application over the patch increase the available buprenorphine and increase plasma levels, which can potentially further contribute to misuse and abuse. Finally, CSS has concluded that the potential withdrawal phenomena after discontinuation of BTDS are not fully characterized in the NDA submission. CSS notes that some of the drug accountability data suggest that abuse and diversion may be a problem with this product.

CSS has recommended that the rescheduling effort of the buprenorphine substance be completed prior to the approval of Norspan. They have also recommended further characterization of the abuse potential and risk of overdose in the transdermal formulation. They have recommended exploration of modifications of the BTDS matrix to reduce the ease of extractability of buprenorphine from the patch, and modification that could require less of the drug substance in the patch. Finally, they have recommend that a complete Risk Management Plan acceptable to the Agency be required prior to the approval of the drug. Of note, the Sponsor submitted a Risk Management Plan on July 16, 2001. Because of the late date of this submission, it has not been formally reviewed.

2.5 Office of Post-Marketing Drug Risk Assessment

The Office of Post-Marketing Drug Risk Assessment (OPDRA) has reviewed the Sponsor's proposed trade name, Norspan™. OPDRA has no objections to the use of that name. However, OPDRA does not recommend the practice of associating the proprietary name with the strength of the product (eg, Norsapn 5, Norspan 10, Norspan 20), since the modifier number may be erroneously interpreted as the number of patches to be applied at one time or the number to be dispensed. Furthermore, OPDRA has suggested that the abbreviation for "micrograms" on the container label and on the carton label be "mcg" and not "µg". OPDRA has also noted that the symbol "C" for controlled substance should be moved to the lower right hand corner of the container label, so that the "C" is not erroneously interpreted as part of the product name.

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The Sponsor performed 17 clinical pharmacology studies. These single-dose and repeated-dose studies were designed to assess dose proportionality, bioavailability, bioequivalence at various applications sites, effects of subject age, pharmacokinetics, the effect of elevated body temperature, the effect of hepatic impairment, interaction between BTDS and midazolam, apparent absorption and kinetics, interaction between BTDS and prochlorperazine, and the effect

of external heat on BTDS. These studies have been reviewed in detail by the Office of Clinical Pharmacology and Biopharmaceutics, in a review by Dr. Suliman AlFayoumi.

3.1 Pharmacokinetics

The pharmacokinetic rationale of delivering buprenorphine for the management of pain via a continuous transdermal release system is that both orally and sublingually administered buprenorphine have poor bioavailability (about 1/15 and 2/3 as potent, respectively, as parenteral buprenorphine). Parenteral buprenorphine, however, has a relatively short duration of action, about 6 to 8 hours.

Following application of a single BTDS 10 patch, approximately 17 hours elapse before detectable systemic levels of buprenorphine (25 pg/ml) appear (see Study BP96-0803). Cmax (142 ± 57 pg/ml) is reached at a Tmax of 107 ± 26 hours (see Study BP97-0501). The absolute bioavailability of buprenorphine from BTDS 5, 10, and 20 are 16%, 15%, and 16%, respectively, after a 7-day application period (see Study BP97-0501). Fever (internal heat) does not alter the pharmacokinetics of buprenorphine with BTDS applications (see Study BP96-1102). However, external heat application results in a 26-55% higher Cmax relative to application without heat (see Study BP98-1204).

The mean flux rates of BTDS 5, 10, and 20 are about 5, 10, and 20 ug/hr over a 7-day application period. However, over a 3-day application period, the mean flux rates are 6-7.5, 5.8-17, and 34-39 ug/hr for BTDS 5, 10, and 20, respectively (see Study BP96-0104).

Dose proportionality on AUC and Cmax exists for the three BTDS strengths (5, 10, and 20) over a 7-day period, but not over a 3-day period (see Study BP96-0102 and Study BP96-0104)).

Application of BTDS 10 to the midaxillary line, the upper outer arm, the upper chest, or the upper back all result in comparable systemic buprenorphine levels, suggesting that BTDS may be applied interchangeably to all sites for an application period of 7 days (see Study BP96-0501).

Buprenorphine is highly bound (96%) to plasma proteins. A large apparent volume of distribution (V_d = 430 L) is evidence of extensive distribution throughout the body. Cerebrospinal fluid (CSF) concentrations are about 15-20% of concurrent plasma concentrations.

In vitro studies have demonstrated little skin metabolism of buprenorphine. Bioavailable buprenorphine is eliminated by hepatic metabolism, with subsequent biliary and renal clearance. Two major metabolites are the result of hepatic metabolism – norbuprenorphine via the CYP3A4 system and buprenorphine-3-O-glucuronide via the UGT1A1/1A3 system.

No studies of the pharmacokinetics of buprenorphine have been conducted in patients with renal impairment. Dr. AlFayoumi has noted that because buprenorphine is cleared primarily by metabolism, impaired renal function is unlikely to have a major effect on buprenorphine pharmacokinetics. He has further noted that there is no need for dose adjustment with impaired renal function.

The Sponsor has conducted a single study evaluating the pharmacokinetics of buprenorphine in patients with mild or moderate hepatic impairment. Results of this study indicate that similar systemic exposures (AUC) but a 50% reduction in Cmax are observed when comparing systemic buprenorphine levels from healthy subjects to those of patients with mild or moderate hepatic

impairment. Systemic exposure to norbuprenorphine did not appear to be affected by mild or moderate hepatic impairment. However, this analysis is based on pooling of subjects with mild and moderate impairment. Such pooling may obscure clinically important changes in subjects with moderate hepatic impairment (see Study BP97-0112).

No significant effect of age, gender, or ethnicity was noted in the clinical pharmacology studies (see Study BP96-0702 for age). With increasing body weight, there is a small decrease in AUC and Cmax.

Based on *in vitro* studies, buprenorphine does not appear to inhibit the metabolism of CYP450 enzymes at clinically relevant concentrations. The Sponsor did not conduct any *in vivo* metabolic drug-drug interaction studies. Although the Sponsor has indicated that metabolism of buprenorphine is not expected to be affected by CYP3A4 inhibition as multiple pathways are involved, Dr. Al-Fayoumi has noted that published data suggest that potent CYP3A4 inhibitors such as some antiretroviral medications (eg, ritonavir, indinavir, and saqinivir) as well as ketoconazole may result in clinically relevant drug-drug interactions when co-administered with buprenorphine.

In pharmacodynamic interaction studies, no clinically relevant drug-drug interactions were noted when buprenorphine was co-administered with midazolam, prochlorperazine, or thiazide diuretics (see Studies BP97-1001, BP98-0202, and BP97-0303).

3.2 Pharmacodynamics

Buprenorphine is a lipophilic, mixed partial agonist, semi-synthetic narcotic opioid of the oripavine series. At the opiate receptor, it has partial agonist activity at the mu receptor and antagonist activity at the kappa receptor. At the opiate receptor, buprenorphine binds with a stronger potency than morphine. Buprenorphine is hypothesized to dissociate slowly from the opiate receptor once bound. Thus, while pretreatment with a narcotic antagonist can prevent pharmacologic effects, narcotic antagonists do not readily reverse pharmacologic effects once they have been established. Buprenorphine also binds to the orphanin (nociceptin) receptor.

To assess the relationship between buprenorphine concentration and pharmacodynamic outcome measures, the Sponsor performed a pooled analysis of multiple safety variables. Because of the variable and subjective nature of measures of analgesia, this outcome measure was not analyzed. Safety variables used in the analysis included systolic and diastolic blood pressure, pulse, respiratory rate, and adverse event such as nausea, dizziness, and sleepiness. Over a range of buprenorphine concentrations from 0 to 500 pg/ml, there was no clear relationship of any of these measures to buprenorphine concentration

4 REVIEW METHODS

4.1 Conduct of Review

The review was conducted by initially determining that all applicable items in the clinical section were in place, and that the NDA was suitable for filing. During the process of determining that the NDA was fileable, it was determined that the adverse event data listings did not contain study day of an event (relative to first day of study medication), but rather the calendar date of the event. The Agency requested that the listings contain study day, and the Sponsor supplied such listings.

The review consisted of a detailed analysis of the efficacy findings from two of the six Phase 2/3 studies, Study BP96-0604 and BP99-0203. Each of these two placebo-controlled studies met the criterion for statistical significance in the Sponsor's analysis, and were thus chosen for review. Of the other three Phase 3 studies, two did not achieve statistical significance in the Sponsor's analysis of the primary efficacy endpoint (Studies BP96-0101 and BP96-0102), and one other (BP98-1201) was an active-controlled study which lacked internal assay sensitivity to detect a therapeutic benefit of the drug. The efficacy findings of the Phase 2 study in post-operative pain (BP96-0104) were not reviewed because the Sponsor has already determined that the post-operative setting is not appropriate for Norspan use.

The safety review consisted primarily of a review of the Integrated Summary of Safety (ISS), with review of selected elements of the safety sections of individual study reports when further information was required. The Sponsor's database was also used during the safety review.

From time to time during the review process, questions regarding various aspects of the clinical review were sent to the Sponsor to clarify issues of study design, conduct, and analysis, or to request either additional analyses or clarification of selected data points. The dates of these requests and the general topics addressed in the requests are summarized in the table below. A copy of all of the questions sent to the Sponsor is included in Appendix A (Section 11 of this review).

Date of Request	General Topics Addressed
February 22, 2001	Study conduct of BP99-0203 Extent of CRFs transmitted with NDA Study conduct of BP96-0604 Request for LOCF data Request for more appropriate dataset descriptions
March 7, 2001	Study conduct of BP96-0604 Request for additional analysis of lab data in BP96-0604 Request to put LAB dataset into two files
March 21, 2001	Request for analysis of NDA data for neutropenia Request for additional information on neutropenia SAE
April 3, 2001	Request for additional efficacy analyses in BP96-0604 Request for additional analysis of age effect in ISE
April 16, 2001	Request for by-dose analyses of adverse event data Request for clarification of ISS methodology
June 1, 2001	Request for clarification of discrepancy in ISS table
June 7, 2001	Request for missing page from BP96-0604 statistical analysis plan Request for additional exposure data
June 11, 2001	Request for information about SAE data sources Request for clarification of adverse event coding issues
June 12, 2001	Request for information about SAEs Request for clarification of adverse events versus intercurrent illness
June 29, 2001	Request for by-dose analyses of adverse events leading to discontinuation, drug interruption, or dose reduction
July 5, 2001	Request for information about abuse liability methodology Request for additional adverse event analyses
July 10, 2001	Request for information about lab test analysis methodology Reqeust for clarification of implausible lab values
July 16, 2001	Request for information about lab test analysis methodology Reqeust for clarification of implausible lab values

4.2 Materials Consulted

The material consulted included the initial IND submission as well as the additional submissions provided by the Sponsor, summarized in the table below.

Date of Submission	Description
November 3, 2000	Initial IND Submission
December 15, 2000	Clarification about extent fo exposure in ISS
December 18, 2000	Responsse to questions raised during filing review
January 9, 2001	Clarification of meeting minutes of December 15, 2000
February 20, 2001	Proposed Pediatric Study Request
March 9, 2001	Response to Controlled Subztances Staff (CSS) questions and request for meeting with CSS
March 13, 2001	Follow-to March 9, 2001 responses to CSS
March 21, 2001	Response to clinical questions of February 22, 2001 about BP96-0604 and BP99-0203
March 26, 2001	Four-Month Safety Update
March 30, 2001	Response to clinical questions of March 7, 2001 about BP96-0604
April 18, 2001	Response to clinical questions of April 3, 2001 about BP96-0604
April 26, 2001	Additional response to March 7, 2001 clinical questions
April 27, 2001	Response to CSS questions of December 22, 2000
May 3, 2001*	Draft study report for BP98-1202 (abuse liability study)
May 4, 2001	Response to clinical questions of April 16, 2001
May 4, 2001	Response to clinical questions of March 21, 2001
May 25, 2001	Further response to clinical questions of March 7, 2001
June 4, 2001	Further response to clinical questions of March 21, 2001
June 6, 2001	Further clarification of extent of exposure in ISS
June 7, 2001	Response to clinical question of June 1, 2001
June 8, 2001	Response to clinical questions of June 7, 2001
June 11, 2001	Clarification of coding of skin adverse events
June 15, 2001	Further response to clinical questions of June 7, 2001
June 20, 2001	Further clarification of clinical question of February 22, 2001
June 21, 2001	Responses to clinical questions of June 12, 2001
June 23, 2001	Response to clinical questions of June 11, 2001
June 26, 2001	Request for teleconference re: 505b(1) vs 505b(2)
June 27, 2001	Request for teleconference re: 505b(1) vs 505b(2)
June 28, 2001*	Final Study Report: BP98-1202 (Abuse liability study)
June 29, 2001	Table inadvertently omitted from four-month safety update
July 16, 2001*	Proposed Risk Management Plan
July 19, 2001*	Responses to clinical questions of June 29, 2001
July 23, 2001*	Further responses to clinical questions of June 29, 2001
July 25, 2001	Response to clinical questions of July 16, 2001
July 26, 2001	Responses to clinical questions of July 5, 2001
July 30, 2001*	Responses to clinical questions of July 10, 2001
August 3, 2001*	Sponsor response to Agency comments on pediatric proposal
*Not reviewed because of time constraints	

4.3 Evaluation of Data Quality and Integrity

During the course of the clinical review, there were many instances where the data presented were internally inconsistent. At times, there were discrepancies between the data presented in the text compared to the data presented in the tables and listings in the appendices. At other times, data within or between tables were inconsistent with each other. At still other times, clinical lab data included values that were clinically implausible. In some instances, lab data did not match source document data. These instances were most striking for clinical laboratory data. The breadth and extent of the abnormalities call into question the presentation of the clinical lab data in the ISS to such an extent that no conclusions about clinical lab data can be made. These findings also call into question the quality control measures that were in place to insure the accuracy of the safety database, the accuracy of the analyses of the safety data, and the accuracy of the presentation of the safety analyses.

Some examples are given below. The Sponsor has been asked to address some, but not all, of these issues.

1. Review of Table 8.14.2.3.3.1 of the ISS (Laboratory Tests and Their Change From Screening – Summary Statistics) reveals that the mean change from baseline for Specific Gravity in the Placebo group in the forced titration studies is 234.65. Other clinically implausible values include a maximum final value of 20000, a screening mean value of 19.15, and final mean value of 248.69. The minimum and maximum values at screening are 3 and 31, respectively. By way of example, review of the patient data listings (Data Listing 16.2.8 in Study BP96-0101) reveals that Patient 4001 (Investigator 100) had an End of Study specific gravity of 25.00, with normal range for that test reported as L0W – 1.00 and HIGH – 30.00. That patient's case report form (CRF), however, indicates a specific gravity value at that time of 1.025, with no normal ranges reported on the CRF. Further review of the LAB3_A dataset reveals that certain studies, such as BP96-0101 and BP96-0102 have LOW values ranging from 0.00 to 15.00, while the LOW value for BP960104 is 10.00 and the corresponding value for BP96-0604 is 1.00. Similarly, the HIGH values for studies BP96-0101 and BP96-0102 range from 25.00 to 35.00, while the HIGH value for study BP96-0104 is 30.00 and the HIGH value for study BP96-0604 is 1.03.

2. Patient 4007 in Study BP96-0101 has two sets of lab values in Listing 16.2.8 (BP96-0101) – one at study screening (3/24/97) and one at the end of the study (7/8/97). This patient's Patient Profile lists the end-of-study labs on 5/30/97. Although this patient ended the study on 5/30/97, the narrative for this patient's neutropenia says this patient had no end-of-study labs for Study BP96-0101. The lab database for Study BP96-0101 has two dates listed in it, one called DATE and the other called LAB_DATE. This patient's Visit-1 labs correspond to DATE and LAB_DATE 3/24/97. This patient's visit 99 labs correspond to DATE 5/30/97 and to LAB_DATE 7/8/97. This patient then entered open-label study BP96-0103 as Patient 4309. The laboratory data listing (BP96-0103 – Data Listing 16.2.8.1) and the Patient Profile has two sets of lab values for this patient – one at baseline (7/8/97) and one at the end of the study (8/5/97). The narrative for this patient states that no baseline labs were available for study BP96-0103, and that only labs at the end of the study were taken. Review of the patient's data in Listing 16.2.8.1 is notable for the fact that most entries for 7/8/97 are identical to the entries for 8/5/97. In fact, the only discrepancies are for WBC differential count (differential percentage appear to be reported for 8/5/97 while absolute neutrophil counts appear to be erroneously reported for 7/8/97) and for albumin/globulin ratio (though albumin is 3.2 on both dates and globulin is 3.8 on both dates, the A/G ratio is 18.2 on 7/8/97

and it is 1.2 on 8/5/97). It is thus likely that the patient had only two sets of lab tests through the course of the two studies, yet study results can be found for four different dates.

3. Table 8.13.7.2.2B.1 in the ISS text does not agree with its source table 8.14.2.3.1.2.

4. Review of hepatic function data from Study 96-0103 indicates that two subjects had isolated marked abnormalities of total bilirubin: Subject 21361 had and end-of-study value of 6.9 mg/dl (no follow-up values available), and Subject 2307 has a value of 7.3 mg/dl, which returned to normal (0.5 mg/dl) at the end of the study. In each case, review of the CRFs revealed that these values were recorded in the "Value Within Normal Range" column, not in the "Abnormal Value" Column. In each case there was no entry in the "Indicate Clinical Significance of Abnormal Value". In each case, the patient's total protein value (in g/dl) at the visit was identical to the total bilirubin value (in mg/dl). It is possible that these two total bilirubin values are data entry errors – for example, transcription errors from the original lab report form to the CRFs. There was no explanation for the lack of comments for such markedly abnormal values.

5. In Section 8.13.7.2.3.1, the Sponsor notes that "no patient had an AST or ALT value > 3 x ULN and a total bilirubin > 1.3 mg/dL at the end of study or post-treatment" Review of Table 8.14.3.3.8 validates this statement. However, further review indicates that one patient (4334) had both an elevated AST and ALT and an elevated total bilirubin during the dosing interval. The presentation of these data imply (though do not directly state) that these are measurements made at the same time. Further review of Table 8.14.3.3.9 reveals two sets of values for the baseline period and two sets of values for the dosing period. Further inspection reveals that the lab dates and the lab values for the baseline period are identical to those of the dosing period. It's thus unclear which is the baseline value and which is the dosing period value, although presumably the baseline value is the earlier of the two. This table also indicates that the elevated AST and ALT occurred at a different time from the elevated total bilirubin. The difference in interpretation of these two presentation may be clinically significant, though the confusing presentation of the data in Table 8.14.3.3.9 make a definitive interpretation difficult. These data are presented in yet another way in Table 8.14.3.3.10 – in this case two date columns are used, and the Visit Date and the Lab Dates do not match, nor do they distinguish between the baseline and dosing periods. Review of this patient's CRFs indicates that lab data for both dates was recorded on the Baseline Visit CRF (perhaps explaining why both results are associated with baseline.) Of note, this patient had participated in a controlled trial (BP96-0104) during which she received active treatment (BTDS) and she developed abnormal LFTs during that trial as well.

6. There appears to be a discrepancy in the two tables presenting subject disposition for the Phase 1 clinical studies in the ISS. The *Clinical Pharmacology Studies* subsection of section 8.13.3.2 of the ISS, as well as Table 8.13.A.2A in the Appendix, note that 21 subjects discontinued from a Phase 1 clinical study. Tables 8.14.1.1.1 and 8.14.1.1.2 also note that 21 subjects discontinued. In Table 8.14.1.1.3, the *All Studies* subheading indicates that 21 subjects discontinued. However, the sum of the patients in the six subgroups below in Table 8.14.1.1.3 totals 24. Specifically, under each of the subheadings of *Interaction Studies*, *Hepatic Impaired*, and *Elderly Hypertensives*, there is one patient who received BTDS 20 who is listed as Discontinued, though the corresponding percentage is 0. These three patients are not accounted for in Table 8.14.1.1.2.

7. Review of Tables 8.14.1.3.3.1, 8.14.2.3.3.1 (ISS) and 14.3.4.5 (BP96-0103) reveals some values suggestive of data entry errors, which might affect the summary statistics.

Table	Laboratory Test	Summary Statistic	Time Point	Value
8.14.1.3.3.1 (ISS)	Globulin	Maximum	Final	38
8.14.1.3.3.1 (ISS)	Phosphorus Inorganic	Maximum	Final	547.99
8.14.2.3.3.1 (ISS)	Hematocrit %	Maximum	Final	399
8.14.2.3.3.1 (ISS)	Chloride	Maximum	Screening	711
14.3.4.5 (BP96-0103)	Calcium	Maximum	Worst Case High Value	94.0
14.3.4.5 (BP96-0103)	Phosphate	Maximum	Baseline	43.0

8. Section 8.13.7.2.1 of the ISS notes that "There were no clinically meaningful changes in mean values for any laboratory parameter." Reference is made to Table 14.3.4.2C in Clinical Study Report BP96-0104. That table is a shift table, not a table of mean changes from baseline. The Division has asked the Sponsor to indicate the location in the NDA of the supporting data for this statement. If a table of mean changes from baseline for laboratory values exists for Phase 2 study BP96-0104, the Division asked the Sponsor to indicate its location in the NDA. If not, the Division asked the Sponsor to generate a table for this study, similar information to Table 8.14.2.3.3.1 in the ISS.

9. The Sponsor' summary of the extent of exposure in the ISS is internally inconsistent. It took two reviews of the data to get the Sponsor to correct the erroneous graph and the erroneous table.

10. There are multiple inconsistencies in coding. [The Sponsor has answered a question in this regard, and has noted that manual input into an automated coding system can sometimes be inconsistent.]

11. The datasets for the inclusion criteria (INCLUDE) and exclusion (EXCLUDE) criteria for Study BP96-0604, as well as the corresponding DEFINE.PDF files, can not be located in the NDA. [NOTE: The Sponsor sent in the required data files in response to Agency request.]

12. The Sponsor was asked the following question: Are the actual Case Report Forms the most recently corrected version? For example, Patient 100-2194 is listed in Data Listing 16.2.1 as having discontinued due to an adverse event related to test medication (itching), and the AE listing (Data Listing 16.2.7.1) indicates that the "TEST MED ACTION TAKEN" was "MED DISCONT". However, the AE CRF for this patient does not capture the fact that an episode of itching led to study drug discontinuation. Please explain. [NOTE: The Sponsor sent in the most recent case report forms, and noted that for one study, the most updated case report forms had not been sent into the Agency. These were sent to the Agency. The Sponsor noted that the database accurately reflected the most updated case report forms, and thus no database changes were required.]

13. In the ISS, it was not clear if data from Study BP96-0104 included in ISS Table 8.13.7.2.3.1A, since the data listings in Table 8.14.2.3.5.1 in the ISS includes patients from Study BP96-0104.

14. The Comments section in the ECG Data Listing 16.2.9.4 in the BP96-0104 Study Report contains truncated comments, and thus does not permit review of potentially important ECG information that is on the CRFs.

15. The coding of the following two AEs was not clear. The Sponsor was asked if the gastrointestinal hemorrhage should have been a serious adverse event, or was the bleeding not a gastrointestinal hemorrhage?

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP981201	1878	2028	BLEEDING	GASTROINTESTINAL HEMORRHAGE	DIG	PT. WENT TO ER FOR PRESSURE DRESSING PT. SCRATCHED HIS LEG S
BP960604	100	2601	DIVERTICULITIS	PERIODONTAL ABSCESS	DIG	FLAGYL AND CIPRO

4.4 Financial Disclosure

To comply with 21CRF54.4 Certification and Disclosure Requirements, the Sponsor submitted certification on the financial interest and arrangements of the Norspan™ clinical investigators for clinical studies ongoing or beginning after February 2, 1999.

Review of the Sponsor's Table of Studies (Section 8.2 of the NDA) indicates that there were six studies that were ongoing on or after February 2, 1999: Studies BP98-1204, BP96-0204, BP98-1201, BP99-0203, BP96-0103, and BP98-1202. Study BP96-0103 was a large, multicenter open-label study of safety, and as such is not considered a "covered clinical study" and therefore requires no financial disclosure from the investigators. This study, however, is the source of all of the Sponsor's long-term (ie, greater than 3 months) safety data.

The Sponsor has submitted certifications for Studies BP98-1204, BP96-0204, BP98-1201, BP99-0203, and BP98-1202. All investigators who responded to the survey sent by the Sponsor reported no financial interests. At two sites (site 1754 in Study BP98-1201 and 1708 in BP96-0103), some sub-investigators were no longer with the practice and did not submit FDA Form 3455 to the Sponsor.

5 DESCRIPTION OF DATA SOURCES

5.1 Primary Source Data

The primary source of data for this NDA review was the NIA submitted by the Sponsor, as well as all of the additional submissions received during the review period.

5.2 Postmarketing Experience

No transdermal formulations of buprenorphine are currently marketed.

One report of abnormal liver function associated with abuse and misuse of the marketed sublingual products was submitted other IND 50,273 by the Sponsor. On March 27, 2001, the Sponsor submitted an initial IND safety report consisting of an article form the medical literature (Journal of Hepatology 34 (2001) 346-350), which describes four heroin addicts infected with Hepatitis C whose addiction is being treated with sublingual buprenorphine. Each of them developed marked elevations of serum transaminases (ALT 13-50 times the upper limit of

normal) after intravenous injection of the buprenorphine. Liver function abnormalities resolved after the intravenous injections ceased

5.3 Literature Search

The Sponsor has conducted an extensive review of the literature and has supplied copies of numerous articles. Clinical topics covered by the articles submitted include methods of measuring pain, current pain treatment polices, and current practices regarding pain treatment.

6 REVIEW OF EFFICACY

6.1 Individual Review of Studies (by indication)

6.1.1 Study BP99-0203: A Double-blind Placebo-controlled Study of Buprenorphine Transdermal System (BTDS) in Patients With Osteoarthritis of the Hip or Knee.

6.1.1.1 Findings vs. Labeling Claims

The Sponsor has included the results of this study in its proposed labeling. As the Agency finds that this study does not demonstrate the effectiveness of the product, the Sponsor's labeling claims are not relevant.

6.1.1.2 Study Plan

The initial version of the Protocol BP99-0203 was dated February 25, 1999. Amendments were dated April 15, 1999 (Amendment 1), May 20, 1999 (Amendment 2), June 21, 1999 (Amendment 3), and October 18, 1999 (Amendment 4). The study was conducted between June 4, 1999 and October 27, 1999.

6.1.1.3 Population, Design, and Objectives

The protocol-specified objective of the study was:

> "To evaluate the analgesic efficacy of BTDS applied every 7 days compared with placebo in patients suffering with osteoarthritis pain secondary to a flare in the knee or hip."

The protocol was designed as a multi-center, joint site-stratified, randomized, double-blind, parallel, placebo-controlled study. Patients meeting the entry criteria were to discontinue all current analgesic medication. They the entered a Run-In Period, during which they were to begin taking ibuprofen around the clock until their pain became unacceptable. The Run-In Period could be as long as 7 days. The dose of ibuprofen was specified in the initial protocol as 200 mg QID, but this was changed in Amendment 1 to 400 mg TID. Patients were instructed to return to the study center when their pain was unacceptable. At that time, the Average Pain Intensity was to be assessed. Patients having an Average Pain Intensity Score of 7 or higher on an 11-point Average Pain Intensity Scale could then be randomized to either BTDS or placebo. Amendment 1 of the

protocol changed the minimum average pain intensity for randomization from 7 to 6. Upon randomization, patients were to stop taking ibuprofen and were to enter a 21-day Titration Period, during which they were allowed to allowed to titrate to one of three dose levels (BTDS 5, BTDS 10 , and BTDS 20). The dose level to which a patient titrated was to be the dose level that allowed sufficient pain control. If adverse events occurred at a dose that provided analgesia, patients were allowed to titrate to the next lowest dose, or they were allowed to discontinue. Patients were then to be remain on the optimal dose during the Maintenance Period (Day 21 – Day 28). The dose levels were 5 mg BTDS, 10 mg BTDS, and 20 mg BTDS. Study medication was applied every seven days. Patients were not allowed to receive any other medication, including NSAIDs, opiates, non-opiate analgesics, or other therapy for pain during the study. Aspirin 325 mg being taken to prevent thrombotic disease was acceptable, provided the patient had been taking it for at least one month prior to study entry.

The schematic below, Figure 9.1 from the Protocol BP9903-0203 Final Study Report, summarizes the study design:

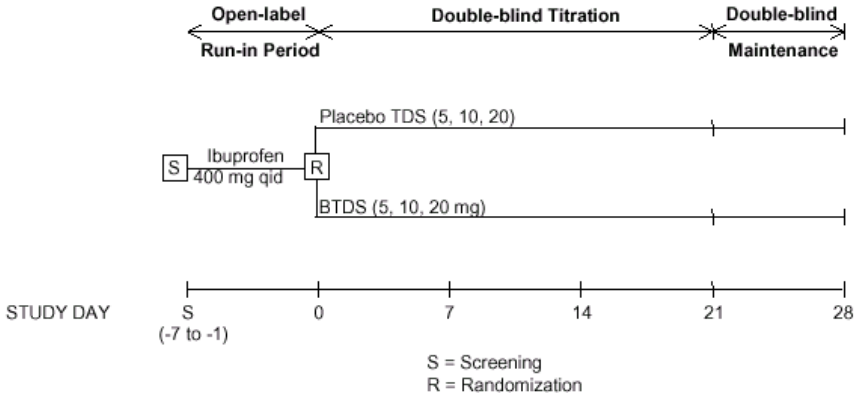


FIGURE 9.1.

Study BP99-0203
Overall Study Design

Each patient's participation in the study could last as long as 35 days. The protocol-specified visits included a Screening Visit, a Baseline Visit (Day 0), on-treatment visits (Visits 1-3) and a visit at the end of treatment (Visit 4). The patient was to telephone the study center when experiencing unacceptable pain, when experiencing serious adverse events, or when planning to discontinue from the study for any reason. The Study Schematic from the initial version of the protocol is reproduced below:

Study BP99-0203. Study Schematic of Time and Events.							
	Screening	Run-in (to Flare)	Baseline	Titration Period			Maintenance Period
Study Days		Days -7 to -1	Day 0	Days 0 to 7	Days 7 to 14	Days 14 to 21	Days 21 to 28
Visit number (day of visit)	No. -1		No. 0	No. 1 (7)	No. 2 (14)	No. 3 (21)	No. 4 (28)
Consent form	X						
Demography	X						
Pregnancy test	X						
Medical history	X						
Physical exam	X						X
Prior medications	X						
Ibuprofen administration	X	X					
Interactive Voice Response (IVR)[a]		X	X	X	X	X	X
Randomization			X				
TDS application (X) and removal (O)			X	OX	OX	OX	O
Average pain intensity score			X	X	X	X	X
Patient satisfaction score				X	X	X	X
Adverse events			X	X	X	X	X
Study medications usage			X	X	X	X	X
Vital signs	X		X	X	X	X	X
Concomitant medications			X	X	X	X	X
Clinical laboratory evaluation	X						X
Global assessment							X
Completion/Discontinuation							X
[a]Patients were to call the IVR every 24 hours.							

The study planned for 260 patients to be enrolled, with a 1:1 BTDS:placebo. The protocol also contemplated that one-half of the patients would have osteoarthritis of the hip, and the other half would have osteoarthritis of the knee.

The inclusion criteria were:

1. Male or female patients 18 years or older with a documented history and radiologic evidence of chronic osteoarthritis of the hip or knee.

2. At the end of the Run-In Period, patients must have an Average Pain Intensity score of 7 or above on an 11-point scale in order to be randomized to treatment.

3. Patients must be compliant, rational, reasonably responsive, capable of subjective evaluation and able to read, understand and sign a written informed consent statement.

The exclusion criteria were:

1. Patients already receiving opioids at an average daily dose of greater than 90 mg of oral morphine equivalents or patients receiving greater than 12 tablets or capsules per day of short-acting opioid-containing products.

2. Women who are pregnant, nursing, or at risk of becoming pregnant during the study.

3. Patients who are allergic to buprenorphine, other opioids, ibuprofen or skin adhesives.

4. Patients who for any reason cannot take ibuprofen including patients with a documented history of NSAID intolerance, gastropathy or ulcer.

5. Patients who are scheduled to have surgery (including dental) during the study period that involves the use of pre- and/or post- operative analgesics or anesthetics.

6. Patients who are currently taking medications that are contraindicated with buprenorphine or other opioids.

7. Patients with evidence of substance abuse at present or within the last 5 years.

8. Patients with clinically significant organ dysfunction or serious unstable disease or who have been hospitalized for a mental illness or suicide attempt.

9. Patients with hepatic dysfunction evidenced by liver enzyme elevation greater than three times the upper limit of normal.

10. Patients presently taking, or who have taken, another investigational new drug within 30 days prior to study entry.

11. Patients who formerly participated in a buprenorphine TDS investigational study.

12. Patients who are currently involved in any litigation which is related to their pain.

13. Any condition which the investigator feels may cause the patient increased risk by being exposed to the medication in this study or which might confound the interpretation of this investigation.

14. Patients with any clinically significant dermatological disorder.

Review of the Case Report Forms (CRFs) indicates that a fourth inclusion criterion was on the CRFs:

> "Patients must have received opioid therapy for osteoarthritis related pain within the past year or have experienced pain that has been inadequately controlled with a full standard dose of NSAIDs."

Review of the database indicates that this entry criterion was completed for all patients.

Further review of the CRFs indicates that Inclusion Criterion 2, which specified that patients must have a Pain Intensity Score of 7 or greater, stated on the CRF that the Pain Intensity Score must be 6 or greater. The change from 7 to 6 was specified in Amendment 1.

Although the objective of the protocol stated that patients were to have osteoarthritis pain secondary to a flare in the knee or hip, there was no specification of a "flare" in the entry criteria.

date on the foil pouch. Although the patch was to be replaced at 7-day intervals, patients could titrate upwards to the next dose level if their pain was unacceptable after three days on Level 1 or Level 2. In these cases, the original weekly schedule was to be maintained. In the event that a patch fell off, the patient could replace it with the extra patch for the currently assigned dose level. During the Maintenance Period, patients who were on Level 1 or Level 2 could titrate upward if their pain was unacceptable.

Patients were encouraged to titrate up to Level 3, if side effects permitted, before they were removed for lack of efficacy. If a patients was still experiencing unacceptable pain 48 hours after applying Level 3 study medication, they could be removed and discontinued.

The patch application site was to be relatively hairless and clean. If the designated site was too hairy, the hair was to be clipped (not shaved); if the site required cleansing, this was to be done with water, and not with soaps, alcohol, oils, or lotions. Patients were to apply the patch to one of the following sites:

- Right upper arm/shoulder
- Left upper arm/shoulder
- Right anterior thorax (subclavicular)
- Left anterior thorax (subclavicular)
- Right lower anterior axillary line
- Left lower anterior axillary line
- Right upper back
- Left upper back

The patch was to be removed by touching only the outermost edges.

Patients were considered compliant if they took between 75% and 125% of the prescribed study medication.

The CRF for recording study medication recorded the dose level (1, 2, or 3), the date applied, the date removed, and the reason for change (ie, fell off, lack of effectiveness, adverse event, or discontinuation. A space was provided for comments for each application.

Ibuprofen usage was recorded on the CRFs by noting the number of tablets dispensed, the number of tablets returned, and the number of days since the screening visit at the end of the Run-In Period. A space was provided for comments.

The following concomitant medications and treatments were prohibited:

- Elective surgery (including dental) involving the use of pre- and/or post-operative analgesics prohibited.
- NSAIDs (other than the ibuprofen administered according to this protocol).
- Aspirin 325 mg or less per day taken as an anti-thrombotic (M.I., stroke prophylaxis) was permitted, provided it had been taken at a stable dose for more than 1 month prior to baseline.
- Opioid and non-opioid analgesics
- Other analgesic products (ie, alternative natural products, oral or topical analgesics, any corticosteriods or muscle relaxants for the treatment of osteoarthritis pain)
- Other therapies (eg, therapy which involves direct external heat sources such as heat lamps, electric blankets, saunas, heated water beds and hot tubs)

- IND investigational drugs and devices (ie, any drug/device which has not been approved for use in the U.S. and is considered investigational under an IND)

Other medications and treatments necessary for the patient's well being were permitted. All concomitant treatments were to be recorded on the CRFs.

6.1.1.3.2 Assessments

Efficacy measures included the Average Pain Intensity Scale and the Patient Satisfaction Score.

The Average Pain Intensity Scale is an 11-point scale, ranging from 0 (no pain at all) to 10 (worst pain that the patient can imagine). This scale was recorded at Baseline, at each of the visits during the Titration Period (Visits 1-3), and at the end of the Maintenance Period (Visit 4). The CRF recorded this measure in the following way:

Please circle the one number that tells how much OA pain you have had on average within the last 24 hrs.

0	1	2	3	4	5	6	7	8	9	10
NO PAIN AT ALL										THE WORST PAIN YOU CAN IMAGINE

TIME: _____
(military time)

The Patient Satisfaction Score asked the patient to answer the question "How would you rate the study medication you received for pain?" with one of the following choices:

- Poor
- Fair
- Good
- Very Good
- Excellent

This measure was completed at each of the visits during the Titration Period (Visits 1-3) and at the end of the Maintenance Period (Visit 4).

6.1.1.3.3 Analysis Plan

Two analysis populations were defined in the protocol. The intent-to-treat population was defined as all patients who satisfied the inclusion/exclusion criteria, were randomized, received study medication, and had at least one post-baseline evaluation. The safety population was defined as all patients who satisfied the inclusion/exclusion criteria, were randomized, and received study medication.

Strata were based on site of osteoarthritis (knee or hip).

The protocol-specified primary outcome measure was the proportion of patients successfully treated in each group, where success is defined as having a Patient Satisfaction Score of Good, Very Good, or Excellent at the final visit. The protocol-specified sample size calculation was based a comparison of success rates between the BTDS and placebo groups, and used the following assumptions:

- 40% success rate in the placebo group
- 5% Type I error rate
- Between-group difference in success rate of 30%
- 80% power

Based on these assumptions, the Sponsor calculated that 62 patients in each treatment group were required prior to stratification to detect the specified between-group difference. In order to have adequate power in each stratum, the Sponsor planned to enroll 130 patients with osteoarthritis of the knee and 130 patients with osteoarthritis of the hip.

Patients were randomly assigned to treatment in a 1:1 (BTDS:placebo) ratio, with separate randomization lists for each site (hip or knee). The protocol provides no information regarding the method of randomization. Four-digit randomization numbers starting with a "1" were to be for patients with OA of the knee, and 4-digit numbers beginning with a "2" were to be used for patients with OA of the hip. The Study Report (Section 9.4.3 and Appendix 16.1.7) notes that the randomization codes as generated for 440 patients, which provided for 110 blocks each of block size 4. There is no mention of stratification of randomization by study center.

The primary efficacy variable, the between-group difference in the proportion of successfully treated patients, was to be analyzed using logistic regression with terms for treatment and center. Terms for treatment-by-center interaction and for baseline variables of clinical importance such as baseline pain, joint site (analysis across strata only), age, gender and weight were to be included in the final model only if significant at the 10% level.

The following secondary variables were specified in the protocol:

- Average Pain Intensity at Day 21 and Day 28.
- Patient Satisfaction scores at Day 21 and Day 28.
- Incidence of and time to early discontinuation due to lack of efficacy.
- Dose level at end of titration.
- Assessment of therapeutic response by the investigator.

Average Pain Intensity and Patient Satisfaction scores at Day 21 and Day 28 were to be analyzed using a linear mixed model with terms for treatment and center. Terms for treatment by center interaction and for baseline variables of clinical importance such as baseline pain, joint site, age, gender and weight were to be included in the final model if significant at the 10% level. Treatment comparisons at each scheduled visit were to be conducted using the Student's t-test . Missing data were to be extrapolated by carrying forward the last non-missing observation (LOCF analysis). Secondary tabulations were to present sample statistics (mean, standard error, minimum and maximum) without extrapolation.

The incidence of early discontinuation due to lack of efficacy was to be analyzed using the Cochran-Mantel-Haenszel test, adjusting by center. The time to early discontinuations due to lack

of efficacy was to be compared between treatment groups using Cox proportional hazard methodology.

The between-treatment differences with respect to the dose level at the end of titration and the assessment of therapeutic response by the investigator were to be tested using the Cochran-Mantel-Haenszel test, adjusting by center.

6.1.1.3.4 Protocol Amendments and Changes in the Planned Analyses

There were four protocol amendments to Protocol BP99-0203.

Amendment 1 (Amendment Date April 15, 1999; FDA Submission No. 098 on April 26, 1999) provided the following changes:

- an inclusion criterion that defined the patient population as those patients suffering from pain due to osteoarthritis for which an opioid analgesic was appropriate treatment or had already been prescribed.
- an increase in the dose of ibuprofen that patients took during the run-in period to 1200 mg/day from 800 mg/day. The Sponsor notes that this change was made to ensure that the selected study population was in need of additional analgesia beyond standard doses of ibuprofen.
- a change in the pain score required for randomization into the study from ≥7 to ≥6, which the Sponsor notes was made to be consistent with the increased analgesic dose during the run-in period.

Amendment 2 (Amendment Date May 20, 1999; FDA Submission No. 106 on June 18, 1999) provided the following changes:

- an increase in the dose of ibuprofen that patients took during the run-in period to 1600 mg/day. The Sponsor notes that this change made to further ensure that the selected study population was in need of additional analgesia beyond standard doses of ibuprofen.
- a return of the pain score needed for randomization into the study from ≥6 to ≥7. The Sponsor notes that this change was made to be certain that patients were experiencing pain sufficient to require an opioid analgesic.

Amendment 3 (Amendment date June 21, 1999; FDA Submission No. 114 on July 30, 1999) provided the following changes:

- detail of the procedures to be followed in using the Interactive Voice Response (IVR) system. Patients called the IVR every 24 hours during the run-in period and while wearing the transdermal system during the titration and maintenance periods. At each call, the patient entered a pain intensity score between 0 and 10 (to indicate pain during the previous 24 hours) and indicated the day of the week corresponding to the call.

Amendment 4 (Amendment date October 18, 1999; FDA Submission No. 135 on December 28, 1999) provided the following changes:

- a Study Site Survey in order to obtain information regarding the potential misuse, abuse, or diversion of BTDS in this trial. The survey was conducted by interviewing the clinical coordinator (or principal investigator) at each site after completion of the trial at that site, and

prior to breaking the blind. At the time of the survey, both the interviewer and the person being interviewed (clinical coordinator or principal investigator) were unaware of individual patient treatment assignments. The Sponsor notes that amendment did not affect the conduct of the trial in any way, and the information obtained did not affect analysis of the trial results as outlined in the protocol and the Statistical Analysis Plan.

In review of the sequence of amendments, it appears that Amendment 2 should have changed the dose of ibuprofen from 400 mg TID to 400 mg QID. The Sponsor was asked in a letter from the Agency on February 22, 2001 if the change in Amendment 2 should have been from 400 mg TID to 400 mg QID, and responded on March 21, 2001 that this was the correct interpretation. The reference to 200 mg QID was from the original protocol, and not from Amendment 1.

No patient had received study drug at the time of IRB approval of Amendments 1 and 2. (This information was provided by the Sponsor on March 21, 2001, in response to a question from the Agency on February 22, 2001.)

There was one change in the planned analysis of vital signs. The Sponsor had originally planned to present a listing of patients with a decrease in systolic blood pressure of 30 mmHg or more from the baseline value or a decrease in diastolic blood pressure of 20 mmHg or more from the baseline value. The cutoff value for decreases in systolic blood pressure was changed from more than 30 mmHg to greater than or equal to 30 mmHg and the cutoff values for decreases in diastolic blood pressure was changed from more than 20 mmHg to greater than or equal to 15 mmHg. The Sponsor's reason for the change was to maintain consistency with the cutoff values used in the previous Phase 2 and Phase 3 studies.

6.1.1.4 Study Conduct

In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and that the following measures to assure data quality assurance:

- On-site study monitoring
- 100% on-site comparison of CRFs with source documents
- Dual data entry
- Answering of all data clarification or queries, with changes made to CRF initialed by staff at study site
- Prior to release of database, 100% verification of a random sample of 19 patients by comparing CRFs to SAS data listings. 0.00% error rate found for critical fields, and 0.01% error rate for non-critical fields.

6.1.1.4.1 Patient Disposition

The Study Report does not indicate how many patients were screened for the study, nor does it indicate how many patients who entered the ibuprofen Run-In Period were not subsequently randomized. In response to a question from the Agency on February 22, 2001, the Sponsor noted in a response on March 21, 2001 that 437 patients were screened for the study. Of these, 408 entered the double-blind Run-In Phase, and the remaining 29 were screening failures. Of the 408 patients entered into the Double-blind Run-In Phase, 315 were randomized into the Double-blind Treatment Phase, and 93 were Run-In failures. Figure 10.1 of the Study Report summarizes subject disposition of the 315 randomized patients. Review of this flow chart indicates that the

proportion of patients not completing treatment was high in both treatment groups – 45% in the Placebo group and 55% in the BTDS group. The most common reason for premature discontinuation in each treatment group was ineffective treatment – 35% in the Placebo group and 28% in the BTDS group. The second most common reason for premature discontinuation was adverse events – 11% in the Placebo group and 24% in the BTDS group. Other reasons for premature discontinuation (ie, loss to follow-up, protocol violations, and other reasons) accounted for 5% of patients in the Placebo group and 5% of patients in the BTDS group. Thus, the overall higher discontinuation rate in the BTDS group is explained by the higher rate of discontinuations due to adverse events.

Discontinuations in the BTDS group were more common in the patients with osteoarthritis of the hip than in patients with osteoarthritis of the knees. Of 66 BTDS-treated patients with hip OA, only 25 (37.9%) completed the study, while 21 (31.8%) dropped out due to lack of effectiveness and 18 (27.3%) dropped out due to an adverse event related to test medication. The overall completion rate in the 76 placebo-treated patients was 52.6% (40 completed patients), with 27 (35.5%) discontinuing due to ineffective treatment and 6 (7.9%) discontinuing due to an adverse event related to test medication. (See Sponsor Table 14.1.1.3. and table below)

Of 86 BTDS-treated patients with knee OA, 44 (51.2%) completed the study, while 22 (25.6%) dropped out due to lack of effectiveness and 16 (18.6%) dropped out due to an adverse event related to test medication. The overall completion rate in the 87 placebo-treated patients was 52.9% (46 completed patients), with 30 (34.5%) discontinuing due to ineffective treatment and 9 (10.3%) discontinuing due to an adverse event related to test medication. (See Sponsor Table 14.1.1.2. and table below)

Discontinuations in both BTDS-treated patients and placebo-treated patients were common in the first two weeks of treatment (See Sponsor Appendix 16.1.9.23). For example, of the 57 discontinuations due to lack of effectiveness in placebo-treated patients, 24 occurred in the first week, 19 occurred in the second week, 12 in the third week, and 2 after the third week. Of the 43 discontinuation due to lack of effectiveness in BTDS-treated patients, 17 occurred in the first week, 14 occurred in the second week, 10 in the third week, and 2 after the third week. Of the 31 discontinuations due to a treatment-related adverse event in BTDS-treated patients, 12 occurred in the first week, 13 occurred in the second week, 4 in the third week, and 2 after the third week.

Study BP99-0203. Reasons for Discontinuation*								
	Complete	Ineffective Treatment	Lost to Follow-up	Protocol Violation	Other	Adverse Event		TOTAL Patients
						Not related to Test Medication	Related to Test Medication	
All								
Placebo	86	57	2	4	1	3	15	163
BTDS	69	43	2	2	5	2	34	152
Hip								
Placebo	40	27	1	3	1	2	6	76
BTDS	25	21	0	1	2	1	18	66
Knee								
Placebo	46	30	1	1	0	1	9	87
BTDS	44	22	2	1	3	1	16	86
Source: Sponsor Appendix 16.1.9.23 and Tables 14.1.1.1E, 14.1.1.2, *Some patients had more than one reason for discontinuation.								

6.1.1.4.2 Protocol Deviations and Violations

A total of 134 protocol deviations or violations were reported in 107 of the 315 enrolled patients. Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. The table below, a based on Sponsor's Table 10.2, summarizes the protocol deviations and violations.

Study BP99-0203: Protocol Deviations and Violations			
Type of Deviation/Violation	Placebo	BTDS	Total
Study medication compliance	18	16	34
Procedures not followed	18	12	30
Study visits missed	14	18	32
Tests not done	4	7	11
Inclusion/Exclusion criteria	4	0	4
Blind broken	0	1	1
Concomitant medication	6	6	12
Other	6	4	10
Total	70	64	134
Source: Sponsor Table 10.2 and Appendix 16.2.2			

Most of the protocol deviations involved poor medication compliance, not following study procedures, or missed visits. These deviations occurred with similar frequencies between the two treatment groups.

Six patients had protocol deviations that required removal from the study because of the potential to affect study outcome. These patients are summarized in the table below.

Study BP99-0203. Summary of Sponsor-Defined Protocol Violations			
Investigator No.	Patient No.	Treatment Group	Protocol Violation
1820	1021	Placebo	Poor compliance
2063	1157	BTDS	Poor compliance
639	2108	BTDS	Poor compliance
2060	2078	Placebo	Failure to meet inclusion/exclusion criteria (possible kidney disorder)
2094	2113	Placebo	Failure to meet inclusion/exclusion criteria (diagnosis of OA of the hip could not be verified)
2063	2166	Placebo	Prohibited concomitant medication acetaminophen/codeine for 2 days)
Source: Section 10.2 of Study Report NOTE: Subject 1021 (Investigator 1820) is reported in Section 10.2 of the Study Report as having been discontinued due to a protocol violation (poor compliance). Appendix 16.2.2 lists "No deviations/violations" for this subject. However, the DISCON dataset lists this subject as having been discontinued due to a protocol violation.			

6.1.1.4.3 Data Sets Analyzed

All 315 patients who were randomized and received study drug were included in the safety population, and all safety analyses were conducted on the safety population.

The intent-to-treat population included all patients who were randomized, received at least one dose of study drug, and had at least one post-baseline efficacy evaluation. Efficacy analyses were performed using the 311 patients who met these criteria. Four patients were excluded from the efficacy analyses because they had no postbaseline efficacy data:

Study BP99-0203 Patients Excluded from Efficacy Analysis		
Investigator No.	Patient No.	Treatment Group
100	2145	BTDS
1721	1094	BTDS
1995	1173	BTDS
1937	2178	Placebo
Source: BP99-0203 Study Report, Section 10.3		

6.1.1.4.4 Demographics/Group Comparability

Baseline characteristics and other demographic characteristics are summarized in Sponsor's Table 10.4, which is reproduced below. Review of this table indicates that the two treatment groups were comparable with regard to all measured characteristics.

Study BP99-0203 Patient Demographics and Other Baseline Characteristics All Patients Enrolled				
		TOTAL (N=315)	Placebo (N=163)	BTDS (N=152)
		n (%)		
Gender				
	Male	103 (33)	53 (33)	50 (33)
	Female	212 (67)	110 (67)	102 (67)
Race				
	White	268 (85)	142 (87)	126 (83)
	Black	28 (9)	11 (7)	17 (11)
	Hispanic	16 (5)	7 (1)	9 (6%)
	Asian	1 (0.3)	1 (0.3)	0 (0%)
	Other	2 (1)	2 (1)	0 (0%)
Age Group (y)				
	18–34	7 (2)	2 (1)	5 (3)
	35–49	51 (16)	27 (17)	24 (16)
	50–64	127 (40)	63 (39)	64 (42)
	65–80	115 (37)	63 (39)	52 (34)
	>80	15 (5)	8 (5)	7 (5)
Osteoarthritis Pain Site				
	Hip	142 (45)	76 (47)	66 (43)
	Knee	173 (55)	87 (53)	86 (57)
Age (y)				
	Mean ± SEM	61 ± 0.71	62 ± 0.96	61 ± 1.05
	Min, Max	30, 89	34, 85	30, 89
Height (cm)				
	Mean ± SEM	168 ± 0.6	168 ± 0.8	169 ± 0.91
	Min, Max	140, 198	142, 196	140, 198
Weight (kg)				
	Mean ± SEM	93 ± 1.28	90 ± 1.77	95 ± 1.83
	Min, Max	50, 192	50, 192	53, 181
Source: Sponsor Table10.4 in BP99-0203 Study Report				

The enrolled subjects' medical histories are summarized in Sponsor Table 14.1.4, and are reproduced in the table below.

Study BP99-0203 Summary of Medical History Population: Enrolled in Study						
Body System	Placebo (N=163)		BTDS (N=152)		Total (N=315)	
	Abnormal		Abnormal		Abnormal	
	N	(%)	N	(%)	N	(%)
Allergy/Immunology	48	(29.4)	50	(32.9)	98	(31.1)
Cardiovascular	90	(55.2)	89	(58.6)	179	(56.8)
Dermatological	26	(16.0)	26	(17.1)	52	(16.5)
EENT	76	(46.6)	69	(45.4)	145	(46.0)
Gastrointestinal	89	(54.6)	77	(50.7)	166	(52.7)
Hematological	19	(11.7)	20	(13.2)	39	(12.4)
Metabolic/Endocrine/Nutritional	69	(42.3)	59	(38.8)	128	(40.6)
Musculoskeletal/Connective Tissue	157	(96.3)	140	(92.1)	297	(94.3)
Neurological	42	(25.8)	44	(28.9)	86	(27.3)
Oral	6	(3.7)	1	(0.7)	7	(2.2)
Other Body System	14	(8.6)	10	(6.6)	24	(7.6)
Psychiatric	38	(23.3)	27	(17.8)	65	(20.6)
Renal	12	(7.4)	8	(5.3)	20	(6.3)
Respiratory	39	(23.9)	52	(34.2)	91	(28.9)
Social	9	(5.5)	8	(5.3)	17	(5.4)
Urogenital	94	(57.7)	81	(53.3)	175	(55.6)
TOTAL	162	(99.4)	152	(100)	314	(99.7)
Source: Sponsor Table 14.1.4 in BP99-0203 Study Report						

Review of Appendix 16.2.3.3, which provides a by-patient listing of all medical history items, indicates that the spectrum of medical disorders in the study population is consistent with the expected range of disorders in such a population.

The frequency of normal and abnormal findings on the screening physical examinations of enrolled subjects is in Sponsor Table 14.1.5, and the frequency of abnormal findings is reproduced in the table below.

Study BP99-0203 Summary of Abnormal Physical Examination Findings at Screening Population: Enrolled in Study						
	Placebo (N=163)		BTDS (N=152)		Total (N=315)	
	Abnormal		Abnormal		Abnormal	
	N	(%)	N	(%)	N	(%)
Abdomen	38	(23.3)	37	(24.3)	75	(23.8)
Cardiovascular	8	(4.9)	10	(6.6)	18	(5.7)
Chest and Lungs	8	(4.9)	5	(3.3)	13	(4.1)
Extremities	135	(82.8)	123	(80.9)	258	(81.9)
General Appearance	3	(14.1)	24	(15.8)	47	(14.9)
HEENT	28	(17.2)	24	(15.8)	52	(16.5)
Lymph Nodes	1	(0.6)	0	(0.0)	1	(0.3)
Neck	16	(9.6)	11	(7.2)	27	(8.6)
Neurological	8	(4.9)	10	(6.6)	18	(5.7)
Psychiatric	1	(0.6)	2	(1.3)	3	(1.0)
Skin	28	(17.2)	26	(17.1)	54	(17.1)
Spine	32	(19.6)	21	(13.8)	53	(16.8)
Source: Sponsor Table 14.1.5 in BP99-0203 Study Report						

Review of Appendix 16.2.10.1, which provides a by-patient listing of all physical examination findings, indicates that the spectrum of findings in the study population is consistent with the expected findings in such a population. The high frequency of findings on the extremities reflects the osteoarthritis in the study population.

Mean and median values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate) at screening were normal and were similar between the two treatment groups (see Sponsor Tables 14.3.5.1.3, 14.3.5.1.4, and 14.3.5.1.5).

Mean and median values of clinical laboratory values at screening were normal and were similar between the two treatment groups (see Sponsor Table 14.3.4.3).

6.1.1.4.5 Treatment Compliance

Investigators assessed patient compliance with study medication by counting the medication and the used and unused treatment systems that patients returned to the clinical at Day 7, 14, 21, and 28. At each of these visits, patients were instructed to return all previously dispensed systems, both used and unused.

If compliance was less than 75% or greater than 125%, the patient could be considered for discontinuation from the study. Two patients on BTDS (patient 1157, investigator 2063; and patient 2108, investigator 639) were discontinued due to medication noncompliance. One patient on placebo (patient 1021, investigator 1820) was discontinued due to medication noncompliance.

6.1.1.4.6 Unplanned Analyses

No unplanned analyses were substituted for the planned analyses.

6.1.1.5 Sponsor's Efficacy Results

6.1.1.5.1 Primary Efficacy Variables

The primary efficacy measure was the percentage of patients who were treated successfully for pain management. Patients who discontinued the study due to "ineffective treatment" were defined as treatment failures. Additionally, patients whose Patient Satisfaction Score at the final visit (Day 28 or discontinuation) was either "poor" or "fair" were defined as treatment failures. Patients who did not discontinue the study due to ineffective treatment and whose Patients Satisfaction Score at the last visits was "Good", "Very Good", or "Excellent" were defined as "treatment successes." The proportions of treatment successes and treatment failures in each treatment group were calculated. The odds of success versus failure in each treatment group were then calculated, and an odds ratio (ratio BTDS/ratio Placebo) was calculated. Using a logistic regression model with terms for center and treatment, an adjusted odds ratio and its 95% confidence interval were computed. The results are presented in Sponsor Figure 11.1B, and the proportions, ratios, odds ratio, and adjusted odds ratio are reproduced below:

Treatment	Success (n/N) %	Failure (n/N) %	Ratio
BTDS (n/N) %	(65/149) 44%	(84/149) 56%	0.77
Placebo (n/N) %	(52/162) 32%	(110/182) 68%	0.47
Observed Odds Ratio (Ratio BTDS/Ratio Placebo)			1.64
Adjusted Odds Ratio [95% CI], P	1.66 [1.035, 2.93], P = 0.036*		
*P-value for the adjusted odds ratio = 1.0 Source: Sponsor Figure 11.1B in BP99-0203 Study Report			

Review of the above table indicates that the between-group difference in treatment successes is not very large, about 12%. The protocol had planned for a between-treatment difference of 30%, assuming a 40% response rate in the placebo group. While the results in the placebo group are close to those contemplated in the protocol, the results in the BTDS group do not approach the intended success rate. The statistical significance of the findings may be due, in part, to the large study sample size, which was based on the ability of each of the two study subgroups (hip and knee) to demonstrate separately a statistically significant finding.

Further review of individual subject outcome data (see Sponsor's Data Listing 16.2.6.1) indicates that several subjects in each treatment group were discontinued due to adverse events related to treatment. As the table below indicates, several of these subjects were judged to be treatment successes, even though they required discontinuation of study medication due to adverse events.

Investigator No.	Patient No.	OA Site	Treatment	Adverse Event Leading to Discontinuation	Patient Satisfaction	Outcome
100	1030	Knee	BTDS	Nausea	Excellent	Success
1215	1015	Knee	BTDS	Shortness of breath.	Unsatisfactory	Failure
1215	1017	Knee	BTDS	Vomiting	Poor	Failure
1215	2016	Hip	BTDS	Abdominal pain	Poor	Failure
1627	2076	Hip	BTDS	Headache, severe	Good	Success
1630	2109	Hip	BTDS	Headache	Unsatisfactory	Failure
1721	1087	Knee	BTDS	Nausea	Unsatisfactory	Failure
1721	2151	Hip	BTDS	Headache	Unsatisfactory	Failure
1741	1138	Knee	BTDS	Vomiting	Very Good	Success
1820	1023	Knee	BTDS	Drowsiness	Unsatisfactory	Failure
1820	2023	Hip	BTDS	Nausea	Good	Success
1892	2126	Hip	BTDS	Headache	Poor	Failure
1937	2070	Hip	BTDS	Vomiting	Unsatisfactory	Failure
1937	2179	Hip	BTDS	Light headedness	Unsatisfactory	Failure
1944	2035	Hip	BTDS	Nausea	Good	Success
1944	2129	Hip	BTDS	Nausea	Excellent	Success
1944	2188	Hip	BTDS	Vomiting	Good	Success
1995	1102	Knee	BTDS	Extreme tiredness	Unsatisfactory	Failure
1995	1104	Knee	BTDS	Nausea	Good	Success
1995	2084	Hip	BTDS	Nausea	Unsatisfactory	Failure
1995	2175	Hip	BTDS	Flu	Good	Success
2060	1078	Knee	BTDS	Frontal headache	Good	Success
2061	1044	Knee	BTDS	Vomiting	Good	Success
2061	1136	Knee	BTDS	Dizziness, 2	Poor	Failure
2062	2058	Knee	BTDS	Migraine	Good	Success
2063	2168	Hip	BTDS	Vomitting	Unsatisfactory	Failure
2064	1090	Knee	BTDS	Dizziness	Unsatisfactory	Failure
2065	2117	Hip	BTDS	Dizziness, bradycardia, ha	Very Good	Success
2065	2120	Hip	BTDS	Dizziness	Good	Success
2067	1154	Knee	BTDS	Vomiting	Good	Success
2068	2056	Hip	BTDS	Nervousness	Poor	Failure
100	2194	Hip	Placebo	Itching	Very Good	Success
1215	1014	Knee	Placebo	Itching mouth & throat	Good	Success
1215	1018	Knee	Placebo	Fatque	Unsatisfactory	Failure
1215	1020	Knee	Placebo	Ecchymoses left leg	Good	Success
1721	2192	Hip	Placebo	Rash #5 discontinued study	Poor	Failure
1892	1126	Knee	Placebo	Dizziness	Very Good	Success
1944	2034	Hip	Placebo	Back pain, possible relation	Unsatisfactory	Failure
2061	1042	Knee	Placebo	Vertigo	Unsatisfactory	Failure
2061	1133	Knee	Placebo	Headache	Unsatisfactory	Failure
2061	1162	Knee	Placebo	Loss of appetite	Unsatisfactory	Failure
2061	2042	Hip	Placebo	Chest pain	Unsatisfactory	Failure
2063	2165	Hip	Placebo	Vomiting & headache	Unsatisfactory	Failure
2065	1061	Knee	Placebo	Heart palpatation	Unsatisfactory	Failure
2094	1113	Knee	Placebo	Possible nausea	Unsatisfactory	Failure

Review of the above table indicates that of the 45 patients whose primary reason for discontinuation was for an adverse event related to study drug, 31 were in the BTDS group and 14 were in the Placebo group. Of the 31 BTDS-treated patients, 15 were judged to be "treated successfully", while 16 were judged to be "treated unsuccessfully." Of the 14 placebo-treated patients, 4 were judged to be "treated successfully", while 10 were judged to be "treated unsuccessfully." The 15 BTDS-treated patients whose outcome was "Success" represent 10.1% (15/149) of the entire BTDS-treated population, while the 4 placebo-treated patients whose outcome was "Success" represent 2.5% (4/162) of the placebo-treated population. Thus, much of the apparent increase in treatment success rate in the BTDS group, compared to the placebo group, is due in large part to the favorable treatment response of patients who could not tolerate the study drug. However, from a clinical point of view, the "success" of a treatment is questionable if the intended therapeutic effect is achieved at a dose that requires discontinuation of the drug. This point is especially true for chronic conditions such as pain, for which ongoing therapy is needed. If the patients in each of the two treatment groups whose outcome was "Treated successfully" at the time of discontinuation due to a drug-related adverse event are actually classified as "Treated unsuccessfully", then the results of the primary efficacy outcome are as follows:

Treatment	Success (n/N) %	Failure (n/N) %	Ratio
BTDS (n/N) %	(50/149) 34%	(99/149) 66%	0.51
Placebo (n/N) %	(48/162) 30%	(114/162) 70%	0.42
Observed Odds Ratio (Ratio BTDS/Ratio Placebo)			1.20

The above analysis is equivalent to defining a composite binary outcome, in which "success" requires both a Patient Satisfaction score indicating satisfactory analgesia and an ability to tolerate the drug at doses that result in satisfactory analgesia. Review of the above tables indicates that the difference in "Success" rates between the BTDS group and the Placebo group is small, and not clinically significant.

6.1.1.5.2 Secondary Efficacy Variables

The Sponsor performed a number of secondary efficacy analyses. Each of these analyses is summarized below.

The Sponsor analyzed treatment outcome ("Success" versus "Failure"), as defined above for the primary efficacy analysis, for the two subgroups of patients based on site of OA., hip or knee. The Sponsor's results, presented in Figure 11.2A of the Study Report and summarized in the table below:

Treatment	**BTDS**			**Placebo**			**Odds Ratio (OR)**	
	Success	**Failure**	**Ratio**	**Success**	**Failure**	**Ratio**	**Observed**	**Adjusted OR***
Measure	**n/N (%)**	**n/N (%)**		**n/N (%)**	**n/N (%)**		**OR**	**[95% CI]**
Knee	38/84 (45)	46/84 (55)	0.83	26/87 (30)	61/87 (70)	0.43	1.94	2.18 [1.099 to 4.403]
Hip	27/65 (42)	38/65 (58)	0.71	26/75 (35)	49/75 (65)	0.53	1.34	1.44 [0.681 to 3.073]
Combined	65/149 (44)	84/149 (56)	0.77	52/162 (32)	110/162 (68)	0.47	1.64	1.66 [1.035 to 2.693]
Odds ratio adjusted via logistic regression with terms for treatment and center. Source Sponsor Figure 11.2A in BP99-0203 Study Report								

Review of these results indicates that the reported success rate in BTDS-treated patients with knee OA (45%) is minimally higher than the corresponding rate in BTDS-treated patients with hip OA (42%). Similarly, the success rate in placebo-treated patients with knee OA (30%) is slightly lower than the corresponding rate in placebo-treated patients with hip OA (35%). These relatively small differences between hip OA and knee OA patients are reflected in a difference in the observed odds ratios (1.94 for knee OA and 1.34 of hip OA). After adjustment for center, the adjusted odds ratio for treatment in patients with knee OA is statistically significant (adjusted OR=2.18, 95% CI: 1.099 to 4.403), while the adjusted OR for treatment in patients with hip OA is not statistically significant (OR=1.44, 95% CI: 0.681 to 3.073). Of note, the protocol intended that a statistically significant effect be observed in each of the two OA groups based on anatomic site.

Further review of the knee OA patients indicates that of the 14 BTDS-treated knee OA patients who discontinued due to a treatment-related adverse event, 7 were labeled as treatment successes. Of the 9 placebo-treated knee OA patients who were discontinued due to a treatment-related adverse event, 3 were labeled as treatment successes. Similarly, 8 of 17 BTDS-treated patients and 1 of 5 placebo-treated patients with hip OA who discontinued study drug due to treatment-related adverse events were labeled as treatment successes. When these patients are re-classified as treatment failures, for the reasons stated in the review of the primary efficacy analysis, the results are as follows:

Treatment	**BTDS**			**Placebo**			**Odds Ratio (OR)**
	Success	**Failure**	**Ratio**	**Success**	**Failure**	**Ratio**	**Observed**
Measure	**n/N (%)**	**n/N (%)**		**n/N (%)**	**n/N (%)**		**OR**
Knee	31/84 (37)	53/84 (63)	0.58	23/87 (26)	64/87 (74)	0.36	1.62
Hip	19/65 (29)	46/65 (71)	0.41	25/75 (33)	50/75 (67)	0.50	0.82
Combined	50/149 (34)	99/149 (66)	0.51	48/162 (30)	114/162 (70)	0.42	1.20
Source: Reviewer analysis of outcome data in Sponsor data file I1_A_SAT.xpt, with all outcome data for patients whose primary reason for discontinuation (in Sponsor data file DISCON.xpt) was "adverse event related to treatment" recoded to Failure. Outcome data used were the 28-day 1WCF values. Treatment data were taken from data file DRUGASGN.xpt, and site of OA (hip or knee) data were taken from data file BASEEVAL.xpt.							

Review of the above table indicates that for each subgroup based in site of OA, the success rates in both the BTDS group and the placebo group are lower than the corresponding rates in the Sponsor analysis. In addition, the differences in success rates between the BTDS group and the placebo group are lower in the revised analysis, compared to the Sponsor's analysis. These differences are also reflected in the lower observed odds ratios in the revised analysis. Of note, in patients with OA of the hip, the success rate is lower in BTDS-treated patients than in placebo-treated patients.

The Sponsor performed several other secondary analyses, which are summarized in the study report in Table 11.2A, which is reproduced below:

Study BP99-0203. Results of Secondary Efficacy Outcome Measures			
	Placebo	BTDS	
Parameter	(N = 162)	(N = 149)	P Value
	Least Squares Mean ± SEM		
Change from baseline of average pain intensity (over last 24 hours) at Day 21 (scale, 0–10)	-1.29 ± 0.19	-1.67 ± 0.18	.157[a]
Change from baseline of average pain intensity (over last 24 hours) at Day 28 (scale, 0–10)	-1.40 ± 0.21	-1.84 ± 0.22	.139[a]
Change from baseline of average diary pain score (from IVR, Days 21–28)	-1.50 ± 0.19	-1.60 ± 0.20	.535[b]
Patient satisfaction score at Day 21 (scale, 0–4)	1.0 ± 0.10	1.2 ± 0.11	.164[c]
Patient satisfaction score at Day 28 (scale, 0–4)	1.0 ± 0.11	1.3 ± 0.11	.046[c]*
	n (%)		
Incidence of discontinuation due to lack of Efficacy	57 (35)	43 (29)	.316[d]
	Mean ± SEM		
Days to discontinuation due to lack of efficacy	12.6 ± 0.79	13.2 ± 0.88	
Cox proportional hazard ratio	0.825		.348[e]
	n (%)		
Investigator assessment of therapy			
No/Minimal response	111 (69)	80 (54)	
Moderate/Marked response	50 (31)	67 (46)	.003[d,f,*]
Dose level at end of titration (Day 21)	(n = 98)	(n = 79)	
Level 1 (5 mg)	2 (2)	9 (11)	
Level 2 (10 mg)	12 (12)	25 (32)	
Level 3 (20 mg)	84 (86)	45 (57)	<.001*

(Cross-references: Tables 14.1.10, 14.2.2.1, 14.2.3.1, 14.2.5, 14.2.6, and 14.2.7.1.)
See Statistical/Analytical Issues section at the end of Section 11 for discussion of covariates used for the secondary efficacy variables.
[a]*P* value is for treatment comparisons (BTDS vs placebo) from a general linear model with terms for treatment, center, and baseline pain.
[b]*P* value is for treatment comparisons (BTDS vs placebo) from a repeated measures linear model with terms for treatment, center, baseline pain, and study day.
[c]*P* value is for treatment comparison (BTDS vs placebo) from a general linear model with terms for center and treatment.
[d]*P* value for between-treatment comparisons (BTDS vs placebo) from a Cochran-Mantel-Haenszel test adjusting for center.
[e]*P* value for between-treatment comparison (BTDS vs placebo) from a Cox proportional hazard regression model with terms for treatment and age category.
[f]Statistically significant, $P<.05$. Significance tested between no response plus minimal response versus moderate response plus marked response.
*Statistical significance at $P<.05$.
Source: Sponsor Table 11.2A in BP99-0203 Study Report

Review of the above table indicates that on most of the secondary efficacy outcome measures, BTDS treatment did not provide a statistically significant benefit over placebo treatment.

When change from baseline in average pain intensity over the past 24 hours was measured on Day 21 and on Day 28, the between-group differences were not statistically significant. The numeric values of the least-squares mean (LSM) of the changes indicate a larger change from baseline in the BTDS group compared to the placebo group at both Day 21 and Day 28. At both time points, the between-group difference in the LSM values is less than 0.5 on 0-10 scale. Thus,

the lack of statistical significance is accompanied by a lack of clinical significance in these outcome measures.

The between-group difference in the change from baseline in the average diary pain scores on Days 21-28 was small and was neither clinically nor statistically significant.

The Patient Satisfaction scores used a 5-point (0-4) scale (0=Poor, 1=Fair, 2=Good, 3=Very Good, 4=Excellent) to measure patient satisfaction with the treatment for pain. When these categorical data are measured as if they were continuous data, the between-group difference in the LS means is 0.2 at Day 21 and 0.3 at Day 28. For some patients, the data used in these analyses were the LOCF values, which were taken at the time of study discontinuation. For many patients who discontinued due to treatment-related adverse events, the Patient Satisfaction Scores may reflect satisfaction with the pain medication at a time when discontinuation of study medication is required because of treatment-related adverse events. Thus, the clinical meaning of a high score in this situation is not entirely clear. Nonetheless, the between-group differences in mean value are small, and though the Day 28 difference is statistically significant, neither the Day 21 nor the Day 28 between group differences is clinically significant.

The incidence of discontinuation due to lack of efficacy is relatively high in both groups (35% in the placebo group and 29% in the BTDS group). The difference between the two groups is small and is not statistically significant.

The Investigator assessment of therapy was dichotomized into two groups: No or minimal response versus moderate or marked response. The results of this analysis are similar to the results of the primary efficacy analysis. (In fact, there was a high rate of agreement [about 89%] between the patient satisfaction scale and the investigator assessment.) As was the case for the patient satisfaction scale, many patients were assigned a favorable outcome, event though they required discontinuation of study medication because of treatment-related adverse event. These patients are listed in the table below.

Investigator No.	Patient No.	Treatment	Adverse Event Leading to discontinuations	Investigator Assessment	Investigator Assessment Category
100	1030	BTDS	Nausea	Moderate Response	Moderate/Marked Response
1215	1015	BTDS	Shortness of breath.	Minimal Response	No/Minimal Response
1215	1017	BTDS	Vomiting	Minimal Response	No/Minimal Response
1215	2016	BTDS	Abdominal pain	Moderate Response	Moderate/Marked Response
1627	2076	BTDS	Headache, severe	Moderate Response	Moderate/Marked Response
1630	2109	BTDS	Headache	Moderate Response	Moderate/Marked Response
1721	1087	BTDS	Nausea	Minimal Response	No/Minimal Response
1721	2151	BTDS	Headache	No Response	No/Minimal Response
1741	1138	BTDS	Vomiting	Moderate Response	Moderate/Marked Response
1820	1023	BTDS	Drowsiness	Minimal Response	No/Minimal Response
1820	2023	BTDS	Nausea	Marked Response	Moderate/Marked Response
1892	2126	BTDS	Headache	Minimal Response	No/Minimal Response
1937	2070	BTDS	Vomiting	Marked Response	Moderate/Marked Response
1937	2179	BTDS	Light headedness	No Response	No/Minimal Response
1944	2035	BTDS	Nausea	Moderate Response	Moderate/Marked Response
1944	2129	BTDS	Nausea	Marked Response	Moderate/Marked Response
1995	1102	BTDS	Extreme tiredness	No Response	No/Minimal Response
1995	1104	BTDS	Nausea	Moderate Response	Moderate/Marked Response
1995	2084	BTDS	Nausea	No Response	No/Minimal Response
1995	2175	BTDS	Flu	Minimal Response	No/Minimal Response
2060	1078	BTDS	Frontal headache	Marked Response	Moderate/Marked Response
2061	1044	BTDS	Vomiting	Moderate Response	Moderate/Marked Response
2061	1136	BTDS	Dizziness, 2	Minimal Response	No/Minimal Response
2062	2058	BTDS	Migraine	Moderate Response	Moderate/Marked Response
2063	2168	BTDS	Vomitting	Moderate Response	Moderate/Marked Response
2064	1090	BTDS	Dizziness	Minimal Response	No/Minimal Response
2065	2117	BTDS	Dizziness, bradycardia, ha	Moderate Response	Moderate/Marked Response
2065	2120	BTDS	Dizziness	Moderate Response	Moderate/Marked Response
2067	1154	BTDS	Vomiting	Moderate Response	Moderate/Marked Response
2068	2056	BTDS	Nervousness	Moderate Response	Moderate/Marked Response
100	2194	Placebo	Itching	Marked Response	Moderate/Marked Response
1215	1014	Placebo	Itching mouth & throat	Marked Response	Moderate/Marked Response
1215	1018	Placebo	Fatque	Minimal Response	No/Minimal Response
1215	1020	Placebo	Ecchymoses left leg	Moderate Response	Moderate/Marked Response
1721	2192	Placebo	Rash #5 discontinued study	Moderate Response	Moderate/Marked Response
1892	1126	Placebo	Dizziness	Marked Response	Moderate/Marked Response
1944	2034	Placebo	Back pain, possible relation	No Response	No/Minimal Response
2061	1042	Placebo	Vertigo	No Response	No/Minimal Response
2061	1133	Placebo	Headache	No Response	No/Minimal Response
2061	1162	Placebo	Loss of appetite	No Response	No/Minimal Response
2061	2042	Placebo	Chest pain	No Response	No/Minimal Response
2063	2165	Placebo	Vomiting & headache	No Response	No/Minimal Response
2065	1061	Placebo	Heart palpatation	No Response	No/Minimal Response
2094	1113	Placebo	Possible nausea	No Response	No/Minimal Response

If the patients in each of the two treatment groups whose outcome was "Moderate/Marked Response" at the time of discontinuation due to a drug-related adverse event are actually classified as "No/Minimal Response", then the results of this efficacy outcome are as follows:

Treatment	Moderate/Marked	No/Minimal
BTDS (n/N) %	(49/148) 33%	(99/148) 67%
Placebo (n/N) %	(45/161) 28%	(116/161) 72%

In this revised analysis, the differences between the BTDS group and the placebo group are small and are of negligible clinical significance.

Analysis of the dose level at the end of titration indicates a statistically significant difference between the BTDS group and the placebo group. Specifically, substantially more patients in the placebo group attained the highest dose level (Level 3) than did patients in the BTDS group. The reason for this may be due the lack of efficacy of lower doses in the placebo group, or intolerance of higher doses in the BTDS group. Though this different pattern of dose levels at the end of titration is statistically significant, the findings do not, per se, measure the efficacy of the drug.

A potential problem with the design of the study, which was not explored in either the Sponsor's analysis or in this review, was the fact that during the titration period patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reach at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both.

The Sponsor performed many of the above secondary analyses for the hip and knee subgroups. These analyses demonstrated that the results for patients with OA of the knee were similar to the results for all patients. For patients with OA of the hip, the results were not statistically significant.

6.1.1.6 Discussion of Efficacy Findings in Study BP99-0203

Taken as a whole, the efficacy findings in Study BP99-0203 do not support the effectiveness of the BTDS for the treatment of pain. In the Sponsor's primary efficacy analysis, the between-group difference in treatment successes is not very large, about 12%. The protocol had planned for a between-treatment difference of 30%, assuming a 40% response rate in the placebo group. While the results in the placebo group are close to those contemplated in the protocol, the results in the BTDS group do not approach the intended success rate. The statistical significance of the findings may be due, in part, to the large study sample size, which was based on the ability of each of the two study subgroups (hip and knee) to demonstrate separately a statistically significant finding. While a 12% between-group difference may be clinically significant in some circumstances, further review of the data underlying this results reveals that much of the apparent increase in treatment success rate in the BTDS group, compared to the placebo group, is due in large part to the favorable treatment response of patients who could not tolerate the study drug. However, from a clinical point of view, the "success" of a treatment is questionable if the intended therapeutic effect is achieved at a dose that requires discontinuation of the drug. This point is especially true for chronic conditions such as pain, for which ongoing therapy is needed. If the patients in each of the two treatment groups whose outcome was "Treated successfully" at

the time of discontinuation due to a drug-related adverse event are actually classified as "Treated unsuccessfully", the between-group difference becomes small and is not clinically significant.

The secondary analyses are also not supportive of the effective of BTDS for the treatment of pain. The between-group differences in the change from baseline in average pain intensity over the past 24 hours at Days 21 and 28 were small and not statistically significant.

6.1.2 Study BP96-0604 A Comparative Study of Buprenorphine TDS, Oxycodone/Acetaminophen Tablets qid and Placebo in Patients With Chronic Back Pain.

6.1.2.1 Findings vs. Labeling Claims

The Sponsor has included the results of this study in its proposed labeling. As the Agency finds that this study does not demonstrate the effectiveness of the product, the Sponsor's labeling claims are not relevant.

6.1.2.2 Study Plan

The initial version of the Protocol BP96-0604 was dated September 18, 1997. Amendment 1 and Amendment 2 were both dated March 11, 1998. The study was conducted between May 8, 1998 and March 28, 2000.

6.1.2.2.1 Population, Design, and Objectives

The protocol-specified objective of the study was:

> "To evaluate the analgesic efficacy, safety, therapeutic acceptance, and pharmacoeconomics of buprenorphine TDS, immediate-release oxycodone/acetaminophen tablets, and placebo in patients with chronic back pain."

The protocol was designed as a randomized, placebo- and active-controlled, multiple-dose, double-blind, double-dummy, parallel-group, multicenter, titration-to-effect, safety and efficacy study, adding opioid or placebo treatment to an established nonopioid therapy in patients with chronic back pain not managed adequately with a non-steroidal anti-inflammatory drug (NSAID). The study was planned to be conducted in 120 evaluable patients with chronic back pain (about 40 per treatment group). Patients meeting the entry criteria were randomized to 1 of 3 treatment groups: placebo, active oxycodone/acetaminophen (Oxy/APAP), or active BTDS. There were three dose levels for each treatment group. Patients continued on their prestudy stable dose of NSAIDs throughout the duration of the study.

Following randomization, patients entered a three-week (21-day) double-blind Titration Phase, during which they were to titrate their dose level at weekly intervals to an acceptable analgesic effect. If back pain was intolerable (defined as 5 or greater on the global back pain scale) after three days of study medication, the patients could be assigned to the next highest dose level, provided that the study staff obtained permission from the Sponsor. Patients remained on the established dose for the 63-day double-blind Maintenance Phase. Participation in the double-blind

phase was to be 84 days, but could be up to 89 days, since the protocol allowed for a 5-day "visit window".

The schematic below, Figure 9.1 from the Protocol BP96-0604 Final Study Report, summarizes the study design:

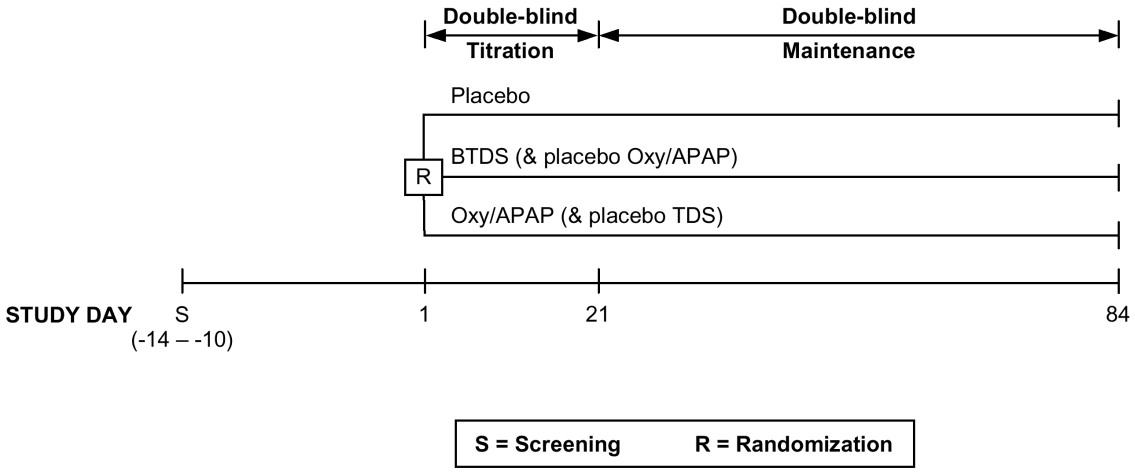


FIGURE 9.1.

Study BP96-0604
Overall Study Design

Patients who experienced lack of efficacy or intolerable side effects could discontinue study medication at any time. Patients could then take standard analgesic therapy, prescribed by their physician, to control their back pain. All patients, however, were required to return to the study sties at scheduled visits and to complete tall evaluations for the duration of the 84-day study.

The protocol-specified visits included a Screening Visit, a Baseline Visit (Day 1), two on-treatment visits during the Titration Period (Days 7 and 21), and five on-treatment visits during the Maintenance Period (Days 30, 45, 60, 75, and 84). During both treatment phases, patients were to call a telephone central diary service every 24 hours.

The Study Schematic for the Screening and Titration Periods from the Study Report is reproduced below:

Study BP99-0203. Study Schematic of Time and Events – Titration Period								
		Titration Period						
		Baseline						
Study Day	Screening	1[2]	3	5	7[3,5]	8	15	21[3,5]
Office Visit[5]	X	X[1]			X			X
Patient Selection Criteria	X							
Consent Form	X							
Demography	X							
Medical History	X							
Surgical History	X							
Back Pain Syndrome Etiology	X							
Laboratory	X							
Physical Exam		X[1]						
Vital Signs/Pregnancy Test		X[1]						
Baseline Medications/Analgesics		X[1]						
Dispense Oxycodone/Apap Medication[9]		X			X			X
Fresh Tds Application[9]		X				X	X	
Global Back Pain Intensity		X[1,4]			X			X
Elicited Opioid Side Effects[9]		X[1]			X			X
Health Economics Questionnaires, Oswestry,								
Euroqol		X[1]			X[1]			X
Sf-36 Questionnaire		X						
Randomization		X						
Telephone Diary[6]		X	X	X	X	X	X	X
Drug Compliance Check[9]					X			X
Update Aes					X			X
Update Concomitant Medications					X			X
Assessment Of Therapeutic Response/Patient								
Preference								
Completion/Discontinuation								

1 = Just prior to placement of the systems.
2 = Baseline = Day 1.
3 = Systems to be changed every 7 days.
4 = Opioid-naive patients must have scored greater than 5 on the back pain intensity scale, rating average pain, to qualify for study entry.
5 = Scheduled visits were to be done no sooner than the visit day and up to 5 days after if required.
6 = Patients must have called central diary service every 24 hours.
7 = Was not done at the early termination of study drug visit.
8 = Was not to be done at Day 84 visit if patient had an early termination of study drug visit.
9 = Was not to be done at visits after early termination of study drug.

The Study Schematic for the Maintenance Period from the Study Report is reproduced below:

Study BP96-0604. Study Schematic of Time and Events – Maintenance Period													
	Maintenance Period												
Study Day	22	30[3,5]	36	43	45[3,5]	50	57	60[3,5]	64	71	75[3,5]	78	84[3,5]
Office Visit[5]		X			X			X			X		X[7]
Patient Selection Criteria													
Consent Form													
Demography													
Medical History													
Surgical History													
Back Pain Syndrome Etiology													
Laboratory													X[7,8]
Physical Exam													X[7,8]
Vital Signs/Pregnancy Test													X[7,8]
Baseline Medications/Analgesics													
Dispense Oxycodone/APAP Medication[9]		X			X			X			X		
Fresh TDS Application[9]	X		X	X		X	X		X	X		X	X
Global Back Pain Intensity		X			X			X			X		X[7]
Elicited Opioid Side Effects[9]		X			X			X			X		X[7]
Health Economics Questionnaires, Oswestry,													
Euroqol		X			X			X			X		X[7]
Sf-36 Questionnaire		X						X					X[7]
Randomization													
Telephone Diary[6]		X	X	X	X	X	X	X	X	X	X	X	X
Drug Compliance Check[9]		X			X			X			X		X[7,8]
Update Aes		X			X			X			X		X[7]
Update Concomitant Medications		X			X			X			X		X[7]
Assessment Of Therapeutic Response/Patient													
Preference													X[7,8]
Completion/Discontinuation													X

1 = Just prior to placement of the systems.
2 = Baseline = Day 1.
3 = Systems to be changed every 7 days.
4 = Opioid-naive patients must have scored greater than 5 on the back pain intensity scale, rating average pain, to qualify for study entry.
5 = Scheduled visits were to be done no sooner than the visit day and up to 5 days after if required.
6 = Patients must have called central diary service every 24 hours.
7 = Was not done at the early termination of study drug visit.
8 = Was not to be done at Day 84 visit if patient had an early termination of study drug visit.
9 = Was not to be done at visits after early termination of study drug.

The inclusion criteria were:

1. Male or female patients 18 years of age or older with clinical evidence of stable, chronic (>2 months) back pain related to intervertebral disc disease, nerve root entrapment, spondylolisthesis, and osteoarthritis or other, similar nonmalignant conditions.

2. Patients for whom an opioid was indicated for back pain and who were currently taking a nonsteroidal anti-inflammatory drug (NSAID) that the investigator considered to be at a therapeutic and/or tolerated dose, and that was stable with daily treatment (not prn) for no less than 2 weeks prior to baseline Day 1.

3. Patients who were opioid-naive or relatively opioid-naive (those not currently receiving an opioid-containing analgesic or those receiving 2 or fewer short-acting opioid tablets or capsules per day). These patients should have had a history supporting unacceptable back pain control at baseline Day 1 by both of the following criteria:

- Frequent or persistent back pain for at least 2 months.

- Average overall back pain score of 5 or greater on the global 0–10 ordinal scale rating AVERAGE back pain on baseline Day 1.

OR

- Patients who were opioid-exposed (those receiving a controlled-release opioid analgesic at a dose of 90 mg of morphine equivalents or less per day and those receiving 3 to 12 capsules or tablets of short-acting opioid analgesics per day (Appendix 16.1.1; Protocol, Appendix V). These patients may have been entered into the study regardless of their pain intensity.

4. Patients must have been compliant, rational, reasonably responsive, capable of patient evaluation, and able to understand the written informed consent agreement.

5. Patients must have been able to read and write English, had daily access to a phone, and been willing and able to sign the written informed consent agreement.

The exclusion criteria were:

1. Patients who were already receiving opioids at an average daily dose of >90 mg of oral morphine equivalents or patients receiving more than 12 tablets per day of short-acting opioid-containing products.

2. Women who were pregnant or nursing. Women of childbearing potential must have had a negative urine pregnancy test on baseline Day 1 and must have been practicing a medically recognized method of pregnancy prevention for the duration of the study.

3. Patients who were truly allergic to buprenorphine or oxycodone or who had a history of allergies to other opioids. This did not include patients who experienced common opioid side effects (eg, nausea, constipation, etc).

4. Patients who for any reason could not take nonsteroidal anti-inflammatory drugs.

5. Patients who had an allergy, contraindication, or hypersensitivity to transdermal delivery systems or to skin adhesives.

6. Patients who for any reason could not take acetaminophen.

7. Patients who were scheduled to have surgery (including dental) involving the use of preoperative or postoperative analgesics or anesthetics during the study period.

8. Patients who had an unstable coexisting disease.

9. Patients who had cancer with ongoing active chemotherapy or radiotherapy.

10. Patients who had a history of substance abuse in the last 5 years.

11. Patients with a history of, or active, severe organ dysfunction, a physical or psychological disease, or a laboratory diagnosis that might have subjected the patient to increased risk by

having been exposed to the medication in this study or that might have confounded the interpretation of this investigation.

12. Patients who had a hepatic dysfunction, as evidenced by liver enzyme elevations greater than 3 times the upper limit of normal.
13. Patients who were currently or formerly enrolled in any Purdue Pharma L.P. BTDS study.
14. Patients who were presently taking, or who had taken, another investigational new drug (IND) within 30 days prior to study entry.
15. Patients who were currently involved in any litigation that was related to the patient's pain and/or injury.
16. Patients who, for the study period, required and could not discontinue therapy that involved direct external heat sources, such as heat lamps, electric blankets, saunas, heating pads, heated water beds, and hot tubs.
17. Patients who had intra-articular or intramuscular steroid injections within 4 weeks prior to baseline Day 1 or during the study, if they involved the back.
18. Patients with any dermatological disorder at any relevant TDS application site.
19. Patients with hairy areas who could not or would not cut the hair of the TDS site for proper placement of the TDS.
20. Patients with personal hygiene habits that would compromise the conduct of the study.

6.1.2.2.2 Treatment Summary

BTDS, Oxy/APAP, and their matching placebo were supplied so that a double-blind, double-dummy study design could be employed. Identity of the study drugs is presented in the Sponsor's Table 9.4.2 in the Study Report, which is reproduced below:

Study BP99-0604. Summary of Study Medication				
	Test Drugs			Active Reference Drug
	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP
Dosage form	TDS	TDS	TDS	Tablet
Dosage strength	5 mg	10 mg	20 mg	5 mg oxycodone/325 mg acetaminophen
Route of administration	Transdermal	Transdermal	Transdermal	Oral
Frequency of administration	q7d	q7d	q7d	qid
Lot number of active drug	7/00499/6	7/00499/6A	7/00499/6B	CB25-13
Expiration date of active drug	02/28/1999	02/28/1999	02/28/1999	06/14/1999
Lot number of matching placebo	7/00500/6	7/00500/6A	7/00500/6B	CB25-12 and CB25-40
Expiration date of matching placebo	02/28/1999	02/28/1999	02/28/1999	06/14/1999
Sponsor Table 9.4.2 in BP99-0604 Study Report, which cross-references Appendix 16.1.6.				

The BTDS patch and its placebo control were supplied in three sizes, corresponding to the three dose levels of BTDS (5 mg, 10 mg, and 20 mg), as follows:

Level	Transdermal System		Patch Size
	Active BTDS	Placebo Control	
Level 1	5 mg BTDS	5 mg TDS	Small
Level 2	10 mg BTDS	10 mg TDS	Medium
Level 3	20 mg BTDS	20 mg TDS	Large

Oxy/APAP was supplied in tablets containing 5 mg oxycodone and 325 mg acetaminophen. A matching placebo tablet was also supplied.

Three dose levels of study medication were supplied in a double-dummy fashion, as summarized below:

	Treatment Group		
	BTDS	Oxy/APAP	Placebo
Level 1	• 1 BTDS 5 q7d (small) • 1 placebo tablet of oxy/APAP 5/325 qid	• 1 TDS q7d (small) • 1 tablet of oxy/APAP 5/325 qid	• 1 TDS q7d (small) • 1 placebo tablet of oxy/APAP 5/325 qid
Level 2	• 1 BTDS 10 q7d (medium) • 2 placebo tablets of oxy/APAP 5/325 qid	• 1 TDS q7d (medium) • 2 tablets of oxy/APAP 5/325 qid	• 1 TDS q7d (medium) • 2 placebo tablets of oxy/APAP 5/325 qid
Level 3	• 1 BTDS 20 q7d (large) • 3 placebo tablets of oxy/APAP 5/325 qid	• 1 TDS q7d (large) • 3 tablets of oxy/APAP 5/325 qid	• 1 TDS q7d (large) • 3 placebo tablets of oxy/APAP 5/325 qid

Each patient's study medication was to be supplied in a carton containing the following items:

- 13 weekly dosing cards, with each weekly dosing card consisting of
    - a 7-day supply of either placebo or Oxy/APAP tablets and
    - 1 BTDS or placebo TDS at each dosing level
    - 6 boxes of replacement systems, with each box containing 1 active or placebo TDS 5, TDS 10, and TDS 20

Blinded transdermal medication (active BTDS patch or placebo TDS patch) was to be applied every seven days. Although the patch was to be replaced at 7-day intervals, patients could titrate upwards to the next dose level if their pain was unacceptable after three days on Level 1 or Level 2.

Patients were encouraged to titrate up to Level 3, if side effects permitted, before they were removed for lack of efficacy. If a patients was still experiencing unacceptable pain 48 hours after applying Level 3 study medication, they could be removed and discontinued.

The patch application site was to be relatively hairless and clean. If the designated site was too hairy, the hair was to be clipped (not shaved); if the site required cleansing, this was to be done with water, and not with soaps, alcohol, oils, or lotions. Patients were to apply the patch to one of the following sites:

- Right upper arm/shoulder
- Left upper arm/shoulder
- Right upper chest, just below the collarbone
- Left upper chest, just below the collarbone
- Right lower side, just below the underarm area
- Left lower side, just below the underarm area
- Right upper back
- Left upper back

Patients were instructed to remove the current patch after wearing it for 7 days, fold it on its adhesive side, place it back in its foil pouch, and return it to the study center with the rest of their study medication at the next visit. The patch was to be removed by touching only the outermost edges. In the event that a patch fell off, the patient could replace it with the extra patch for the currently assigned dose level.

Study tablets were to be taken from the dosing card, from the dose level assigned. Study tablets were to be taken four times daily, even if the patient was not in pain.

Compliance for both TDS and tablet use was calculated based on information contained in the Case Report Form at Days 7, 21, 30, 45, 60, 75, and 84. Patients were considered compliant if they took between 75% and 125% of the prescribed study medication. Patients who were not compliant with either of the two study medications (TDS or tablets) were considered for study termination.

The CRF for recording TDS study medication recorded the dose level (1, 2, or 3), dosing card week number, the date applied, the date removed, and the reason an extra TDS was used (ie, fell off or removed). The CRF for recording Oxy/APAP study medication recorded data, dose level, number of tablets taken at each of the four daily dosings, and the reason for change in dosing level (ie, lack of effectiveness, adverse event, or other, for which a space was left for a comment).

The following concomitant medications and treatments were prohibited:

- Elective surgery (including dental) that involved the use of pre- and postoperative analgesics was prohibited.

- NSAIDs must have been taken by the patient during the study, the dose must have been stable for >2 weeks prior to baseline Day 1, and changes were to be discouraged during the study period. Patients should not have received an "as needed" (prn) dosing of their NSAIDs.
- Aspirin taken as an antithrombotic (prophylaxis for myocardial infarction, stroke, etc) at a stable low dose (≤325 mg/day) was allowed provided that the current dose was stable ≥1 month prior to baseline Day 1 and that no changes in dosing were made during the study. Aspirin taken for relief of back pain was allowed provided that it was used as an NSAID, as previously described.
- Opioid and nonopioid analgesics (other than NSAIDs, as described earlier) were not permitted for the treatment of back pain during the patient's participation in this study.
- The use of benzodiazepines during the study was prohibited.
- Intra-articular or intramuscular steroid injections were not allowed ≤4 weeks prior to baseline Day 1 or during the study if they involved the back.
- Oral steroids (eg, prednisone) ≤7.5 mg/day that were received by the patient for ≥6 months prior to baseline Day 1 were allowed, provided that the current dose had been stable for ≥1 month prior to baseline Day 1 and that no changes in dosing were made during the study.
- Muscle relaxants were permitted.
- "Alternative" medications (herbal and natural medications) were permitted for indications other than pain relief. Any herbal or natural medication taken for back pain must have been discontinued on baseline Day 1.
- Topical creams, oils, or natural skin products that are claimed to have analgesic effects were prohibited for use for back pain.
- TENS (transcutaneous electric nerve stimulation), biofeedback, physical therapy, and relaxation therapy were permitted.
- Therapy that involved direct external heat sources such as heat lamps, electric blankets, saunas, heated water beds, and hot tubs was prohibited during the study.
- Acupuncture for back pain was prohibited during the study.
- Investigational drugs and devices that had not been approved for use in the United States and that were considered investigational under an IND were prohibited.
- All other medications, including those taken to relieve side effects (eg, Senokot-S for constipation or antiemetics for nausea) were not prohibited by this protocol and, if considered necessary for the patient's welfare, may have been given and/or continued under the supervision of the investigator.

Other medications and treatments necessary for the patient's well being were permitted. All concomitant treatments were to be recorded on the CRFs.

6.1.2.2.3 Assessments

The primary efficacy measures included the "Pain on the Average" and the "Pain Right Now."

The "Pain on the Average" and "Pain Right Now" scales are 11-point (0-10) ordinal scales from 0 = "No pain" to 10 = "Pain as bad as you can imagine it." This scale was recorded at Baseline, at each of the visits on Study Days 7, 21, 30, 45, 60, 75, and 84.

The CRF recorded these measures in the following way:

Please circle the one number that best describes your back pain on the AVERAGE since your last visit.

0	1	2	3	4	5	6	7	8	9	10
NO PAIN AT ALL										THE WORST PAIN YOU CAN IMAGINE

Please circle the one number that tells how much back pain you have RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
NO PAIN AT ALL										THE WORST PAIN YOU CAN IMAGINE

Pt. Initials

Secondary efficacy variables are summarized in the table below:

Study BP96-0604. Secondary Efficacy Variables			
Item	Rater	Description	Timing of Rating
Dropout due to lack of efficacy	-----	Time after dosing of dropout due to lack of efficacy	Throughout study
MOS 36-Item Short-Form Health Survey	Patient	36 questions in 8 categories of functionality	Days 1, 30, 60, and 84
Therapeutic Response	Patient	0-3 ordinal scale, 0=No Response, 3=Marked Response	Day 84 or early termination
Therapeutic Response	Investigator	0-3 ordinal scale, 0=No Response, 3=Marked Response	Day 84 or early termination
Patient Preference	Patient	0-2 ordinal scale, 0=Worse than prestudy, 2=Better than prestudy	Day 84 or early termination
Patient Satisfaction	Patient	0-3 ordinal scale, 0=No Response, 3=Marked Response	Day 84 or early termination
Patient Telephone Diary	Patient	Rating of average pain over past 24 hours, on a 0-10 ordinal scale, 0=No pain, 10=Worst pain you can imagine.	Daily, with review by study staff on Days 1, 3, 5, 7, 8, 15, 21, 29, 30, 36, 43, 45, 50, 57, 60, 64, 72, 75, 78, and 84
Time to stable pain management	-----	First time during titration when "diary pain" is ≤4 (or at least 2 points lower than baseline) for 3 consecutive daily records or "pain in the average" at Day 7 or Day 21 is ≤4 (or at least 2 points lower than baseline)	Daily diary for pain, as well as at clinical visits
Number of post-titration dose adjustments	-----	Number of post-titration dose adjustments	Days 1, 7, 21, 30, 45, 60, 75, and 84, and early termination

Health economic evaluations were also included in the protocol, as follows:

Item	Timing of Rating
Baseline Interview	Day 1
Interim Interview	Days 7, 21, 30, 45, 60, 75, and 84
Oswestry Low Back Pain Disability Questionnaire	Days 1, 7, 21, 30, 45, 60, 75, and 84
EuroQoL EQ-5D Instrument	Days 1, 7, 21, 30, 45, 60, 75, and 84
MOS 36-Item Short-Form Health Survey (SF-36)	Days 1, 7, 21, 30, 45, 60, 75, and 84

6.1.2.2.4 Analysis Plan

Two analysis populations were defined in the protocol. The intent-to-treat population was defined as all patients who were randomized, received study medication, and had at least one post-baseline evaluation. The safety population was defined as all patients who received study medication.

The protocol-specified primary efficacy variables were the "Pain on the Average" and "Pain Right Now." The primary comparison was between the active treatment (BTDS) and placebo. The primary efficacy analysis was a repeated measures analysis of the difference in the least squares mean change from baseline between the BTDS and the placebo groups during the Maintenance Period (Days 21-84), using the last observation carried forward (LOCF). The

protocol-specified sample size calculation was based on difference of 1.5 points (on an 11-point scale), and used the following assumptions:

- Standard deviation = 2
- 5% Type I error rate (mentioned in study report but not in original protocol)
- 80% power (mentioned in study report but not in original protocol)

Based on these assumptions, the Sponsor calculated that 35 patients in each treatment group were required to detect the specified between-group difference. The Sponsor therefore planned to have 40 evaluable patients in each treatment arm.

Patients were randomly assigned to treatment in a 1:1:1(BTDS:Oxy/APAP:placebo) ratio. The protocol provides no information regarding the method of randomization. The Study Report (Appendix 16.1.7) indicates that the randomization code was generated for 240 patients, which provided for 40 blocks each of block size 6. There is no mention of stratification of randomization by study center.

For the primary efficacy variable, the least squares mean change from baseline in each of the two pain scores ("Pain on the Average" and "Pain Right Now") were to be compared amongst the three treatment groups using a repeated measures analysis to assess the effects due to treatment, center, and treatment-by-center interaction. Missing values were extrapolated by the last observation carried forward (LOCF). Terms for treatment-by-center interaction and for baseline variables of clinical importance such as baseline pain, age, gender, weight, race, and previous opioid use were to be included in the final model only if significant at the 10% level.

The time to early discontinuations due to lack of efficacy was to be compared between treatment groups using Cox proportional hazard methodology.

MOS SF-36 scales were transformed, and were then compared among groups using an analysis of covariance model, with terms for treatment and center in the model. Additional covariates for gender, age, race, weight, baseline pain, and previous opioid use were incorporated into the model if significant.

Other efficacy variables were summarized over time.

6.1.2.2.5 Protocol Amendments and Changes in the Planned Analysis

There were two protocol amendments to Protocol BP96-0604.

Amendment 1 (Amendment Date March 11, 1998) provided the following changes:

- Clarify that intra-articular and intramuscular steroid injections were not allowed ≤4 weeks prior to Baseline Day 1 or during the study if they involved the back.
- Prohibited the use of benzodiazepines during the study.

Amendment 2 (Amendment Date March 11, 1998) provided the following changes:

- Revised the statistical model specified for the primary outcome measure to include terms for treatment, center, and treatment-by-center interaction, as well as clinically important baseline

covariates. The amendment also specified which baseline variables would be considered for inclusion as covariates.

After database lock, it was determined that the initial coding of adverse events according to COSTART terms did not distinguish between local (ie, at the site of TDS) and generalized skin reactions. To overcome this lack of distinction between the two types of skin reactions, new terms were assigned before the study blind was broken to identify local reactions, where possible.

Initial review of the health economics data indicated no difference in utilization of direct medical services and indirect measures of lost work and school time. Thus, a formal economic analysis was not performed.

6.1.2.3 Study Outcome

In the Study Report (Section 9.6), the Sponsor notes that the study was conducted in accordance with Good Clinical Practice (GCP) Guidelines and that the following measures to assure data quality assurance were performed:

- On-site study monitoring
- 100% on-site comparison of CRFs with source documents
- Dual data entry
- Answering of all data clarification or queries, with changes made to CRF initialed by staff at study site
- Prior to release of database, 100% verification of a random sample of 13 patients by comparing CRFs to the database. A 0.006% error rate was found.

6.1.2.3.1 Patient Disposition

The Study Report does not indicate how many patients were screened for the study. In response to a question from the Agency on February 22, 2001, the Sponsor noted in a response on March 21, 2001 that 143 patients were screened for the study. One-hundred-thirty-four patients were enrolled and entered the Double-blind Run-In Period, and 134 patients were randomized and received study drug. Figure 10.1 and Table 14.1.1.E of the Study Report summarize subject disposition. The table below, based on Sponsor Table 14.1.1.E, also summarizes subject disposition.

Study BP96-0604. Patient Disposition								
	Placebo		Oxy/APAP		BTDS		Total	
	N	%	N	%	N	%	N	%
Enrolled	45	100.0	43	100.0	46	100.0	134	100.0
Competed Study While on Study Treatment	18	40.0	27	62.8	22	47.8	67	50.0
Discontinued Treatment – All Cases	27	60.0	16	37.2	24	52.2	67	50.0
Related to Test Medication	6	13.3	11	25.6	15	32.6	32	23.9
Not Related to Test Medication	1	2.2	1	2.3	0	0	2	1.5
Ineffective Treatment	16	35.6	1	2.3	7	15.2	24	17.9
Lost to Follow-up	1	2.2	0	0	1	2.2	2	1.5
Protocol Violation	2	4.4	0	0	1	2.2	3	2.2
Other	1	2.2	3	7.0	0	0	4	3.0
Source: Sponsor Table 14.1.1.1E								

Review of this table indicates that the proportion of patients not completing treatment was highest in the Placebo group (60.0%), somewhat lower in the BTDS group (52.2%), and lowest in the Oxy/APAP group (37.2%). The most common reason for premature discontinuation in the BTDS and Oxy/APAP treatment groups was adverse events related to study medication – 32.6% in the BTDS group and 25.6% in the Oxy/APAP group, compared to 13.3% in the Placebo group. The most common reason for premature discontinuation in the Placebo group was ineffective treatment – 35.6% in the Placebo group, compared to 15.2% in the BTDS group and 2.3% in the Oxy/APAP group. Other reasons for premature discontinuation (ie, loss to follow-up, protocol violations, and other reasons) accounted for 7% or less of patients in each of the treatment groups. The difference in the rate of discontinuations due to lack of efficacy between the Oxy/APAP group (2.3%) and the BTDS group (15.2%) is notable.

Discontinuations in all three treatment groups were common in the first three weeks of treatment, as noted in Sponsor Appendix 16.1.9.5 and in the table below.

Study BP96-0604. Patient Discontinuation By Study Day								
	Placebo		Oxy/APAP		BTDS		Total	
	N	%	N	%	N	%	N	%
0	0	0.0	1	2.3	0	0.0	1	0.7
<= 7	6	13.3	9	20.9	7	15.2	22	16.4
>7, <=21	10	22.2	1	2.3	7	15.2	18	13.4
>21, <=30	3	6.7	0	0.0	3	6.5	6	4.5
>30, <=45	4	8.9	3	7.0	4	8.7	11	8.2
>45, <=60	3	6.7	0	0.0	2	4.4	5	3.7
>60, <=75	0	0.0	1	2.3	1	2.2	2	1.5
>75, <=84*	8	17.8	15	34.9	13	28.3	36	26.9
>84	11	24.4	13	30.2	9	19.6	33	24.6
TOTAL	45	100.0	43	100.0	46	100.0	134	100
Source: Sponsor Appendix 16.1.9.5 *Many "discontinuations" between Study Day 75 and Study Day 84 represented completion of the study.								

Review of the above table indicates that most discontinuations occurred during the first 21 days of the study, with relatively fewer discontinuations between days 21 and 75. Retention was higher in the Oxy/APA groups than in the other two groups. Most (10 of 16) discontinuations in the Placebo group in the first 21 days were due to lack of effectiveness, while most (9 of 14) discontinuations in the BTDS group in the first 21 days were due to adverse events.

6.1.2.3.2 Protocol Deviations and Violations

At least one protocol deviation or violation was reported in 55 of the 134 enrolled patients. Protocol violations were defined as those deviations that had the potential to affect the outcome of the study. The table below, based on the Sponsor's narrative in Section 10.2 of the Study Report, summarizes the distribution of the most common protocol deviations.

Study BP99-0604: Protocol Deviations and Violations				
Type of Deviation/Violation	Placebo	Oxy/APAP	BTDS	Total
Study medication compliance	4	5	4	13
Procedures not followed	6	6	7	19
Study visits missed	13	10	13	36
Source: Based on data in Sponsor narrative in Section 10.2 of Study Report				

Most of the protocol deviations involved poor medication compliance, not following study procedures, or missed visits. These deviations occurred with similar frequencies among the three treatment groups.

Other deviations included not meeting eligibility/inclusion criteria (6 patients), test not done (3 patients), and concomitant medications taken (2 patients).

Three patients had protocol deviations that required removal from the study because of the potential to affect study outcome. These patients are summarized in the table below.

Summary of Sponsor-Defined Protocol Violations		
Patient No.	Treatment Group	Protocol Violation
6605	BTDS	Missed study visit days
2605	Placebo	Study medication noncompliance (wore TDS but did not take study tablets)
4609	Placebo	Did not follow study procedures (did not call telephone diary)
Source: Section 10.2 of BP96-0604 Study Report		

Patient 5603 (Oxy/APAP treatment group) was withdrawn from the study because informed consent was never obtained. This patient was also non-compliant with study medication (applied TDS patch on baseline Day 1 but did not take study tablets) and study visits (did not return to the site for early termination evaluation). No efficacy data was recorded for this patient, and this patient is not included in the efficacy evaluation, except for the analysis of discontinuation due to lack of efficacy.

6.1.2.3.3 Data Sets Analyzed

All 134 patients who were randomized and received study drug were included in the intent-to-treat and safety populations, and all safety analyses were conducted on the safety population.

The intent-to-treat efficacy population included all patients who were randomized, received at least one dose of study drug, and had at least one post-baseline efficacy evaluation. Efficacy analyses were performed using the 133 patients who met these criteria. Once patient (5603) was excluded from the efficacy analyses because postbaseline efficacy data were obtained. Patient 5603 did not return for an early termination evaluation after the Baseline Day 1 visit.

6.1.2.3.4 Demographics/Group Comparability

Baseline characteristics and other demographic characteristics are summarized in Sponsor's Table 10.4A, which is reproduced below. Review of this table indicates that the three treatment groups were comparable with regard to most measured characteristics.

Study BP96-0604. Patient Demographics and Other Baseline Characteristics All Patients Enrolled, Intent-to-Treat Population (N=134)					
		TOTAL	Placebo	Oxy/APAP	BTDS
		(N = 134)	(N = 45)	(N = 43)	(N = 46)
		n (%)	n (%)	n (%)	n (%)
Gender					
	Male	54 (40%)	20 (44%)	16 (37%)	18 (39%)
	Female	80 (60%)	25 (56%)	27 (63%)	28 (61%)
Race					
	White	123 (92%)	40 (89%)	40 (93%)	43 (93%)
	Black	4 (3%)	1 (2%)	1 (2%)	2 (4%)
	Hispanic	7 (5%)	4 (9%)	2 (5%)	1 (2%)
Age Group (Y)					
	18–34	15 (11%)	4 (9%)	6 (14%)	5 (11%)
	35–49	50 (37%)	16 (36%)	20 (47%)	14 (30%)
	50–64	40 (30%)	16 (36%)	9 (21%)	15 (33%)
	65–80	26 (19%)	9 (20%)	6 (14%)	11 (24%)
	>80	3 (2%)	0 (0%)	2 (5%)	1 (2%)
Opioid Experience					
	Naive	107 (80%)	39 (87%)	34 (79%)	34 (74%)
	Experienced	27 (20%)	6 (13%)	9 (21%)	12 (26%)
Age (Y)					
	Mean ± SEM	52 ± 1.31	52 ± 2.2	49 ± 2.5	54 ± 2.2
	Min, Max	19–85	20–77	19–85	29–85
Height (Cm)					
	Mean ± SEM	169 ± 0.9	167 ± 1.6	170 ± 1.5	168 ± 1.5
	Min, Max	135–198	135–185	152–193	152–198
Weight (Kg)					
	Mean ± SEM	82 ± 1.6	81 ± 2.7	81 ± 2.2	83 ± 1.6
	Min, Max	36–136	36–120	52–109	36–136
Source: Sponsor Table 104.A. in BP96-064 Study Report, which cross-references Tables 14.1.3.1E and 14.1.3.2E					

Review of the above table indicates that patients assigned to the BTDS group were, on average, slightly older than patients assigned to the other two groups. Specifically, the proportion of

BTDS-treated patients over age 50 (59%) is notably higher than the corresponding proportion in the Oxy/APAP group (40%). Another notable difference among the three groups is that the proportion of opioid-experienced patients is higher in the Oxy/APAP and BTDS groups (21% and 26%, respectively) than the corresponding proportion in the placebo group (13%).

The etiologies of the patients' back pain syndromes are summarized in the table below:

Study BP96-0604. Summary of Back Pain Etiology
All Patients Enrolled, Intent-to-Treat Population (N=134)

		TOTAL	Placebo	Oxy/APAP	BTDS
		(N = 134)	(N = 45)	(N = 43)	(N = 46)
		N (%)			
Predominant Pain Site[a]					
	Bone	73 (54%)	26 (58%)	19 (44%)	28 (61%)
	Nerve	33 (25%)	13 (29%)	12 (28%)	8 (17%)
	Viscera	7 (5%)	2 (4%)	3 (7%)	2 (4%)
	Other	40 (30%)	12 (27%)	15 (35%)	13 (28%)
Disease/Condition Causing the Back Pain[a]					
	Intervertebral disc disease	66 (49%)	26 (58%)	22 (51%)	18 (39%)
	Nerve root entrapment	4 (3%)	3 (7%)	1 (2%)	0
	Spondylolisthesis	2 (1%)	0	0	2 (4%)
	Osteoarthritis	52 (39%)	17 (38%)	12 (28%)	23 (50%)
	Similar nonmalignant condition	23 (17%)	5 (11%)	9 (21%)	9 (20%)
	Other	13 (10%)	4 (9%)	5 (12%)	4 (9%)
Time Since Diagnosis (y)		(N = 131)	(N = 45)	(N = 43)	(N = 43)
	Mean ± SEM	8.0 ± 0.9	7.4 ± 1.4	7.3 ± 1.2	9.3 ± 1.9
	Min, Max	0.07, 57	0.08, 50	0.31, 30	0.07, 57

[a]The categories are not mutually exclusive. More than one condition may apply to each patient.
Source: Sponsor Table 10.4B, which cross-references Sponsor Table 14.1.6E.

The "similar nonmalignant condition" category included a variety of conditions, including ankylosing spondylitis, degenerative arthritis, fibromyalgia, inflammatory arthritis, lumbar spondylosis, myofascial pain, osteoporosis, rheumatoid arthritis, scoliosis, spinal stenosis, and a thoracic disc syndrome s/p trauma. (These data were taken from the dataset BASEEVAL, variable name "SPECIFY" where "NONMALGI" equals 1.)

The "other" conditions included a back fracture secondary to a motor vehicle accident, bone spurs on lumbar spine, bone spurs/lumbar degenerative changes of spine, degenerative disc disease, fibromylagia, ligament and joint pain, myofascial, non-specific musculoskeletal pain, and scoliosis. (These data were taken from the dataset BASEEVAL, variable name "OTHRSPEC" where "OTHER" equals 1.)

The "other" predominant sites of pain included disc, intervertebral disc L5-S1, L/S spine intervertebral disc, L4-L5 intervertebral disc, L4-L5 S1 intervertebral disc, low back, muscle, muscular, myofascial, myofacial and disc, myofascial and discogenic, and myofascial pain.

Overall, the predominant pain sites were similar among the three groups. The disease and conditions causing back pain were also similar among the three groups, and were mainly due to

intervertebral disc disease and osteoarthritis. Of note, the Sponosr was asked by the Agency in a letter dated March 7, 2001 if standardized criteria were used across all study sites for determination of "Pain Site" and "Disease/Condition Causing the Back Pain". In a response dated March 30, 2001, the Sponsor noted that "the evaluation of both *Pain Site* and *Disease/Condition Causing Back Pain* was standardized across investigational sites by use of multiple responses to questions included on the CRF."

The enrolled subjects' medical histories are summarized in Sponsor Table 14.1.4, and are reproduced in the table below.

Study BP96-0604
Summary of Medical History
Population: All Patients Enrolled

Body System	Placebo Abnormal		Oxy/APAP Abnormal		BTDS Abnormal	
	n/N	(%)	n/N	(%)	n/N	(%)
Dermatological	7/45	14.6	7/43	15.3	5/46	10.2
Eye, Ear, Nose, Throat	20/45	41.8	18/43	39.3	23/46	47.0
Oral	1/45	2.1	1/43	2.2	2/46	4.1
Respiratory	10/45	20.9	9/43	19.7	7/46	14.3
Cardiovascular	19/45	39.7	15/43	32.8	22/46	45.0
Gastrointestinal	18/45	37.6	22/43	48.1	20/46	40.9
Renal	3/45	6.3	3/43	6.6	3/46	6.1
Urogenital	12/45	25.1	13/43	28.4	13/46	26.6
Musculoskeletal/Connective Tissue	41/45	85.6	42/43	91.8	40/46	81.7
Metabolic/Endocrine/Nutritional	13/45	27.2	15/43	32.8	10/46	20.4
Hematological	7/45	14.6	6/43	13.1	2/46	4.1
Allergy/Immunology	16/45	33.4	16/43	35.0	14/46	28.6
Neurological	20/45	41.8	19/43	41.5	20/46	40.9
Psychiatric	8/45	16.7	10/43	21.9	14/46	28.6
Social	8/45	16.7	9/43	19.7	10/46	20.4
Other	4/45	8.4	2/43	4.4	6/46	12.3

Source: Sponsor Table 14.1.4E in BP96-0604 Study Report

Review of Appendix 16.2.4.3, which provides a by-patient listing of all medical history items, indicates that the spectrum of medical disorders in the study population is consistent with the expected range of disorders in such a population. The high frequencies of musculoskeletal and neurolgical abnormaoites are related, in most cases, to the underlying causes of the back pain.

The frequency of normal and abnormal findings on the screening physical examinations of enrolled subjects is in Sponsor Table 14.1.5, and the frequency of abnormal findings is reproduced in the table below.

Study BP96-0604 Summary of Baseline Physical Examination Population: All Patients Valid for Safety						
	Placebo (N=45)		Oxy/APAP (N=43)		BTDS (N=46)	
	Abnormal		Abnormal		Abnormal	
	N	%	N	%	N	%
General Appearance	1	2.22	0	0.00	1	2.17
Skin	4	8.89	7	16.28	3	6.52
Head, Eye, Ears, Nose, Throat	8	17.78	7	16.28	7	15.22
Neck	2	4.44	7	16.28	4	8.70
Lymph Nodes	0	0.00	0	0.00	0	0.00
Chest and Lungs	0	0.00	3	6.98	2	4.35
Cardiovascular	0	0.00	2	4.65	1	2.17
Abdomen	7	15.56	2	4.65	3	6.52
Urogenital	1	2.22	0	0.00	0	0.00
Pelvic	0	0.00	0	0.00	0	0.00
Spine	31	68.89	28	65.12	30	65.22
Extremities	11	24.44	12	27.91	10	21.74
Neurological	4	8.89	3	6.98	1	2.17
Psychiatric	0	0.00	0	0.00	0	0.00
Source: Sponsor Table 14.1.5.C in BP96-0604 Study Report						

Review of Appendix 16.2.10.1, which provides a by-patient listing of all physical examination findings, indicates that the spectrum of findings in the study population is consistent with the expected findings in such a population. The high frequency of findings in the spine reflects the diagnosis of back pain in the study population.

Mean values of vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and temperature) at screening were normal and were similar between the two treatment groups (see Sponsor Table 14.3.5.1.C).

The three treatment groups were well matched with regard to mean baseline laboratory values, which the Sponsor provided in a correspondence on March 30, in response to a request from the Agency on March 7, 2001.

6.1.2.3.5 Treatment Compliance

Investigators assessed patient compliance with TDS system by counting the used and unused treatment systems that patients returned to the clinical at Days 7, 21, 30, 45, 60, 75, and 84. At each of these visits, patients were instructed to return all previously dispensed systems, both used and unused.

If compliance was less than 75% or greater than 125%, the patient could be considered for discontinuation from the study. The Sponsor notes that at least 95% of the patients in each treatment group at each visit had a compliance ratio between 95% and 105%. On Days 21, 75, and 84, 1 patient from the Oxy/APAP group had a compliance ratio between 50% and <75%. On Day 30, 1 patient from the BTDS group had a compliance ratio of <50%. No patients were terminated because of noncompliance with regard to system wear.

Compliance with Oxy/APAP tablets (or its placebo) was determined by counting the number of returned tablets at Days 7, 21, 30, 45, 60, 75, and 84. Patients who were found to be <75% or >125% compliant at any visit could be considered for study termination. The Sponsor notes that for each of the visits, 90% to 100% of the patients from each treatment group had a compliance ratio between 75% and 125%. Two patients (patient 3604 in the Oxy/APAP group and patient 2605 in the placebo group) were terminated because of noncompliance. Patient 3604 did not return any study medication. Patient 2605 did not continue taking study tablets but continued wearing the TDS. Also, patient 5603 was noncompliant as he did not take any study tablets. However, he was withdrawn from the study because he did not sign his consent form.

6.1.2.3.6 Unplanned Analyses

No unplanned analyses were substituted for the planned efficacy analyses.

6.1.2.4 Sponsor's Efficacy Results

6.1.2.4.1 Primary Efficacy Variables

The primary efficacy variables were the least-square mean changes in "Pain on the Average" and "Pain Right Now" from the Brief Pain Inventory (BPI). In the primary efficacy analysis, data from the Maintenance Period (Days 21-84) were compared between treatment groups with a repeated measures analysis of variance using the last observation carried forward (LOCF). Covariates including gender, age, race, weight, baseline pain, and previous opioid use were incorporated into the final model when statistically significant ($P<0.10$) using backward elimination. Baseline pain, center, and opioid experience were included in the final model for "Pain on the Average." Age, baseline pain, center, and opioid experience were included in the final model for "Pain Right Now."

The results of the Sponsor's primary efficacy analysis are presented in Table 11A of the Study Report, which is reproduced below:

TABLE 11A.
Study BP96-0604
Summary of Primary Efficacy Variables—Mean Change From Baseline, Days 21–84 (LOCF): Intent-to-treat Population With Efficacy Data (N = 133)

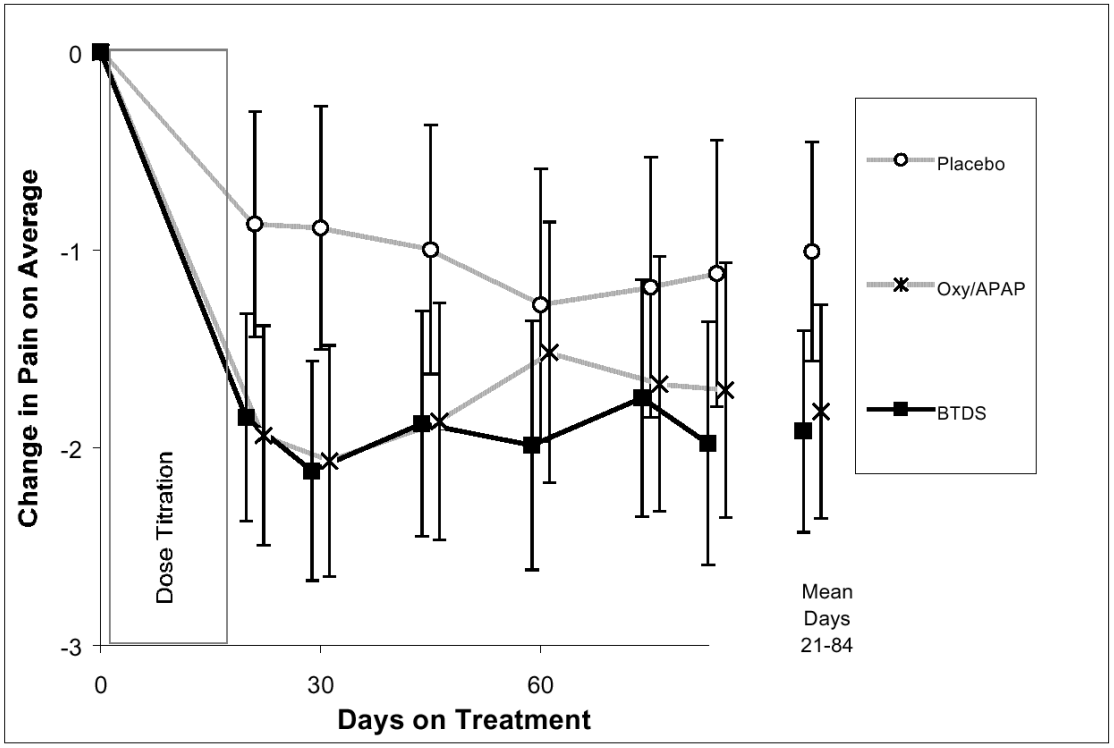
Primary Variables	Baseline Range	Placebo (N = 45)	Oxy/APAP (N = 42)[a]	BTDS (N = 46)
		Change From Baseline ± SEM (Days 21–84)[b]		
		Least Squares Means[c]		
Back Pain Intensity (Scale 0–10)				
Pain on the average	7.07–7.19	-1.01 ± 0.37	-1.82 ± 0.36	-1.92 ± 0.34*
P value vs placebo			0.0624	0.0350
Pain right now	6.43–6.91	-0.80 ± 0.38	-1.53 ± 0.37	-1.66 ± 0.34*
P value vs placebo			0.0962	0.0452

(Cross-references: Tables 14.2.1.1.B2–14.2.1.2.B2.)
[a]One patient from the intent-to-treat population (the Oxy/APAP group) was not included in the pain measure analysis. The patient discontinued and had no efficacy data.
[b]Repeated measures: results of comparison with placebo combining Days 21–84 using SAS Proc Mixed.
[c]Least squares means: for pain on the average, corrected by SAS Proc Mixed for baseline pain, center, and opioid experience; for pain right now, corrected by SAS Proc Mixed for age, baseline pain, center, and opioid experience.
*Statistically significant results (P<0.05).

Source: Sponsor Table 11A in BP96-0604 Study Report

The protocol-specified BTDS-placebo difference in pain measures was 1.5. The BTDS-placebo differences from the above table are about 0.91 for "Pain on the Average" and about 0.86 for "Pain Right Now." These measures of efficacy thus do not attain the level of effect contemplated in the protocol. The statistical significance of the BTDS results above may be due, in part, to the fact that the actual sample sizes (42 to 46 patients in each treatment group) is larger than the per-group size determined by the sample size calculation in the protocol (35 per group).

To explore further these results, the Sponsor has analyzed the between-group differences least-squares mean in change from baseline for both "Pain on the Average" and "Pain Right Now" at each post-baseline visit during the Maintenance Period (Days 21-84), using the LOCF method. The by-visit results for "Pain on the Average" are presented in the Figure 11.1A in the study report, which is reproduced below:



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo	LS Mean ± SEM	-0.87 ± 0.38	-0.89 ± 0.41	-1.00 ± 0.42	-1.28 ± 0.46	-1.19 ± 0.44	-1.12 ± 0.45	-1.01 ± 0.37
N=45	N with data	34	23	22	18	18	18	45
Oxy/APAP	LS Mean ± SEM	**-1.94 ± 0.37**	**-2.07 ± 0.39**	-1.87 ± 0.40	-1.52 ± 0.44	-1.68 ± 0.43	-1.71 ± 0.43	-1.82 ± 0.36
N= 42	N with data	**31**	**32**	29	29	28	27	42
	Pairwise vs. Placebo	***P*=0.015**	***P*=0.013**	ns	ns	ns	ns	ns
BTDS	LS Mean ± SEM	**-1.85 ± 0.35**	**-2.12 ± 0.37**	-1.88 ± 0.38	-1.99 ± 0.42	-1.75 ± 0.40	-1.98 ± 0.41	**-1.92 ± 0.34**
N= 46	N with data	**33**	**29**	25	23	21	22	**46**
	Pairwise vs. Placebo	***P*=0.025**	***P*=0.0093**	ns	ns	ns	ns	***P*=0.035**

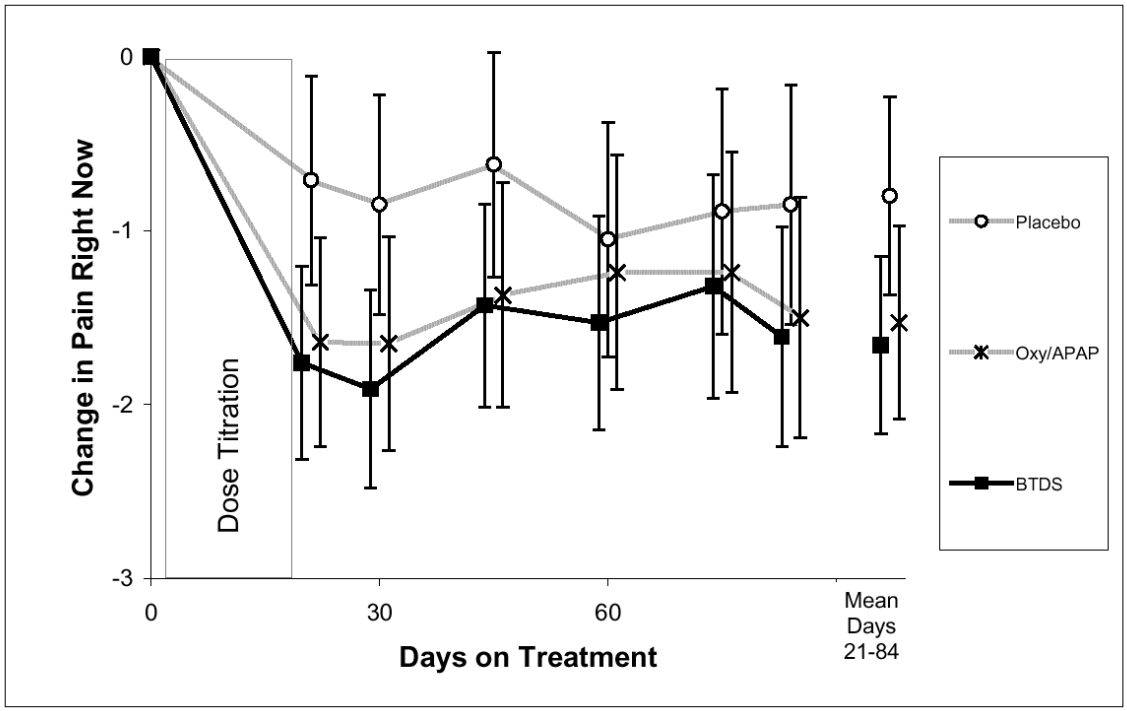
(Cross references: LS Means from Table 14.2.1.1.B2; Ns from Table 14.2.1.1.B3.)
Least squares (LS) means - corrected by SAS Proc Mixed for baseline pain, center and opioid experience
Bar indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14
N = Number of patients with data at that visit; N for LOCF = N for the treatment group and was consistent over time
Bars at each data point indicate ± 1.5 SEM
RM 21-84 values calculated via repeated measures analysis of all available data from Days 21-84 using SAS Proc Mixed
Pairwise vs. Placebo - results of comparison with placebo using SAS Proc Mixed
ns = difference not statistically significant (P> 0.05)
Bolding indicates statistically significant reesults

FIGURE 11.1A.

Study BP96-0604
Pain on the Average by Day (Change From Baseline) Assessed at Each Visit—
Least Squares (LS) Means ±1.5 SEM, Last Observation Carried Forward:
Intent-to-treat Population With Efficacy Data (N = 133)

Review of the above table indicates that only at Day 21 and Day 30 were the BTDS group and the Oxy/APAP groups statistically significantly superior to Placebo. Further review also indicates that at no time point was the difference between BTDS and Placebo 1.5 or greater.

The by-visit results for "Pain Right Now" are presented in the Figure 11.1B in the study report, which is reproduced below:



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo	LS Mean ± SEM	-0.71 ± .040	-0.85 ± 0.42	-0.62 ± 0.43	-1.05 ± 0.45	-0.89 ± 0.47	-0.85 ± 0.46	-0.80 ± 0.38
N=45	N with data	34	23	21	18	18	18	45
Oxy/APAP	LS Mean ± SEM	**-1.64 ± 0.40**	-1.65 ± 0.41	-1.37 ± 0.43	-1.24 ± 0.45	-1.24 ± 0.46	-1.50 ± 0.46	-1.53 ± 0.37
N= 42	N with data	**31**	32	29	29	28	27	42
	Pairwise vs. Placebo	***P*=0.049**	ns	ns	ns	ns	ns	ns
BTDS	LS Mean ± SEM	**-1.76 ± 0.37**	**-1.91 ± 0.38**	-1.43 ± 0.39	-1.53 ± 0.41	-1.32 ± 0.43	-1.61 ± 0.42	**-1.66 ± 0.34**
N= 46	N with data	**33**	**29**	25	23	21	22	**46**
	Pairwise vs. Placebo	***P*=0.022**	***P*=0.028**	ns	ns	ns	ns	***P*=0.045**

(Cross references: LS Means from Table 14.2.1.2.B2; Ns from Table 14.2.1.2.B3.)
Least squares (LS) means - corrected by SAS Proc Mixed for age category, baseline pain, center and opioid experience
Bar indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14
N = Number of patients with data at that visit; N for LOCF = N for the treatment group and was consistent over time
Bars at each data point indicate ± 1.5 SEM
RM 21-84 values calculated via repeated measures analysis of all available data from Days 21-84 using SAS Proc Mixed
Pairwise vs. Placebo - results of comparison with placebo using SAS Proc Mixed
ns = difference not statistically significant (P> 0.05)
Bolding indicates statistically significant results

FIGURE 11.1B.

Study BP96-0604
Pain Right Now by Day (Change From Baseline) Assessed at Each Visit—
Least Squares (LS) Means ±1.5 SEM, Last Observation Carried Forward:
Intent-to-treat Population With Efficacy Data (N = 133)

Review of the above table indicates that only at Day 21 and Day 30 was the BTDS group statistically significantly superior to Placebo. Only at Day 21 was the Oxy/APAP group statistically significantly superior to Placebo. Further review also indicates that at no time point was the difference between BTDS and Placebo 1.5 or greater.

Because group mean data in the above table are based on an LOCF approach, the Day 84 data in the above two tables provide an "endpoint" analysis – that is, an analysis of each patient's last recorded observation. This endpoint analysis, based on data from all patients in the ITT group with efficacy data (n=133) indicates that there is no statistically significant difference among the three treatment groups. For "Pain on Average" at the endpoint (ie, at the last observation for each patient), the magnitude of change from baseline is similar for the BTDS and Oxy/APAP groups (-1.98 ± 0.41 and -1.71 ± 0.43, respectively). This degree of improvement is numerically greater than the mean improvement in the Placebo group (-1.12 ± 0.45), though the difference between the Placebo group and either of the active treatment groups is much less than 1.5. For "Pain Right Now" at the endpoint, the magnitude of change from baseline is again similar for the BTDS and Oxy/APAP groups (-1.61 ± 0.42 and -1.50 ± 0.46, respectively). This degree of improvement is numerically greater than the mean improvement in the Placebo group (-0.85 ± 0.46), though the difference between the Placebo group and either of the active treatment groups is much less than 1.5.

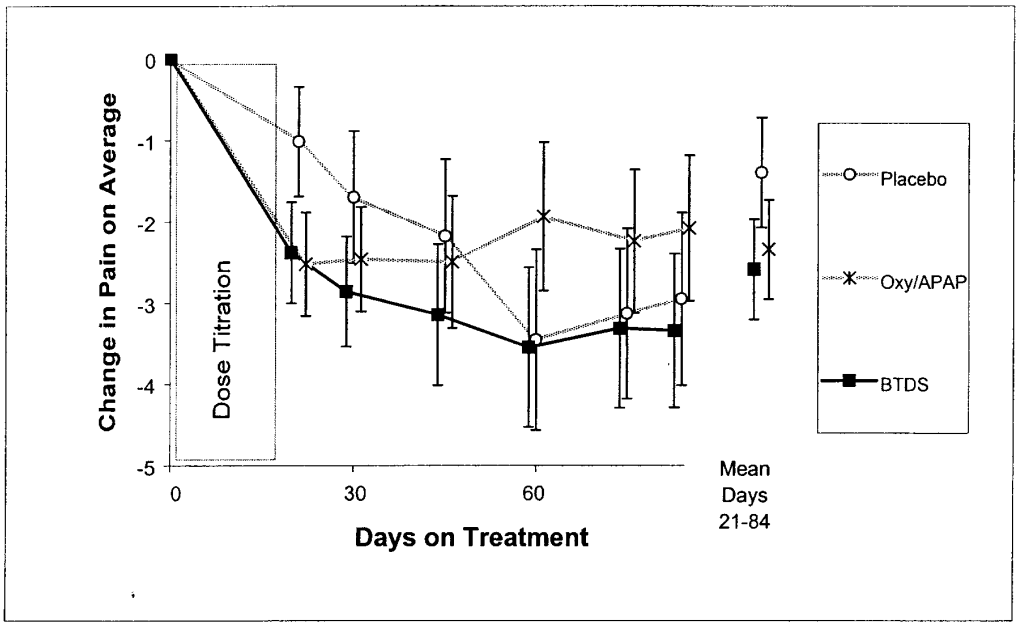
The above analyses all make use of the LOCF method to impute missing data for prematurely discontinued patients. This method assumes that the imputed (ie, LOCF) value is a valid measure of the effect of the drug if the patient had continued taking it. For patients whose premature discontinuation is due to lack of efficacy, the imputed efficacy outcome value is presumably a poor one, and thus reflective of what the patient would presumably have continued to experience. For patients whose premature discontinuation is due to reasons unrelated to either the disease or the drug (eg, patient is lost to follow-up or experiences an adverse event unrelated to the drug), the imputed LOCF value is probably the best, and least biased, estimate of what the patient would have continued to experience. For patients whose premature discontinuation is due to a drug-related adverse event, however, the LOCF value may not be appropriate. From a clinical perspective, it is not reasonable to assume that the patient would have continued to experience a beneficial analgesic effect, since the patient could not tolerate the drug. In fact, it is possible that in some patients the dose that provides acceptable analgesia may be the dose that is associated with intolerable drug-related side effects, which require study medication discontinuation. The LOCF values in these cases may thus produce a biased overestimate of efficacy. From an analytic perspective, imputation using LOCF values may bias the study results in favor of BTDS if 1) the LOCF values are higher in the BTDS patients prematurely discontinued due to drug-related adverse events than in placebo-treated patients prematurely discontinued due to drug-related adverse events, and 2) the proportion of BTDS-treated patients prematurely discontinued to drug-related adverse events is higher than the proportion of placebo-treated patients prematurely discontinued due to drug-related adverse events.

Review of the pattern of discontinuations reveals that discontinuations due to drug-related adverse events were more common in the BTDS group (32.6%), than in either the placebo group (13.3%) or the Oxy/APAP group (25.6%). To determine if the LOCF values of patients discontinued prematurely due to drug-related adverse events is higher in the BTDS group than in the placebo group, the Agency asked the Sponsor to provide a line listing of the LOCF value of all patients, as well as study completion status, and, if appropriate, the reason for discontinuation. Analysis of the LOCF values and the change- from-baseline values for patients discontinued prematurely due to drug-related adverse events is presented in the table below:

Means Change-from-Baseline Values Carried Forward in LOCF Analyses			
	BTDS Mean (SD*)	Oxy/APAP Mean (SD)	Placebo Mean (SD)
Pain on Average			
Completed Study	-3.7 (2.4)	-2.8 (2.6)	-4.2 (2.4)
Discontinued Treatment – All Cases	-0.9 (1.6)	-0.9 (1.8)	-0.5 (1.4)
Related to Test Medication	-1.2 (1.5)	-0.3 (0.6)	-0.7 (2.2)
Not Related to Test Medication	---	-6.0 (-)	-2.0 (-)
Ineffective Treatment	0.1 (1.5)	1.0 (-)	-0.4 (1.2)
Lost to Follow-up	-1.0 (-)	---	0.0 (-)
Protocol Violation	-3.0 (-)	---	0.0 (1.0)
Other	---	-2.5 (2.1)	0.0 (-)
Pain Right Now			
Completed Study	-3.3 (2.4)	-2.6 (2.6)	-3.4 (3.4)
Discontinued Treatment – All Cases	-0.6 (2.1)	-0.3 (1.3)	-0.5 (2.0)
Related to Test Medication	-1.1 (2.0)	-0.2 (0.8)	-1.2 (3.4)
Not Related to Test Medication	---	-1.0 (-)	0.0 (-)
Ineffective Treatment	1.0 (1.7)	1.0 (-)	-0.7 (1.3)
Lost to Follow-up	-2.0 (-)	---	0.0 (-)
Protocol Violation	-2.0 (-)	---	0.0 (-)
Other	---	-3.0 (0.0)	2.0 (-)
*SD = Standard deviation Source: Based on Sponsor datasets LOCFLIST and I1_A_BPI, analyzed by Dr. Stella Grosser, Statistical Reviewer			

Review of the above table indicates that for "Pain on Average", the mean change from baseline in the BTDS group is numerically larger than the corresponding value in the other two groups. For "Pain Right Now", the mean change from baseline is nearly equal in the BTDS group and the Placebo group, and is smallest in the Oxy/APAP group. Nonetheless, the larger number of patients in the BTDS group who withdrew prematurely due to drug-related adverse events may impact the results of the LOCF analysis.

To assess the primary efficacy data using only actual data obtained at each visit (ie, without carrying forward the last observation), the Agency asked the Sponsor to repeat the above repeated measures analyses without carrying forward the last observation. Results for Pain on Average are presented in Figure 11.1C, which is contained in the Sponsor's submission of April 18, 2001 (received April 21, 2001), and is reproduced below:



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo	LS Mean ± SEM	-1.02 ± 0.45	-1.7 ± 0.54	-2.18 ± 0.63	-3.45 ± 0.74	-3.13 ± 0.70	-2.95 ± 0.71	-1.4 ± 0.45
N = 45	N with data	34	23	22	18	18	18	34
Oxy/APAP	LS Mean ± SEM	**-2.52 ± 0.43**	-2.46 ± 0.43	-2.49 ± 0.54	-1.94 ± 0.61	-2.24 ± 0.59	-2.08 ± 0.6	-2.34 ± 0.41
N = 42	N with data	**31**	32	29	29	28	27	32
	Pairwise vs. placebo	***P* = 0.004**	ns	ns	ns	ns	ns	ns
BTDS	LS Mean ± SEM	**-2.38 ± 0.42**	**-2.86 ± 0.45**	-3.14 ± 0.58	-3.54 ± 0.66	-3.31 ± 0.65	-3.34 ± 0.63	**-2.58 ± 0.41**
N = 46	N with data	**33**	**29**	25	23	21	22	**33**
	Pairwise vs. placebo	***P* = 0.008**	***P* = 0.046**	ns	ns	ns	ns	***P* = 0.019**

(Cross-references: LS means from Appendix 16.1.9.1; N with data from Table 14.2.1.1.B3.)
Box in figure indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14.
Bars at each data point indicate ±1.5 SEM.
N = number of patients with data at that visit; N for RM = number of patients with both baseline and at least one post-baseline efficacy measurement.
Least squares (LS) means – corrected by SAS Proc Mixed for baseline pain, center and opioid experience.
Repeated measure (RM) 21-84 values calculated via repeated measures analysis of all available data from Days 21 through 84 using SAS Proc Mixed.
Pairwise vs. placebo – results of comparison with placebo using SAS Proc Mixed.
ns = difference not statistically significant ($P>0.05$).
Boldface indicates statistically significant results.

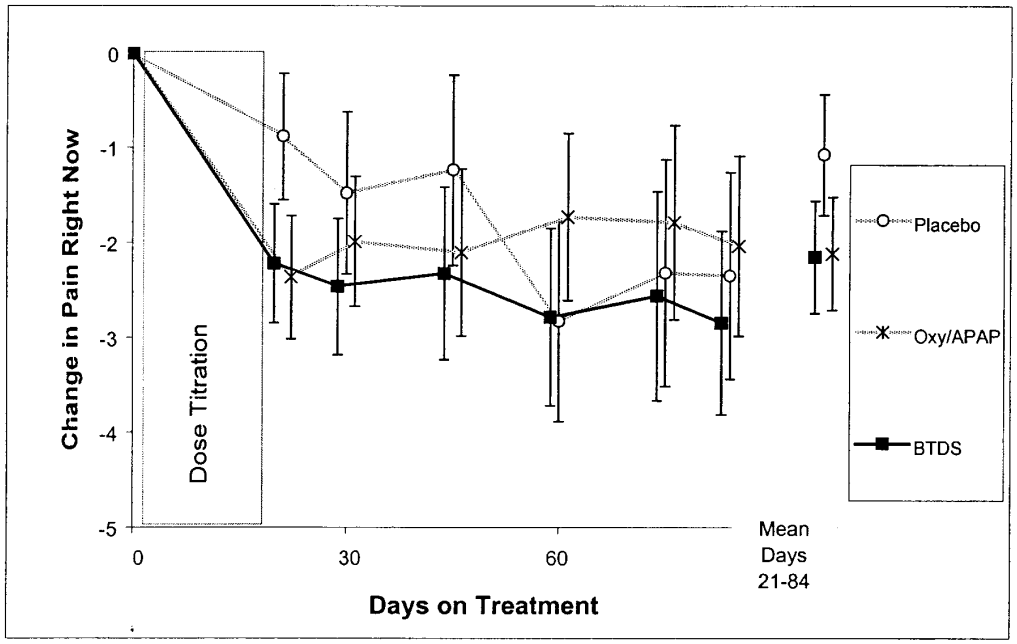
FIGURE 11.1C.

Study BP96-0604
Pain on Average by Day (Change From Baseline)
Least Squares (LS) Means ±1.5 SEM, Last Observation **NOT** Carried Forward
Intent-to-treat Patients With Efficacy Data (N = 133)

Review of the above graph and accompanying data table reveals both qualitative and quantitative differences compared to the corresponding analysis with LOCF. First, at each visit during the Maintenance Period, the LS mean value for change from baseline in "Pain on Average" is of a numerically greater magnitude in the non-LOCF analysis compared to the LOCF analysis for each of the three treatment groups. The reason for this difference is not clear, but may be due to the fact that patients who discontinued during the Titration Period had poorer pain score than patients who continued into the Maintenance Period. The proportion of patients who discontinued prior to the beginning of the Maintenance Period on Day 21 was relatively high (around 25% for each treatment group), so mean values that do not include this group may be numerically different from mean values that do include this group. Second, the numerical superiority of BTDS over Placebo throughout the Maintenance Period in the LOCF analysis is no longer seen. Rather, from Day 60 onward in the non-LOCF analysis the LS mean values for the BTDS and Placebo groups are barely distinguishable. Third, the general similarity of the BTDS and Oxy/APAP responses during the Maintenance Period in the LOCF analysis is not seen in the non-LOCF analysis. Rather, in the non-LOCF analysis, the BTDS and Oxy/APAP responses are similar through Day 30, but from Day 45 onward, the Oxy/APAP responses is notably poorer than both the BTDS and Placebo responses. Thus, the non-LOCF analysis of "Pain on the Average" provides a different interpretation of the performance of BTDS relative to Placebo over time, compared to the LOCF analysis. While the Day 21-84 repeated measures analysis is statistically significant, the actual performance of BTDS after Day 60 is nearly indistinguishable from Placebo in the non-LOCF analysis, which uses only data available at each time point.

The Day 84 results in the above table provide a "Completers' Analysis", ie, an analysis of the last time point for patients who completed the entire 84-day study. The LS mean change from baseline in BTDS completers at Day 84 (-3.34 ±0.63) is not very different, from both a clinical and statistical perspective, from the LS mean change from baseline in Placebo completers (-2.95 ± 0.71). It is interesting to note that the proportion of patients in each of these two treatment groups who complete the study is similar: 40.0% in the BTDS group and 47.8% in the BTDS group. Thus, the estimate of the effect at Day 84 in each of the two groups is based on a similar amount of data, making a between-group comparison more meaningful than if one group were substantially larger than the other group. A completers' analysis is subject to certain biases. First, the Placebo patients still in the trial at Day 84 may be "placebo responders", and thus not entirely representative of the group initially randomized to placebo treatment. Second, the BTDS patients still enrolled at Day 84 are those who can both tolerate the drug and have presumably have experienced sufficient benefit to continue taking the drug. In this respect, they may not be entirely representative of the group initially randomized to BTDS treatment. Because the effect of treatment over the long-term (ie, over 84 days) is important in the evaluation of a drug intended for chronic administration, the results of this completers' analysis, despite its potential biases, must be considered in the overall efficacy evaluation of this study.

The Sponsor's results of a non-LOCF analysis for Pain Right Now are presented in Figure 11.1D, which is contained in the Sponsor's submission of April 18, 2001 (received April 21, 2001), and is reproduced below:



		Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	RM 21-84
Placebo	LS Mean ± SEM	-0.88 ± 0.44	-1.48 ± 0.57	-1.24 ± 0.67	-2.83 ± 0.70	-2.32 ± 0.80	-2.35 ± 0.73	-1.07 ± 0.43
N = 45	N with data	34	23	21	18	18	18	34
Oxy/APAP	LS Mean ± SEM	**-2.37 ± 0.43**	-1.99 ± 0.46	-2.1 ± 0.59	-1.73 ± 0.59	-1.79 ± 0.68	-2.04 ± 0.63	**-2.12 ± 0.40**
N = 42	N with data	**31**	32	29	29	28	27	**32**
	Pairwise vs. placebo	***P* = 0.0047**	ns	ns	ns	ns	ns	***P* = 0.032**
BTDS	LS Mean ± SEM	**-2.22 ± 0.42**	-2.46 ± 0.48	-2.33 ± 0.60	-2.78 ± 0.62	-2.56 ± 0.73	-2.84 ± 0.65	**-2.15 ± 0.39**
N = 46	N with data	**33**	29	25	23	21	22	**33**
	Pairwise vs. placebo	***P* = 0.0082**	ns	ns	ns	ns	ns	***P* = 0.024**

(Cross-references: LS means from Appendix 16.1.9.1; N with data from Table 14.2.1.2.B3.)
Box in figure indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14.
Bars at each data point indicate ±1.5 SEM.
N = number of patients with data at that visit; N for RM = number of patients with both baseline and at least one post-baseline efficacy measurement.
Least squares (LS) means – corrected by SAS Proc Mixed for age category, baseline pain, center and opioid experience.
Repeated measures (RM) 21-84 values calculated via repeated measures analysis of all available data from Days 21-84 using SAS Proc Mixed.
Pairwise vs. placebo – results of comparison with placebo using SAS Proc Mixed.
ns = difference not statistically significant ($P>0.05$).
Boldface indicates statistically significant results.

FIGURE 11.1D.

Study BP96-0604
Pain Right Now by Day (Change From Baseline)
Least Squares (LS) Means ±1.5 SEM, Last Observation **NOT** Carried Forward
Intent-to-treat Patients With Efficacy Data (N = 133)

As with the analysis of Pain on the Average, review of the above graph and accompanying data table reveals both qualitative and quantitative differences in the non-LOCF versus LOCF analyses of Pain Right Now. First, at each visit during the Maintenance Period, the LS mean value for change from baseline in "Pain Right Now" is of a numerically greater magnitude in the non-LOCF analysis compared to the LOCF analysis for each of the three treatment groups. The reason for this difference is not clear, but may be due to the fact that patients who discontinued during the Titration Period had poorer pain score than patients who continued into the Maintenance Period. The proportion of patients who discontinued prior to the beginning of the Maintenance Period on Day 21 was relatively high (around 25% for each treatment group), so mean values that do not include this group may be numerically different from mean values that do include this group. Second, the numerical superiority of BTDS over Placebo throughout the Maintenance Period in the LOCF analysis is no longer seen. Rather, at Day 60 and at Day 75 in the non-LOCF analysis the LS mean values for the BTDS and Placebo groups are barely distinguishable. Third, the general similarity of the BTDS and Oxy/APAP responses during the Maintenance Period in the LOCF analysis is not seen in the non-LCOF analysis. Rather, in the non-LOCF analysis, the BTDS and Oxy/APAP responses are similar through Day 45, but from Day 60 onward, the Oxy/APAP responses is notably poorer than both the BTDS and Placebo responses. Thus, the non-LOCF analysis of "Pain Right Now" provides a different interpretation of the performance of BTDS relative to Placebo over time, compared tot he LOCF analysis. While the Day 21-84 repeated measures analysis is statistically significant, the actual performance of BTDS at Days 60 and 75 is nearly indistinguishable from Placebo in the non-LOCF analysis, which uses only data available at each time point.

In the Day 84 "Completers' Analysis", the LS mean change from baseline in BTDS completers at Day 84 (-2.84 ± 0.65) is not very different, from both a clinical and statistical perspective, from the LS mean change from baseline in Placebo completers (-2.35 ± 0.73).

6.1.2.4.2 Secondary Efficacy Variables

The Sponsor has analyzed the time to discontinuation due to lack of efficacy as an efficacy outcome measure. Using Cox Proportional Hazards analysis with adjustment for center effect and opioid experience, as well as with censoring for all premature discontinuations other than those due to lack of efficacy, the Sponsor has demonstrated that the proportion discontinuing over time in the Placebo group is statistically significantly higher than the corresponding proportions in either the Oxy/APAP group or the BTDS group. The Sponsor's results are presented in Figure 11.2 of the Study Report, the data table from which is presented below:

Study BP96-0604
Time to Discontinuation Due to Lack of Efficacy—
Proportion Estimated by Cox Proportional Hazards Regression:
Intent-to-treat Population (N = 134)

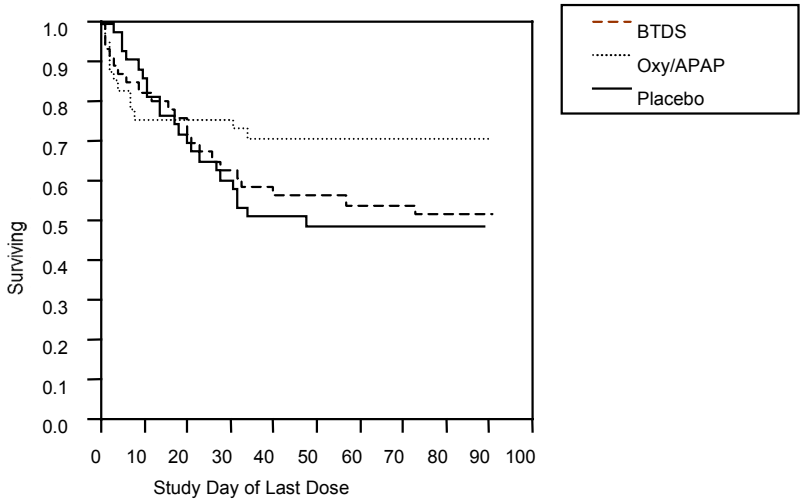
	Day 0	Day 21	Day 30	Day 45	Day 60	Day 75	Day 84	Days 0-84	Pairwise vs.Placebo
Placebo (N=45)									
Proportion discontinuing	0.000	0.260	0.315	0.435	0.435	0.435	0.435	-	
Number (at interval start)	45	29	26	22	19	19	18	-	
Drop out Lack of Efficacy	-	10	3	3	0	0	0	16	
Censored (total)	-	6	0	1	3	0	1	11	
Oxy/APAP (N=43)									
Proportion discontinuing	0.000	0.013	0.016	0.024	0.024	0.024	0.024	-	P= 0.002
Number (at interval start)	43	32	32	29	29	28	27	-	
Drop out Lack of Efficacy	-	0	0	1	0	0	0	1	
Censored (total)	-	11	0	2	0	1	1	15	
BTDS (N=46)									
Proportion discontinuing	0.000	0.086	0.107	0.157	0.157	0.157	0.157	-	P= 0.011
Number (at interval start)	46	32	29	25	23	22	22	-	
Drop out Lack of Efficacy	-	5	0	2	0	0	0	7	
Censored (total)	-	9	3	2	2	1	0	17	

(Cross references: discontinuations from Table 14.1.1.E & Appendix 16.1.9.5; hazard ratios from Appendix 16.1.9.2; statistics from Table 14.2.5.B.)
Proportional hazards model using SAS proc PHREG with covariate correction for center and opioid experience Bar indicates time of dose titration: all BTDS patients started with BTDS 5 and titrated dose on Day 7 and/or Day 14 ns = difference not statistically significant (P> 0.05) Bolding indicates statistically significant results

Source: Data table from Sponsor Figure 11.2 in BP96-0604 Study Report

Discontinuation due to lack of efficacy is an indirect measurement of efficacy, since it does not measure the magnitude of the analgesic effect of the treatment. Nonetheless, a careful analysis of discontinuations due to lack of efficacy can be supportive of a drug's efficacy, if there are fewer such discontinuations over time in the treatment group than in the Placebo group. However, the above analysis necessitates censoring of all discontinuations other than those due to lack of efficacy. However, some reasons for premature discontinuation other than lack of efficacy are informative with regard to patients' experience with the drug. For the same reasons that the LOCF method of imputing missing data are not appropriate for patients whose reason for discontinuation was an adverse event related to the study drug, analysis of time to discontinuation due to lack of efficacy presents an incomplete and biased view of the drug's effects. A more appropriate analysis would be to examine time to discontinuation due either to lack of efficacy or to a drug-related adverse event. This composite binary outcome measure allows for an analysis of "time to treatment failure", which is more clinically relevant than time to discontinuation due to lack of efficacy. A survival curve examining time to treatment failure (defined as discontinuation due to lack of efficacy or due to a drug-related adverse event) is presented below. Though formal statistical analysis has not been performed, visual inspection of the curves indicates that the proportion of patients discontinuing over time is similar between the BTDS and Placebo group.

Furthermore, the proportion of discontinuations due to treatment failure is lower in the Oxy/APAP group, after about Day 21.



The Sponsor measured and analyzed several other secondary efficacy outcome measures, which are summarized in Sponsor's table 11B in the Study Report, and which is reproduced below.

Study BP96-0604
Summary of Secondary Efficacy Variables—Mean Change From Baseline, Days 78–84, or Mean Percent, Day 84 (LOCF): Intent-to-treat Population With Efficacy Data (N = 133)

	Baseline	Placebo	Oxy/APAP	BTDS
Secondary Variables	Range	(N = 45)	(N = 42)[a]	(N = 46)
		Mean Change From Baseline ± SEM		
Daily Patient Diary (Scale 0–10)			(Days 78–84)	
Pain on the Average	5.9–6.2	-0.8 ± 0.3	-1.0 ± 0.4	-1.6 ± 0.4
MOS Health Survey (0%–100%)	Baseline Range	Mean Percent ± SEM (Day 84)		
Physical functioning	36.6–43.4	46.4 ± 4.0	44.5 ± 3.9	46.5 ± 3.6
Physical role	9.4–22.8	18.9 ± 4.8	24.4 ± 5.9	33.9 ± 5.8
Bodily pain	26.1–28.2	35.3 ± 3.1	39.0 ± 3.4	41.9 ± 3.1
General health	50.8–55.3	52.4 ± 3.5	52.5 ± 3.5	57.7 ± 3.4
Vitality	31.2–38.7	39.0 ± 3.7	42.9 ± 3.7	41.2 ± 3.5
Social functioning	49.4–55.7	53.3 ± 4.2	59.5 ± 3.9	65.2 ± 4.4
Emotional role	52.7–59.4	55.3 ± 6.7	56.3 ± 7.1	63.0 ± 6.2
Mental health	66.0–68.2	67.4 ± 3.1	68.8 ± 2.7	67.8 ± 3.3
		Mean ± SEM (Day 84)		
Therapeutic response–investigator (scale 0–3)		1.1 ± 0.2	2.0 ± 0.2	1.9 ± 0.2
Therapeutic response–patient (scale 0–3)		1.1 ± 0.2	2.1 ± 0.1	2.0 ± 0.2
Patient comparison to prestudy analgesic (scale 0–2)		0.9 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
Patient satisfaction (scale 1–3)		2.2 ± 0.1	1.8 ± 0.1	1.7 ± 0.2

(Cross-references: Tables 14.2.2.1.B1–14.2.2.8.B1, 14.2.3B, and 14.2.4.B1.)
[a]One patient from the intent-to-treat population (the Oxy/APAP group) was not included in the pain measure analyses. The patient discontinued and had no efficacy data.
See the Statistical/Analytical Issues section at the end of Section 11 for a discussion of covariates used for the secondary efficacy variables.
Source: Sponsor Table 11B in BP96-0604 Study Report

The Sponsor's discussion of the above outcome variables in the Study Report notes the following:

Apart from social functioning, there were no significant differences among the three treatment groups in any items of the MOS. For social functioning, there was a significant treatment-by-center interaction, which precluded generalization among all centers.

The mean values for Therapeutic Response – Investigator, Therapeutic Response – Patient, Patient Preference (relative to prestudy analgesic), and Patient Satisfaction were similar for the BTDS and Oxy/APAP groups. In each case, the numerical results suggest less efficacy in the Placebo group than in the other two treatment groups. For the Patient and Investigator Therapeutic Response Scales, 0 = No Response, 1 = Minimal Response, 2 = Moderate Response, and 3 = Marked Response. For the Patient Satisfaction Scale, 1 = Satisfied, 2 = Neutral, and 3 = Unsatisfied. For the Patient Comparison to Prestudy Analgesic, 0 = Worse, 1 = No Change, and 2 = Better. Results of formal statistical analyses are not presented. The above descriptive statistics of these scales are presented as if the values were continuous variables. Analyses treating these scales as categorical variables are not presented. The interpretation of such analyses, however, would have to take into account the fact that favorable score may have been assigned to patients who stopped the drug because of a drug-related adverse event.

Analysis of data from the Patients' Daily Diary (Pain on the Average) indicate a numerically greater mean reduction in pain in the BTDS and Oxy/APAP groups, compared to the Placebo group. Details of the statistical methodology, such as the method of handling missing data, are not presented. Inferential statistics are also not presented in the Study Report.

Time to Stable Pain Management was defined as the first time during the titration period when the "diary pain" was 4 or less (or at least 2 points lower than baseline) for 3 consecutive daily records or when the "Pain on the Average" at Day 7 or Day 21 visit was 4 or less (or at least 2 points lower than baseline). By Day 21 (the end of the titration period), 26/45 (57/8%) of patients in the Placebo group, 28/43 (65.1%) of the patients in the Oxy/APAP group, and 34/46 (73.9%) of patients in the BTDS group reached stable pain management. A Cox proportional hazards model, adjusted for center and opioid experience, revealed the following results:

Comparison	Hazard Ratio	P-value
BTDS to Placebo	1.67	0.054
Oxy/APAP to Placebo	1.51	0.138
BTDS to Oxy/APAP	1.11	0.697
Source: Sponsor Table 14.2.6B		

The above findings are consistent with larger number of Placebo-treated subjects who discontinued due to lack of efficacy.

At the end of the titration period, most patients in the Placebo group were at dose level 3 (the highest dose level), while Oxy/APAP patients were evenly distributed among the doses, and a most BTDS patients were at either level 2 or 3. During the maintenance period, most patients stayed at the dose level reached at the end of the titration period, though some did change doses. The distribution of dose levels at the end of the titration period, as well as the post-titration dose adjustments, are summarized in the table below, which is based in Sponsor's Table 14.2.7B.

Treatment Group	Sequence Of Dose Adjustments *	Dose Level At End Of Titration Period		
		1	2	3
Placebo	Same #	2 (66.7%)	6 (75.0%)	15 (100%)
	2	1 (33.3%)	0 (0.0%)	0 (0.0%)
	3	0 (0.0%)	2 (25.0%)	0 (0.0%)
	Total	3	8	15
Oxy./APAP	Same #	8 (80.0%)	6 (75.0%)	13 (92.9%)
	1	0 (0.0%)	1 (12.5%)	0 (0.0%)
	2	1 (10.0%)	0 (0.0%)	1 (7.1%)
	3	0 (0.0%)	1 (12.5%)	0 (0.0%)
	23	1 (10.0%)	0 (0.0%)	0 (0.0%)
	Total	10	8	14
BTDS	Same #	5 (83.3%)	8 (61.5%)	10 (90.9%)
	1	0 (0.0%)	1 (7.7%)	0 (0.0%)
	2	0 (0.0%)	0 (0.0%)	1 (9.1%)
	3	0 (0.0%)	3 (23.1%)	0 (0.0%)
	23	1 (16.7%)	0 (0.0%)	0 (0.0%)
	32	0 (0.0%)	1 (7.7%)	0 (0.0%)
	Total	6	13	11

* 1 - Dose adjusted to level 1.
2 - Dose adjusted to level 2.
3 - Dose adjusted to level 3.
For example, "232" means that after the titration period (i.e. after Day 21), the Dose was adjusted to level 2, then to level 3, and then back to level 2.

\# Same - Dose level not changed after titration period.

Source: Sponsor Table 14.2.7B in BP96-0604 Study Report

While the above table indicates that overall there were not many post-titration changes in dosing, three of 13 BTDS-treated patients who ended the titration at dose level 2 required at increase to dose level 3. There were very few downward dose adjustments in any treatment group.

6.1.2.5 Discussion of the Efficacy Finding in Study BP96-0604

Taken as a whole, the efficacy findings in Study BP96-0604 do not support the effectiveness of the BTDS for the treatment of chronic pain. In the Sponsor's primary efficacy analysis, a repeated measures ANOVA, using the LOCF method to impute missing values after premature discontinuation, was used to demonstrate a statistically significant difference between the placebo group and the BTDS group in the least-squares mean values for the change from baseline in the two primary outcome measures, "Pain on the Average" and "Pain Right Now". The protocol-specified BTDS-placebo difference in pain measures was 1.5. The actual BTDS-placebo differences were about 0.91 for "Pain on the Average" and about 0.86 for "Pain Right Now." The clinical significance of these between-group differences in least-squares mean change from baseline in the two primary efficacy measures is not clear, and no justification of their clinical

significance was provided by the Sponsor. Though these measures of efficacy thus do not attain the level of effect contemplated in the protocol, they did reach statistical significance. The statistical significance of the results may be due, in part, to the fact that the actual sample sizes (42 to 46 patients in each treatment group) is larger than the per-group size determined by the sample size calculation in the protocol (35 per group). A fundamental problem with the Sponsor's analysis, however, is that the LOCF method carries forward efficacy data for patients who prematurely discontinue the study due to a drug-related adverse event. While the LOCF method may be appropriate imputation technique for efficacy data from patients whose discontinuation is due to other reasons, this method is not appropriate for patients whose primary reason for discontinuation is due to a drug-related adverse event. As reviewed and discussed above, such discontinuations are more frequent in the BTDS group. Furthermore, for "Pain on Average", the mean value of the change-from-baseline scores for the discontinuations in the BTDS group is higher than the corresponding mean value for the discontinuations in the Placebo group. However, an imputed value is only appropriate if it reflects a meaningful measure of what the patient would have experienced had he or she continued on the study medication. Patients who discontinue prematurely due to a drug-related adverse event can only be expected to have continued intolerance to the drug requiring discontinuation, and thus could not have the opportunity to derive any benefit from that drug. The effect of this imputation method is thus to produce a biased overestimate of the treatment effect in BTDS-treated patients, which may "drive" the results of the Sponsor's primary efficacy analyses. When the repeated measure analysis was repeated without using the LOCF method, the results was again statistically significant. The repeated measures analysis without LOCF weights more heavily data from time points when more data are available, compared to time points when less data are available. In Study BP96-0604, this results is more heavy weighting of earlier time points, before BTDS patients who can not tolerate the drug but have adequate analgesia are still enrolled, and when Placebo patients who have not yet dropped out due to lack of efficacy are still enrolled. This pattern of data favors the BTDS group, especially in the early portion of the Maintenance Period. When the results of an "endpoint" analysis are reviewed, the differences in "Pain on the Average" and "Pain Right Now" between the Placebo group and the BTDS group are no longer statistically significant, and the magnitude of the between-group difference are of questionable clinical significance. Similarly, the "Completers'" analysis reveals no statistically significant difference between the Placebo and BTDS groups. When actual, by-visit data are examined, the analgesic efficacy over time of BTDS is no different from that of placebo over the last month of treatment in patients who were actually treated during that time period. Nonetheless, the data do demonstrate analgesic activity of BTDS over Placebo during the first 45 to 60 days of treatment. At Day 21 and 30, this effect is statistically significant for both Pain on the Average and Pain Right now using the LOCF methodology.

A potential problem with the design of the study, which was not explored in either the Sponsor's analysis or in this review, was the fact that during the titration period patients could escalate from one dose to the next dose before seven days – in fact, as early as three days after a dose had been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that the maximum concentration is reach at about 107 hours, titration to a higher dose after only 3 or 4 days on a lower dose may be premature, and may lead to either excessive toxicity, overestimation of the minimum effective dose for a given patient, or both.

Review of many of the secondary efficacy endpoints reveals the same problem – the statistical treatment of patients who discontinued prematurely due to drug-related adverse events assumes that these patients would have continued to derive whatever analgesic benefit they were experiencing at the time of discontinuation. However, the drug itself led to the discontinuation, so they could not have continued to derive that benefit. This point is especially relevant to the

analysis of "time to discontinuation due to lack of efficacy", which in the Sponsor's analysis shows a clear difference, in favor of BTDS, between the Placebo and BTDS groups. When "time to discontinuation due to a drug-related adverse event" is also added as an "event" in this analysis (essentially changing the analysis into a "time to treatment failure" analysis), there is no substantial difference between the Placebo and BTDS groups.

Taken as a whole, the efficacy data from Study BP96-0604 do not support the efficacy of BTDS for the treatment of chronic pain.

In addition to the Phase 3 Studies BP99-0203 and BP96-0604, the Sponsor submitted the results of one Phase 2 study (BP96-0104) and three Phase 3 studies (BP96-0101, BP96-0102, and BP98-1201). As none of these studies demonstrates the efficacy of BTDS for chronic pain, these studies and their main results will be only briefly described, but will not be reviewed any further.

6.1.3 Study BP96-0104: A Placebo-controlled Study of the Safety and Pharmacokinetics of BTDS in Patients with Moderate to Severe Pain Following Orthopedic Surgery

6.1.3.1 Study Design, Population, and Outcome Measures

Study BP96-0104, "A Placebo-controlled Study of the Safety and Pharmacokinetics of BTDS in Patients with Moderate to Severe Pain Following Orthopedic Surgery", was a Phase 2 study designed to assess the safety of three strengths of BTDS (5, 10, and 20 mg) for 72 hours in patients following orthopedic surgery, when used with rescue patient- controlled analgesia (PCA) IV morphine. Pharmacokinetic data were also obtained.

The study design was randomized, 3-arm, double-blind, double-dummy, parallel-group, placebo-controlled design. Following surgery and recovery from anesthesia, patients in moderate to severe pain were randomized to 1 of 4 treatment groups (placebo, BTDS 5, BTDS 10, BTDS 20). All patients were able to receive rescue PCA IV morphine. Safety measures included pulmonary function tests, adverse events, clinical laboratory tests, vital signs, medical histories, physical examinations, and application site skin observations. Pharmacokinetic measures were AUCt, Cmax, and tmax. Three-day flux was estimated. Efficacy measures were change from baseline in pain intensity, rescue IV morphine use, acceptability of therapy, and quality of sleep.

6.1.3.2 Study Conduct

Thirty-two males and 78 females were enrolled, of whom 3% were opioid-naïve and 97% were opioid-experienced. The results of the trial are presented in the Sponsor's table, reproduced below, in Section 8.8.3.1 of the NDA:

Sponsor's Table of Results for Study BP96-0104.				
	Placebo	BTDS 5	BTDS 10	BTDS 20
	(N = 11)	(N = 33)	(N = 33)	(N = 33)
Cumulative Morphine Rescue (mg) Hour 72				
Mean ± SEM	64.7 ± 10.6	52.5 ± 9.5	35.7 ± 6.3	41.3 ± 6.5
Median (max, min)	65.0 (24, 103)	47.0 (3, 241)	24.5 (1, 142)	27.0 (2, 148)
Adverse Events, number (%) of patients				
Any Adverse Event	11 (100%)	24 (73%)	24 (73%)	26 (79%)
Somnolence	1 (9%)	2 (6%)	5 (15%)	5 (15%)
Nausea	2 (18%)	7 (21%)	12 (36%)	8 (24%)
Vomiting	0 (0%)	5 (15%)	3 (9%)	2 (6%)
Constipation	3 (27%)	11 (33%)	7 (21%)	7 (21%)
Dizziness	3 (27%)	3 (9%)	7 (21%)	6 (18%)
Rash at TDS Site	1 (9%)	0	0	1 (3%)
Pharmacokinetic (N=99)	BTDS 5 (N=33)	BTDS 10 (N=33)		BTDS 20 (N=33)
Parameter (units)	**(n) Mean ± SD**			
AUCt (pg±h/mL)	(24) 2066 ± 2394	(26) 4021 ± 3266		(27) 12279 ± 7763
Cmax (pg/mL)	(32) 51.1 ± 64.4	(32) 87.1 ± 61.3		(32) 259.8 ± 153.3
tmax (h)	(32) 37.7 ± 34.4	(32) 59.6 ± 25.5		(32) 61.9 ± 17.5
Source: Sponsor Table in Section 8.8.3.1 of the NDA.				

6.1.4 Study BP96-0101: A Placebo- and Active-Controlled Study of BTDS in Osteoarthritis

6.1.4.1 Study Design, Population, and Outcome Measures

Study BP96-0101, "A Placebo- and Active-Controlled Study of BTDS in Osteoarthritis", was designed to compare the analgesic efficacy, safety, and buprenorphine plasma concentration-effect relationship of the 3 dosage strengths of buprenorphine transdermal system (BTDS 5, 10, and 20) given every 6 days for 60 days, to placebo and immediate release 5 mg oxycodone/325 mg acetaminophen tablets (Oxy/APAP) prn. The study was a randomized, double-blind, double-dummy, parallel-group, multicenter, placebo- and active-controlled, forced titration study. Patients were randomly assigned to 1 of 5 treatment groups and evaluated at Visit Days 9, 15, 30, 45, and 60. Patients were maintained on their pre-study stable dose of NSAIDs. Primary efficacy measures were change from baseline in Pain on Average and Pain Right Now from the Brief Pain Inventory (BPI). Secondary efficacy measures included: other BPI items, dropout due to lack of efficacy, Medical Outcomes Survey (MOS) health questionnaire, visual analog scale (VAS) Pain intensity, Therapeutic Response, and Patient Preference. Safety measures included clinical laboratory tests, medical histories, vital signs, physical examinations, elicited opioid side effects, application site observations, and adverse events. The trial was to enroll osteoarthritis patients whose pain was not manageable with non-opioids alone.

6.1.4.2 Study Conduct

One-hundred males and 170 females were enrolled. Seventy-two percent of the study population was opioid-naïve, and 23% were opioid-experienced. The results of the trial are presented in the Sponsor's table, reproduced below, in Section 8.8.3.2 of the NDA:

Sponsor's Table of Results for Study BP96-0101.					
	Placebo	Oxy/APAP	BTDS 5	BTDS 10	BTDS 20
Efficacy Measures	(N=52)	(N=55)	(N=55)	(N=54)	(N=54)
Pain on Average (Days 9-60, LOCF), mean ± SEM[a]	-0.71 ± 0.27	-0.61 ± 0.27	-1.11 ± 0.26	-0.90 ± 0.26	-1.24 ± 0.26
Pain Right Now (Days 9-60, LOCF), mean ± SEM[a]	-0.22 ± 0.32	-0.87 ± 0.31	-0.94 ± 0.30	-0.79 ± 0.30	-0.97 ± 0.30
Percentage Discontinuing due to Lack of Efficacy (Day 60)[b]	46%	30%	31%	25%*	26%
Adverse Events	number (%) of patients				
Any Adverse Event	44 (85%)	49 (89%)	53 (96%)	48 (89%)	49 (91%)
Somnolence	17 (33%)	20 (36%)	30 (55%)	26 (48%)	34 (63%)
Nausea	14 (27%)	24 (44%)	27 (49%)	28 (52%)	23 (43%)
Vomiting	5 (10%)	16 (29%)	13 (24%)	9 (17%)	13 (24%)
Constipation	13 (25%)	27 (49%)	25 (46%)	24 (44%)	26 (48%)
Dizziness	16 (31%)	26 (47%)	26 (47%)	31 (57%)	21 (39%)
Rash at TDS site	8 (15%)	6 (11%)	2 (4%)	4 (7%)	3 (6%)
(Cross-references: CSR BP96-0101, Figure 11.1.1C; Tables 11.1A, 12.2A and 12.2B.) [a]Change from baseline for "Pain on the Average" and "Pain Right Now" (Days 9–60) via repeated measures analysis for Last Observation Carried Forward (LOCF) with least squares means corrected by SAS Proc Mixed for age, baseline pain, center, opioid experience, and treatment group. [b]Percentage discontinuing due to lack of efficacy corrected by center, age, and opioid experience. *Statistically significant differences from placebo (P<.05) before, but not after, adjustment for multiple comparisons.					
Source: Sponsor Table in Section 8.8.3.2 of the NDA					

The Sponsor notes that the differences between Placebo and BTDS, as well as between Oxy/APAP and Placebo for the primary efficacy measures, "Pain on the Average" and "Pain Right Now" were not statistically significant. The Sponsor considered this study a "failed study".

6.1.5 Study BP96-0102: A Placebo- and Active-controlled Study of BTDS in Patients with Chronic Low Back Pain

6.1.5.1 Study Design, Population, and Outcome Measures

Study BP96-0102, "A Placebo- and Active-controlled Study of BTDS in Patients with Chronic Low Back Pain" was designed to compare the analgesic efficacy, safety, and therapeutic acceptance of buprenorphine transdermal system (BTDS) applied every 7 days for 60 days with immediate-release 5 mg oxycodone/325 mg acetaminophen tablets (Oxy/APAP) taken as needed and placebo. The design was a randomized, 5-arm, double-blind, double-dummy, parallel-group, multicenter, placebo- and active-controlled, forced titration study. Patients were randomized to 1 of 5 treatment groups, had study drug dose titrated on Day 7 or 14 for acceptable analgesia, and were evaluated on Visit Days 15, 30, 45, 60. Patients were required to take their prestudy, stable dose of NSAIDs. Primary efficacy measures were change from baseline in "Pain on Average"

and "Pain Right Now" from the Brief Pain Inventory (BPI). Secondary efficacy measures included: other BPI pain variables, discontinuation due to lack of efficacy; Medical Outcomes Survey (MOS) health survey; Visual Analogue Scale (VAS) "pain intensity", daily pain diary scores, therapeutic response, patient preference and satisfaction and amount of Oxy/APAP or placebo tablets taken. Safety measures included clinical laboratory tests, medical histories, vital signs, physical examinations, elicited opioid side effects, application site observations, and adverse events.

6.1.5.2 Study Conduct

The study enrolled patients with chronic low back pain that was not manageable with non-opioids alone. Ninety-seven males and 152 females, ranging in age from 22 to 88 years (mean age = 56 years) were enrolled.

The results of the trial are presented in the Sponsor's table, reproduced below, in Section 8.8.3.3 of the NDA:

Sponsor's Table of Results for Study BP96-0102.

Efficacy Measures	Placebo (N=48)	Oxy/APAP (N=52)	BTDS 5 (N=50)	BTDS 10 (N=49)	BTDS 20 (N=50)
Change in Pain on Average (Days 9-60) mean ± SEM[a]	-1.15 ± 0.23	-1.42 ± 0.22	-1.05 ± 0.23	-1.02 ± 0.23	-1.41 ± 0.23
Change in Pain Right Now (Days 9-60) mean ± SEM[a]	-1.06 ± 0.27	-1.22 ± 0.26	-0.93 ± 0.27	-1.18 ± 0.28	-1.51 ± 0.27
Change in VAS Pain Intensity (Days 9-60) mean ± SEM[a]	-11.1 ± 2.9	-13.7 ± 2.8	-10.7 ± 2.8	-18.5 ± 2.9	-20.1* ± 2.8
Percentage Discontinuing due to Lack of Efficacy (Day 60)[b]	11%	9%	8%	5%	3%
Adverse Events, number (%) of patients					
Any Adverse Event	40 (83%)	47 (90%)	47 (90%)	45 (92%)	47 (94%)
Somnolence	6 (13%)	20 (39%)	13 (26%)	18 (37%)	22 (44%)
Nausea	10 (21%)	17 (33%)	16 (32%)	14 (29%)	26 (52%)
Vomiting	3 (6%)	7 (14%)	0	7 (14%)	16 (32%)
Constipation	11 (23%)	21 (40%)	17 (34%)	14 (29%)	21 (42%)
Dizziness	9 (19%)	16 (31%)	19 (38%)	17 (35%)	25 (50%)
Rash at TDS Site	9 (19%)	11 (21%)	2 (4%)	5 (10%)	7 (14%)

(Cross-references: CSR BP96-0102, Figures 11.1.1A, 11.1.1B and 11.1.2; Tables 11.1A, 12.2.2A and 12.2.2B.)
[a]Change from baseline for "Pain on the Average" and "Pain Right Now" (Days 9–60) via repeated measures analysis for Last Observation Carried Forward (LOCF) with least squares means corrected by SAS Proc Mixed for baseline pain, center, treatment group, age and gender. Change from baseline for "pain intensity" corrected for center, treatment group, age, and gender.
[b]Percentage discontinuing due to lack of efficacy corrected for center and opioid experience.
*Statistically significant differences from placebo (P<.05) before, but not after, adjustment for multiple comparisons.

Source: Sponsor Table in Section 8.8.3.3 of the NDA

The Sponsor notes that the differences between Placebo and BTDS, as well as between Oxy/APAP and Placebo for the primary efficacy measures, "Pain on the Average" and "Pain Right Now" were not statistically significant. The Sponsor considered this study a "failed study".

6.1.6 Study BP98-1201: Double-Blind, Comparative Study of Buprenorphine Transdermal System (BTDS) and Hydrocodone/Acetaminophen Tablets in Patients with Chronic Back Pain

6.1.6.1 Study Design, Population, and Outcome Measures

Study BP98-1201, "Double-Blind, Comparative Study of Buprenorphine Transdermal System (BTDS) and Hydrocodone/Acetaminophen Tablets in Patients with Chronic Back Pain"was designed to compare the analgesic efficacy, safety and therapeutic acceptance of buprenorphine transdermal system (BTDS) applied every 7 days for 56 days in comparison with immediate-release 2.5 mg hydrocodone/250 mg acetaminophen tablets (HCD/APAP) taken 4 times a day. The study design was a randomized, 2-arm, double-blind, double-dummy, multiple-dose, parallel-group, multicenter, active-controlled, titration-to-effect efficacy and safety design in chronic back pain patients. Patients had a 7-day run-in period in which they discontinued all prior analgesic medications and began 400 mg ibuprofen 4 times per day, continued for the entire study. Patients were randomized to either active or placebo BTDS treatment groups when average pain intensity was at least 5 on a 0-10 point scale. Dose was titrated for effective analgesia up to level 3 for up to 21 days, and patients continued on a dosage level that was acceptable for the 35-day maintenance period, if necessary titrating downward to control side effects. Evaluations were on Visit Days 7, 14, 21, 28, 35, 42, 49 and 56. Primary efficacy measures were Average Pain Intensity and Patient Satisfaction with Medication for Pain (Patient Global Efficacy Rating) over Days 21 to 56. Secondary efficacy measures included Average Pain Intensity and Patient Satisfaction with Medication for Pain at Day 21, incidence and time to early discontinuation due to lack of efficacy, investigator's assessment of therapeutic response, and dose level at the end of titration. Safety measures included clinical laboratory tests, medical histories, vital signs, physical examinations, application site observations, and adverse events.

6.1.6.2 Study Conduct

The study enrolled patients with chronic back pain, not controlled with non-opioids alone. One-hundred-twenty-five males and 145 females, ranging in age from 26 to 88 (mean age = 52 years), were enrolled. Forty-three percent were opioid-naïve, and 57% were opioid-experienced.

The results of the trial are presented in the Sponsor's table, reproduced below, in Section 8.8.3.5 of the NDA:

Sponsor's Table of Results for Study BP98-1201			
Efficacy Measurements	HCD/APAP	BTDS	Difference:
	(N=129)	(N=137)	BTDS - HCD/APAP
	Least Squares Mean[a] [95% confidence interval]		
Average Pain Intensity (Days 21-56)	6.04 [5.7, 6.4]	5.96 [5.6, 6.3]	-0.08 [-0.60, 0.44]
Patient Satisfaction with Medication for Pain (Days 21-56)	1.37 [1.2, 1.5]	1.53 [1.4, 1.7]	0.160 [-0.08, 0.39]
	Mean ± SEM		Ratio [CI]
Discontinuations Due to Lack of Efficacy (Days)[b]	22.9 ± 3.29	22.4 ± 2.8	1.130 [0.58, 2.19]
Adverse Events	number (%) of patients		
Any Adverse Event	99 (76%)	117 (84%)	
Somnolence	22 (17%)	23 (16%)	
Nausea	22 (17%)	33 (24%)	
Constipation	13 (10%)	20 (14%)	
Dizziness	18 (14%)	18 (13%)	
Erythema at Site	15 (12%)	13 (9%)	
Pruritis at Site	29 (22%)	34 (24%)	
Rash at TDS Site	10 (8%)	25 (18%)	
(Cross-references: CSR BP96-1201, Figures 11.1A, 11.1B 11.2C, and Tables 12.2.2A, 12.2.2B, and 12.2.2C.) [a] Least squares means were calculated via repeated measures analysis for last observation carried forward (LOCF) corrected by SAS Proc Mixed for baseline pain, center, treatment, day and weight for "pain on the average;" baseline pain, center, treatment, day and weight for "patient satisfaction." [b]Cox proportional hazard regression analysis with center as a stratification variable and effects for baseline pain, gender and treatment.			
Source: Sponsor Table in Section 8.8.3.5 of the NDA			

The Sponsor notes that non-inferiority and equivalence between HCD/APAP and BTDS were demonstrated. The 95% confidence intervals of the difference between the two treatments for the primary variables of Average Pain Intensity and Patients Satisfaction with Medication for Pain (Days 21-56) were within the range of [-2,2] and [-1,1], respectively. However, since there is no placebo control or dose control, the study lacks adequate assay sensitivity to demonstrate efficacy.

6.2 Other Efficacy Analyses

6.2.1 Effects of Gender on Efficacy Outcome

The Sponsor combined efficacy data from the two titration-to-effect studies, BP96-0604 and BP99-0203, to analyze the effects of gender on the analgesic activity of the BTDS. In both males and females, the point estimate of BTDS indicated that it was better than Placebo in pain reduction, as measured by the change from baseline in that measure. The confidence interval around the estimate for males, however, spanned zero, while it did not for women. These data are presented in the data table accompanying Sponsor's Figure 8.11.3.4.1A.

Pain on Average (Days 28-30) by Gender, Descriptive Statistics and Effect Sizes – LOCF, Decrease from Baseline Intent-to-Treat Population, BTDS- or Placebo-Treated Patients from Placebo-controlled Titration-to-Effect Studies (N=402)										
	BTDS			Placebo			Effect Size (ES)			
Patient Group	N	Mean	SD	N	Mean	SD	N	ES	Lo-CI	Hi-Cl
Females	128	2.20	2.26	135	1.50	2.32	263	0.305	0.062	0.548
Males	67	1.7	2.46	72	1.4	2.55	139	0.120	-0.213	0.453
Source: Sponsor's Figure 8.11.3.4.1A in the ISE										

To explore further the effect of gender on analgesic efficacy, the Sponsor reviewed the results the gender terms in the multivariate analyses of "Pain on Average – Change from Baseline" and "Time to Discontinuation Due to Lack of Efficacy" in the pooled titration-to-effect studies and in the pooled forced-titration studies. The results of this analysis are presented in Sponsor's Table 8.11.3.5B, which is reproduced below:

BTDS Integrated Summary of Efficacy Gender Effects in Multivariate Analyses of Outcome Measures				
Outcome Measure	Cross-reference	Female[a]	Male[a]	P Value*
Pain on average, change from baseline, Day 21 to end (TTE)	Appendix 8.11.9.3A	Gender was dropped from the model, P>.1		
Pain on average, change from baseline, Days 9–60 (FT)	Appendix 8.11.9.3B	Gender was dropped from the model, P>.1		
Pain on average, DOSE RESPONSE, Days 9–60 (FT)	Appendix 8.11.9.3C	-1.18	-0.83	.0625
Time to discontinuation due to lack of efficacy (TTE)	Appendix 8.11.9.3F	0.686	1.000	.0757
Time to discontinuation due to lack of efficacy (FT)	Appendix 8.11.9.3G	Gender was dropped from the model, P>.1		
Time to discontinuation due to lack of efficacy, DOSE RESPONSE (FT)	Appendix 8.11.9.3H	Gender was dropped from the model, P>.1		
FT = Forced titration (BP96-0101 and BP96-0102). TTE = Titration to effect (BP96-0604 and BP99-0203). [a]For Pain on the Average, the "effect" is the least squares mean change from baseline. For time to discontinuation due to lack of efficacy, the "effect" is the hazard ratio between levels of gender, with "male" as the reference level. *P value for the contribution of the variable—gender—to the outcome measure in the statistical analysis.				
Source: Sponsor Table 8.11.3.5C				

The above data suggest that there was no significant effect of gender on outcome.

6.2.2 Effects of Age on Efficacy Outcome

The Sponsor combined efficacy data from the two titration-to-effect studies, BP96-0604 and BP99-0203, to analyze the effects of age on the analgesic activity of the BTDS. In two defined age categories (18-49 years and ≥65 years) BTDS was better than Placebo in pain reduction, as measured by the change from baseline in that measure. In patients aged 50-64 years, there was no difference between BTDS and Placebo. The pooled mean- change-from-baseline scores, as well

as the between-group differences and their associated upper and lower 95% confidence bounds, are presented in the table below.

Pain on Average (Days 28-30) by Age Category, Descriptive Statistics and Effect Sizes – LOCF, Decrease from Baseline Intent-to-Treat Population, BTDS- or Placebo-Treated Patients from Placebo-controlled Titration-to-Effect Studies (N=402)										
	BTDS			Placebo			Effect Size (ES)			
Patient Group	N	Mean	SD	N	Mean	SD	N	ES	Lo-CI	Hi-Cl
Age 18–49	48	2.20	2.77	49	0.90	2.10	97	0.529	0.123	0.933
Age 50–64	78	2.00	2.65	78	2.00	2.65	156	0.000	-0.314	0.314
Age ≥65	69	1.9	2.49	80	1.4	2.68	149	0.193	-0.130	0.515
Source: Table accompanying Sponsor Figure 8.11.3.4.1A in ISE										

These results demonstrate that the point estimate of the effect size of pain reduction favors the BTDS group over the placebo group for patients age 18-49 years old and for patients over 65 years old. For patients in the largest age-group category, 50-64 years old, there was no difference in the mean degree of pain reduction between BTDS and Placebo.

To explore further the effect of age on analgesic efficacy, the Sponsor reviewed the results of the age terms in the multivariate analyses of "Pain on Average – Change from Baseline" and "Time to Discontinuation Due to Lack of Efficacy" in the pooled titration-to-effect studies and in the pooled forced-titration studies. The results of this analysis are presented in Sponsor's Table 8.11.3.5B, which is reproduced below:

BTDS Integrated Summary of Efficacy Age Effects in Multivariate Analyses of Outcome Measures					
Outcome Measure	Cross-reference	Age 18–49[a]	Age 50–64[a]	Age ≥65[a]	P Value*
Pain on average, change from Baseline, Day 21 to end (TTE)	Appendix 8.11.9.3A	Age was dropped from the model, P>.1			
Pain on average, change from Baseline, Days 9–60 (FT)	Appendix 8.11.9.3B	-0.37	-0.77	-1.24	.0007
Pain on average, DOSE RESPONSE, Days 9–60 (FT)	Appendix 8.11.9.3C	-0.61	-0.90	-1.52	.0004
Outcome Measure	Cross-reference	Age 18–64[a]	Age ≥65[a]		P Value*
Time to discontinuation due to Lack of efficacy (TTE)	Appendix 8.11.9.3F	Age was dropped from the model, P>.1			
Time to discontinuation due to Lack of efficacy (FT)	Appendix 8.11.9.3G	1.000	0.648		.0603
Time to discontinuation due to Lack of efficacy, DOSE RESPONSE (FT)	Appendix 8.11.9.3H	1.000	0.650		.0945
FT = forced titration (BP96-0101 and BP96-0102); TTE = titration to effect (BP96-0604 and BP99-0203). [a]For Pain on the Average, "effect" is the least squares mean change from baseline. For time to discontinuation due to lack of efficacy, the "effect" is the hazard ratio between levels of age category with "18–64" as the reference level. *P value for the contribution of the variable—age—to the outcome measure in the statistical analysis.					
Source: Sponsor Table 8.11.3.5B (ISE)					

Review of the above table indicates that age was not a statistically significant confounder in the titration-to-effect studies. The results for an interaction term, which would more directly address the issue of whether BTDS has a different effect at different ages, are not presented. Review of

Sponsor's table Table 8.11.3.5B in the ISE (see above) does not indicate what the "effect" actually is; specifically, it is not clear if the effect is the between-group difference in change from baseline, or if it is the overall mean change from baseline in that age group. Review of Sponsor's Table 8.11.3.4B, which present potential covariates for the pooled efficacy analyses, indicates that a treatment-by-age interaction was not included among the potential covariates. In response to a request by the Agency on April 3, 2001 the Sponsor submitted on April 18, 2001 the results of a mixed model for the pooled titration-to-effect studies which included a treatment-by-age interaction term. This model, which includes only data through Day 28 (because the shorter study BP99-0203 was only 28 days in duration), indicated that the treatment-by-age interaction term was not statistically significant.

For the forced-titration studies, the covariate term for age was clinically significant, indicating that age was related to treatment outcome. Review of Sponsor's table Table 8.11.3.5B in the ISE (see above) and the cited appendices indicates that the terms presented are LS mean changes from baseline for pain on average adjusted for other covariates (including treatment assignment) and the Cox proportional hazards ratios adjusted for other coviariates (including treatment). Thus, the relationship of age to response to treatment assignment (ie, BTDS vs. Placebo) can not be ascertained.

Since a treatment-by-age interaction term was the not included in the statistical model as a potential covariate, the statistical significance of this potential interaction could not be assessed. The meaning of the finding of age as a statistically significant covariate in the forced-titration studies, but not in the titration-to-effect studies, is not clear.

The Sponsor's analyses indicate that age did not have a significant effect on time to discontinuation due to lack of efficacy.

6.2.3 Effects of Race on Efficacy Outcomes

Because the population of patients in the Phase 3 randomized trials who were not white was small (N=29) and accounted for only 11% of the total Phase 3 study population, the effect of race on efficacy outcome was not assessed.

6.2.4 Effect of Previous Opioid Experience on Efficacy Outcome

The Sponsor combined efficacy data from the two titration-to-effect studies, BP96-0604 and BP99-0203, to analyze the effects of previous opioid experience on the analgesic activity of the BTDS. In both opioid-naïve and opioid-experienced patients, the point estimate of BTDS indicated that it was better than Placebo in pain reduction, as measured by the change from baseline in that measure. The effect was greater in opioid-naïve patients. The 95% confidence interval spanned zero in opioid-experienced patients, while it did not span zero in opioid-naïve patients. These data are presented in the data table accompanying Sponsor's Figure 8.11.3.4.1A, reproduced below:

Pain on Average (Days 28-30) by Opioid Experience, Descriptive Statistics and Effect Sizes – LOCF, Decrease from Baseline Intent-to-Treat Population, BTDS- or Placebo-Treated Patients from Placebo-controlled Titration-to-Effect Studies (N=402)										
	BTDS			Placebo			Effect Size (ES)			
Patient Group	N	Mean	SD	N	Mean	SD	N	ES	Lo-CI	Hi-Cl
Opioid-naïve	119	2.30	2.18	126	1.70	2.24	245	0.271	0.019	0.522
Opioid-experienced	76	1.6	2.62	81	1.2	2.70	157	0.150	-0.163	0.464

To explore further the effect of previous opioid experience on analgesic efficacy, the Sponsor reviewed the results the opioid-experience terms in the multivariate analyses of "Pain on Average – Change from Baseline" and "Time to Discontinuation Due to Lack of Efficacy" in the pooled titration-to-effect studies and in the pooled forced-titration studies. The results of this analysis are presented in Sponsor's Table 8.11.3.5A, which is reproduced below:

BTDS Integrated Summary of Efficacy Opioid Experience Effects in Multivariate Analyses of Outcome Measures				
Outcome Measure	Cross-reference	Opioid-Naive Effect[a]	Opioid-Experienced Effect[a]	P Value (Between)*
Pain on average, change from baseline, Day 21 to end (TTE)	Appendix 8.11.9.3A	-1.92	-1.40	.0451
Pain on average, change from baseline, Days 9–60 (FT)	Appendix 8.11.9.3B	-1.11	-0.48	.0009
Pain on average, DOSE RESPONSE, Days 9–60 (FT)	Appendix 8.11.9.3C	-1.35	-0.67	.0012
Time to discontinuation due to lack of efficacy (TTE)	Appendix 8.11.9.3F	0.688	1.000	.0616
Time to discontinuation due to lack of efficacy (FT)	Appendix 8.11.9.3G	0.378	1.000	.0001
Time to discontinuation due to lack of efficacy, DOSE RESPONSE (FT)	Appendix 8.11.9.3H	0.365	1.000	.0001
FT = forced titration (BP96-0101 and BP96-0102); TTE = titration to effect (BP96-0604 and BP99-0203). [a]For Pain on the Average, the "effect" is the least squares mean change from baseline. For time to discontinuation due to lack of efficacy, the "effect" is the hazard ratio between levels of opioid experience, with "opioid-experienced" as the reference level. *P value for the contribution of the variable—opioid experience—to the outcome measure in the statistical analysis.				

The above data indicate a consistent effect of previous opioid experience on response to BTDS. As mentioned in the discussion of age above, the above terms are adjusted for treatment assignment, so the effect of previous opioid experience on response to treatment (ie, BTDS vs Placebo) can not be ascertained from these analyses. In general, however, it appears that previous opioid experience results in less pain reduction than no previous opioid experience, regardless of treatment assignment.

6.2.5 Evaluation of Efficacy Dose-Response Relationship

The dose-response relationship of the efficacy outcomes were not evaluated in the titration-to-effect studies, since the final dose was chosen based on efficacy.

The Sponsor has performed some dose-response analyses of efficacy outcomes in the forced-titration studies. Since these studies were labeled by the Sponsor as failed studies, review of the dose-response analyses will not be presented.

7 INTEGRATED REVIEW OF SAFETY

7.1 Findings vs. Labeling Claims

In view of the substantial problems with the laboratory data noted above in the section on data integrity, a definitive conclusion about the safety of the product can not be made. Review of the labeling claims was thus not performed.

7.2 Adequacy of Exposure and Safety Assessment

Safety data come from 6 Phase 3 studies, one Phase 2 study, and 15 Phase 1 clinical pharmacology studies. A total of 1296 patients were exposed to BTDS in these studies, as summarized in Table 8.13.1.1B of the NDA, which is reproduced below:

TABLE 8.13.1.1B.
BTDS Integrated Summary of Safety
BTDS Clinical Development Program: Subjects/Patients Exposed to BTDS

Phase	Exposure	Study Type/Population	Protocol No.	No. Exposed to BTDS
1	Single application	Clinical pharmacology	BC88-0705	0[a]
			BP96-0304	28
			BP96-0803	24
			BP96-0501	24
			BP96-0702	24
			BP96-1102	22
			BP97-0501	36
			BP97-0112	0[b]
			BP98-0201	84
			BP97-1001	12
			BP98-0202	12
			BP98-1204	20
	Multiple application	Clinical pharmacology	BP95-0901	27
			BP97-0303	36
			BP99-0204	28
			Subtotal	**377**
2	Single application	Postorthopedic surgery pain	BP96-0104	99
			Subtotal	**99**
3	Multiple application	Pain due to osteoarthritis	BP96-0101	163
		Chronic low back pain	BP96-0102	149
		Chronic low back pain	BP96-0604	46
		Chronic low back pain	BP98-1201	140
		Pain due to osteoarthritis	BP99-0203	152
	Multiple application	Extended open-label safety study	BP96-0103	170[c]
			Subtotal	**820**
1, 2, 3			**TOTAL**	**1296**

[a]Ten subjects received topically applied buprenorphine HCl (0.3 mg/mL); none received BTDS. This study was part of another drug development program (Betadine Cream), and is not included in the safety database for the Integrated Summary of Safety.
[b]Twenty-four subjects received intravenous buprenorphine; none received BTDS. This study is included in the safety database for the Integrated Summary of Safety.
[c]In BP96-0103, 170 patients were treated with BTDS for the first time, and the remaining 215 patients had been previously treated with BTDS in Phase 3 controlled studies. One of the 215 patients in BP96-0103 was not treated with BTDS.

Source: Sponsor Table 8.13.1.1B in ISS

A total of 1356 patients were enrolled in the Phase 2/3 clinical trials. Of these, 919 were exposed to BTDS for up to 672 days (mean 123 days). Seven-hundred-eighty-four patients were exposed to BTDS 5, 677 were exposed to BTDS 10, and 533 were exposed to BTDS 20. Additionally, 150 patients were exposed to oxycodone/APAP, 130 were exposed to hydrocodone/APAP, and 319 were exposed to placebo. Sponsor's Figure 8.13.4.2 in the ISS (revised in the 120-day safety update and again on May 6, 2001 in response to Agency questions about inaccuracies) presents BTDS exposure in the Phase 2/3 studies by time intervals.

Data Table from Sponsor Figure 8.13.4.2 in ISS, as amended May 6, 2001						
	>0 days	≥ 30 days	≥ 60 days	≥ 6 mos	≥ 12 mos	≥ 18 mos
	Number of patients					
BTDS 5	784	138	92	28	16	3
BTDS 10	677	219	159	62	28	7
BTDS 20	533	263	166	95	42	2
Any BTDS	919	493	339	220	132	37
(Cross-references: ISS, Tables 8.14.2.1.15.1 and 8.14.2.1.15.2.) From studies BP96-0104, BP96-0101, BP96-0102, BP96-0103, BP96-0604, BP98-1201, and BP99-0203.						
Source: Sponsor Figure 8.13.4.2 in ISS, as amended May 6, 2001						

Mean, median, and range of duration of exposure for each dose level of BTDS, as well as for oxycodone/APAP, hydrocodone/APAP, and placebo, are presented in Sponsor Table 8.13.4.2 in the ISS, which is reproduced below.

TABLE 8.13.4.2.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies and Open-Label Study (BP96-0103)
Duration of Exposure by Treatment
All Patients Enrolled (N = 1356)
BP96-0101, BP96-0102, BP96-0103, BP96-0104, BP96-0604, BP98-1201, and BP99-0203 Combined

Duration (d)	Total BTDS N = 919	BTDS 5 N = 784	BTDS 10 N = 677	BTDS 20 N = 533	Oxy/APAP N = 150	Hydro/APAP N = 130	Placebo N = 319
Mean	123	31	58	90	49	38	30
Median	36	9	14	29	60	54	27
Min, max	0.2, 672	0.2, 595	0.2, 630	0.5, 583	0.2, 92	1.0, 66	0.6, 90
(Cross-references: Tables 8.14.2.1.15.1 and 8.14.2.1.15.3.)							
Source: Sponsor Table 8.13.4.2 in ISS							

The distribution of patients exposed to the three dose levels of BTDS is, to a large extent, the result of the design of the clinical trials. In the forced-titration studies, the dose was increased until the assigned dose was reached. Thus, all of patients in these studies received the 5 mg dose, about two-thirds increased to the 10 mg dose by Day 9, and about one-third increased to the 20 mg dose by Day 15. In the titration-to-effect studies, BTDS was increased to the 10 mg or 20 mg dose level in 88% of patients by Day 9. In the titration-to-effect studies, most patients remained at the dose level achieved at the end of the titration period: 65% remained at the 5 mg dose level, 57% remained at the 10 mg dose level, and 94% remained at the 20 mg dose level. Downward titration during the maintenance period was not common: 4 of 70 (6%) BTDS patients at the 10 mg dose level titrated downward, and 7 of 120 (6%) BTDS at the 20 mg dose level titrated downward. By contrast, upward titration was more common during the maintenance period: 8 of 23 (35%) BTDS patients at the 5 mg dose level and 26 of 70 (37%) BTDS patients at the 10 mg dose level titrated upward from the end of the titration period to the end of the study. Open-label study BP96-0103 contributed much of the long-term safety data. Patient exposure over time, accounting for time in any previous protocol as well as in the open-label study and the combined exposure, is presented in the data table accompanying Sponsor's Figure 8.13.4.4.2, which is reproduced below:

TABLE 8.13.4.4.2.
BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103)
Total BTDS Exposure (BP96-0103 and Previous BTDS Studies Combined)
Intent-to-Treat/Safety Population (N = 384)

	Total BTDS Exposure[a]		
	Previous Studies[b]	Open-Label Study BP96-0103	Combined Studies
No. of patients exposed	214[c]	384	384
Total exposure (patient-days)	10,403	89,999	100,402
Mean (d)	48.6	234	262
Median (d)	60.0	190.5	223.5
Min, max (d)	2, 91	1, 609	1, 672
Patient Exposure	No. (%) of Patients		
≤2 wk	29 (8%)	35 (9%)	21 (6%)
> 2 wk–1 mo	32 (8%)	28 (7%)	21 (6%)
2–3 mo	152 (40%)	61 (16%)	58 (15%)
4–6 mo	1 (<1%)	62 (16%)	67 (17%)
7–9 mo	0	38 (10%)	41 (11%)
10–12 mo	0	49 (13%)	47 (12%)
13–15 mo	0	59 (15%)	54 (14%)
16–18 mo	0	33 (9%)	40 (10%)
19–21 mo	0	19 (5%)	31 (8%)
22–24 mo	0	0	4 (1%)

(Cross-reference: Table 8.14.3.1.7.)
[a]Total BTDS exposure includes hiatus during BP96-0103, but does not include time between studies.
[b]BP96-0101, BP96-0102 and BP96-0604.
[c]Of 215 patients enrolled from previous studies, 214 received BTDS in BP96-0103 and 1 did not.

Source: Sponsor Table 8.13.4.4.2

Overall, the extent of exposure in the Phase2/3 studies appears adequate for meaningful review of the safety database.

The clinical pharmacology studies enrolled 449 subjects. Of these, 377 received BTDS, for a total of 635 BTDS exposures. The data table accompanying Sponsor Figure 8.13.4.5 in the ISS, reproduced below, summarizes exposure to BTDS in the clinical pharmacology studies.

Data Table Accompanying Sponosr FIGURE 8.13.4.5.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Duration of Exposure to BTDS
Subjects Exposed to Any BTDS (N = 377)
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1204, and BP99-0204 Combined
(Cross-reference: Table 8.14.1.1.6.1.)

			Number of Subject-Periods of Exposure						
Treatment	N[a]	Exposures[b]	> Day 1	> Day 2	> Day 3	> Day 4	> Day 5	> Day 6	> Day 9
BTDS 5	76	76	76	76	76	40	40	40	28
2 x BTDS 5	26	26	26	26	26	0	0	0	0
BTDS 10	297	407	407	391	379	261	249	237	0
BTDS 20	101	126	125	121	120	70	69	69	24
Total exposures	377	635	634	614	601	371	358	346	52

Source: Sponsor Figure 8.13.4.5 in the ISS

7.3 Methods for Review of Safety

The safety review consisted primarily of a review of the Integrated Summary of Safety (ISS), with review of selected elements of the safety sections of individual study reports when further information was required. The Sponsor's database was also used during the safety review.

From time to time during the review process, questions regarding various aspects of the clinical review were sent to the Sponsor to clarify issues of study design, conduct, and analysis, or to request either additional analyses or clarification of selected data points. The dates of these requests and the general topics addressed in the requests are summarized in the table below. A copy of all of the questions sent to the Sponsor is included in Appendix A (Section 11 of this review).

7.4 Subject Disposition

Subject disposition for the titration-to-effect and forced titration studies are presented in Sponsor Tables 8.13.3.2A and 8.13.3.2B, respectively, which are reproduced below:

TABLE 8.13.3.2A.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Patient Disposition: Titration-to-Effect Studies
All Patients Enrolled (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

	No. (%) of Patients			
	BTDS	Oxycodone/ APAP	Hydrocodone/ APAP	Placebo
Enrolled	338 (100%)	43 (100%)	130 (100%)	208 (100%)
Completed	162 (48%)	27 (63%)	68 (52%)	104 (50%)
Discontinued	176 (52%)	16 (37%)	62 (48%)	104 (50%)
Reason for discontinuation				
Adverse event				
Related	76 (23%)	11 (26%)	25 (19%)	20 (10%)
Not related	3 (<1%)	1 (2%)	6 (5%)	3 (1%)
Ineffective treatment	68 (20%)	1 (2%)	17 (13%)	71 (34%)
Lost to follow-up	8 (2%)	0	3 (2%)	3 (1%)
Protocol violation	8 (2%)	0	3 (2%)	6 (3%)
Other	13 (4%)	3 (7%)	8 (6%)	1 (<1%)
(Cross-reference: Table 8.14.2.1.1.2.)				
Source: Sponsor Table 8.13.3.2.A in ISS				

TABLE 8.13.3.2B.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Patient Disposition: Forced-Titration Studies
All Patients Enrolled (N = 519)
BP96-0101 and BP96-0102 Combined

	No. (%) of Patients					
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo
Enrolled	312 (100%)	105 (100%)	103 (100%)	104 (100%)	107 (100%)	100 (100%)
Completed	147 (47%)	44 (42%)	57 (55%)	46 (44%)	63 (59%)	53 (53%)
Discontinued	165 (53%)	61 (58%)	46 (45%)	58 (56%)	44 (41%)	47 (47%)
Reason for discontinuation						
Adverse event	73 (23%)	21 (20%)	18 (18%)	34 (33%)	15 (14%)	12 (12%)
Ineffective treatment	61 (20%)	25 (24%)	21 (20%)	15 (14%)	25 (23%)	30 (30%)
Intercurrent illness	7 (2%)	4 (4%)	2 (2%)	1 (1%)	1 (<1%)	1 (1%)
Lost to follow-up	6 (2%)	3 (3%)	1 (1%)	2 (2%)	0	2 (2%)
Protocol violation	13 (4%)	7 (7%)	4 (4%)	2 (2%)	2 (2%)	1 (1%)
Other	5 (2%)	1 (1%)	0	4 (4%)	1 (<1%)	1 (1%)

(Cross-reference: Table 8.14.2.1.1.1.)
Source: Sponsor Table 8.13.3.2.B in ISS

In the above table presenting the patient disposition in the forced-titration studies, the column headings “BTDS 5”, “BTDS 10”, and “BTDS 20” appear to refer to the dose to level to which patients were randomized, not to the dose level at which discontinuation occurred.

Patient disposition in the Phase 2 study BP96-0104 is presented in the table below:

Patient Disposition: Phase 2 Study BP96-0104				
	No. (%) of Patients			
	BTDS 5	BTDS 10	BTDS 20	Placebo
Enrolled	33 (100%)	33 (100%)	33 (100%)	11 (100%)
Completed	27 (82%)	28 (85%)	28 (85%)	9 (62%)
Discontinued	6 (18%)	5 (15%)	5 (15%)	2 (18%)
Reason for discontinuation				
Adverse event	6 (18%)	1 (3%)	5 (15%)	1 (9%)
Ineffective treatment	0 (0%)	4 (12%)	0 (0%)	1 (9%)
Intercurrent illness	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lost to follow-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol violation	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Source: Sponsor Figure 10.1 in BP96-0104 Study Report				

Review of the above tables of patient disposition indicates that the longer duration Phase 3 studies had higher discontinuation rates than the short-term Phase 2 study. Over one-half of BTDS-treated patients in the Phase 3 studies discontinued prematurely. In general, discontinuation due to drug-related adverse events was more common for BTDS and other active treatments than for placebo treatment. On the other had, discontinuation due to ineffective treatment was more common for placebo patients. In the Phase 3 studies, the discontinuation rate for ineffective treatment was 20% overall for BTDS patients in both the forced-titration and titration-to-effect studies. Reasons for discontinuation other than adverse events and ineffective treatment accounted for a small proportion of enrolled patients, with no notable differences in rates among treatment groups.

In the open-label study BP96-0103, nearly two-thirds of patients discontinued prematurely, largely due to adverse events or ineffective treatment, as indicated in Sponsor's Table 8.13.3.2C, which is reproduced below:

TABLE 8.13.3.2C. BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103) Patient Disposition All Patients Enrolled (N = 385)	
	No. (%) of Subjects
Enrolled	385 (100%)
Completed[a]	127 (33%)
Discontinued	258 (67%)
Reason for discontinuation	
Adverse event	136 (35%)
Ineffective treatment	56 (15%)
Intercurrent Illness	7 (2%)
Death	1 (<1%)
Lost to follow-up	25 (6%)
Protocol violation	10 (3 %)
Other	23 (6%)
(Cross-reference: Table 8.14.3.1.1.) [a]Patients were considered to have completed the study if they finished the complete course of the study or were terminated due to administrative reasons (eg, sponsor closed the study at 21 months).	
Source: Table 8.13.3.2C in ISS	

The overall subject completion rate in the Phase 1 clinical pharmacology studies was high (95%). Overall, 2% of subjects discontinued because of adverse events. Of the 21 total subjects who discontinued, 11 (52%) discontinued because of adverse events.

INTEGRATED SUMMARY OF SAFETY: PHASE I
TABLE 8.14.1.1.3
REASONS FOR DISCONTINUATION BY SUBGROUP TREATMENT AND PERIOD
POPULATION: All Subjects Enrolled

	Discontinued		Adverse Events		Protocol Violation		Other Reasons	
	N	%	N	%	N	%	N	%
All Studies*								
BTDS 5	1	100.0%	0	0	0	0	1	100.0%
BTDS 2x5	0	0	0	0	0	0	0	0
BTDS 10	7	100.0%	3	42.9%	2	28.6%	2	28.6%
BTDS 10 + endotoxin	1	100.0%	0	0	1	100.0%	0	0
BTDS 20	11	100.0%	7	63.6%	2	18.2%	2	18.2%
BIV	1	100.0%	1	100.0%	0	0	0	0
Duragesic	0	0	0	0	0	0	0	0
Placebo	0	0	0	0	0	0	0	0
Healthy Young								
BTDS 5	1	100.0%	0	0	0	0	1	100.0%
BTDS 2x5	0	0	0	0	0	0	0	0
BTDS 10	7	100.0%	3	42.9%	2	28.6%	2	28.6%
BTDS 20	10	100.0%	6	60.0%	2	20.0%	2	20.0%
BIV	1	100.0%	1	100.0%	0	0	0	0
Healthy Elderly								
BTDS 10	0	0	0	0	0	0	0	0
BTDS 20	1	100.0%	1	100.0%	0	0	0	0
BIV	0	0	0	0	0	0	0	0
Interaction Studies								
BTDS 10	0	0	0	0	0	0	0	0
BTDS 20	1	0	0	0	0	0	0	0
Duragesic	0	0	0	0	0	0	0	0
Placebo	0	0	0	0	0	0	0	0
Hepatic Imparied								
BTDS 20	1	0	0	0	0	0	0	0
BIV	0	0	0	0	0	0	0	0
Elderly Hypertensives								
BTDS 20	1	0	0	0	0	0	0	0
Endotoxin Challenge								
BTDS 10 + endotoxin	1	100.0%	0	0	1	100.0%	0	0

Note: BIV treatment group contains data from studies BP95-0901(0.3mg), BP97-0112(0.3mg) and BP97-0501(0.6mg).
Duragesic treatment group contains data from studies BP97-1001 and BP98-0202.
Placebo treatment group contains data from studies BP97-1001 and BP98-0202.
BTDS 5 treatment group contains data from studies BP97-0501 and BP99-0204.
BTDS 2x5 treatment group contains data from study BP96-0304.
BTDS 10 treatment group contains data from studies BP96-0501, BP96-0304, BP96-0803, BP96-0702, BP96-1102, BP97-0501, BP97-1001,BP98-0201, BP98-0202 and BP98-1204.
BTDS 20 treatment group contains data from studies BP96-0304, BP95-0901, BP97-0501 and BP97-0303.
Adverse Event include Related and Not Related events.

[NOTE: Question was sent to Sponsor on June 1, 2001 about the three extra BTDS 20 patients, with corresponding % of zero, who are not accounted for in other tables of discontinuations in clinical pharmacology studies.]

7.5 Demographic and Other Baseline Characteristics

The demographic characteristics of the patients in the titration-to-effect and forced-titration studies are presented in Sponsor's Tables 8.13.3.3A and 8.13.3.3B, respectively, which are reproduced below.

TABLE 8.13.3.3A.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Demographic Characteristics: Titration-to-Effect Studies
All Patients Enrolled (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

		BTDS	Oxycodone/ APAP	Hydrocodone/ APAP	Placebo	Total
		N = 338	N = 43	N = 130	N = 208	N = 719
GENDER[a]						
	Male	131 (39%)	16 (37%)	62 (48%)	73 (35%)	282 (39%)
	Female	207 (61%)	27 (63%)	68 (52%)	135 (65%)	437 (61%)
RACE[a]						
	White	295 (87%)	40 (93%)	121 (93%)	182 (88%)	638 (89%)
	Black	28 (8%)	1 (2%)	7 (5%)	12 (6%)	48 (7%)
	Hispanic	15 (4%)	2 (5%)	2 (2%)	11 (5%)	30 (4%)
	Asian	-	-	-	1 (<1%)	1 (<1%)
	Other	-	-	-	2 (1%)	2 (<1%)
	AGE (y)					
	Mean	55.9	49.0	52.7	59.7	56.0
	Range	26–89	19–85	28–88	20–85	19□89
AGE GROUP[a] (y)						
	18-□34	20 (6%)	6 (14%)	6 (5%)	6 (3%)	38 (5%)
	35□-49	98 (29%)	20 (47%)	56 (43%)	43 (21%)	217 (30%)
	50-□64	122 (36%)	9 (21%)	40 (31%)	79 (38%)	250 (35%)
	65□-74	57 (17%)	4 (9%)	20 (15%)	46 (22%)	127 (18%)
	≥ 75	41 (12%)	4 (9%)	8 (6%)	34 (16%)	87 (12%)
WEIGHT (kg)						
	Mean	89	82	86	88	88
	Range	44–181	52–109	45–177	36–192	36–192
WEIGHT GROUP[a] (kg)						
	< 45	1 (<1%)	-	1 (<1%)	1 (<1%)	3 (<1%)
	45-□59	25 (7%)	2 (5%)	14 (11%)	14 (7%)	55 (8%)
	60-□89	162 (48%)	28 (67%)	65 (50%)	102 (50%)	357 (50%)
	90□-104	67 (20%)	8 (19%)	29 (22%)	52 (25%)	156 (22%)
	≥ 105	81 (24%)	4 (10%)	21 (16%)	37 (18%)	143 (20%)

(Cross-reference: Table 8.14.2.1.2.2.)
[a]Number (%) of patients.

Source: Sponsor Table 8.13.3.3A.

TABLE 8.13.3.3B.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Demographic Characteristics: Forced-Titration Studies
All Patients Enrolled (N = 519)
BP96-0101 and BP96-0102 Combined

		Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo	Total
		N = 312	N = 105	N = 103	N = 104	N = 107	N = 100	N = 519
GENDER[a]								
	Male	111 (36%)	35 (33%)	40 (39%)	36 (35%)	44 (41%)	42 (42%)	197 (38%)
	Female	201 (64%)	70 (67%)	63 (61%)	68 (65%)	63 (59%)	58 (58%)	322 (62%)
RACE[a]								
	White	274 (88%)	94 (90%)	91 (88%)	89 (86%)	98 (92%)	93 (93%)	465 (90%)
	Black	25 (8%)	7 (7%)	8 (8%)	10 (10%)	5 (5%)	4 (4%)	34 (7%)
	Hispanic	12 (4%)	4 (4%)	4 (4%)	4 (4%)	3 (3%)	2 (2%)	17 (3%)
	Asi an	1 (<1%)	-	-	1 (1%)	1 (<1%)	1 (1%)	3 (<1%)
AGE (y)								
	Mean	57.3	57.4	55.8	58.6	62.0	60.0	58.8
	Range	22–89	25–89	25–84	22–88	28–90	31–86	22□90
AGE GROUP[a] (y)								
	18-□34	19 (6%)	5 (5%)	11 (11%)	3 (3%)	2 (2%)	3 (3%)	24 (5%)
	35-□49	80 (26%)	25 (24%)	23 (22%)	32 (31%)	25 (23%)	20 (20%)	125 (24%)
	50-□64	103 (33%)	42 (40%)	36 (35%)	25 (24%)	26 (24%)	36 (36%)	165 (32%)
	65-□74	72 (23%)	22 (21%)	23 (22%)	27 (26%)	33 (31%)	25 (25%)	130 (25%)
	≥ 75	38 (12%)	11 (11%)	10 (10%)	17 (16%)	21 (20%)	16 (16%)	75 (15%)
WEIGHT (kg)								
	Mean	85	84	86	85	80	84	84
	Range	47–147	47–141	49–147	50–136	45–141	44–134	44–147
WEIGHT GROUP[a] (kg)								
	< 45	-	-	-	-	-	1 (1%)	1 (<1%)
	45-□59	32 (10%)	6 (6%)	14 (14%)	12 (12%)	12 (11%)	8 (8%)	52 (10%)
	60-□89	170 (55%)	66 (64%)	47 (46%)	57 (55%)	63 (59%)	58 (58%)	291 (56%)
	90-□104	52 (17%)	15 (15%)	19 (18%)	18 (17%)	21 (20%)	16 (16%)	89 (17%)
	≥ 105	56 (18%)	16 (16%)	23 (22%)	17 (16%)	11 (10%)	17 (17%)	84 (16%)

(Cross-reference: Table 8.14.2.1.2.1.)
[a]Number (%) of patients.
Source: Sponsor Table 8.13.3.3B in ISS

Review of the above tables indicates that the majority of patients in both the titration-to-effect studies and the forced-titration studies were female (61% and 62%, respectively) and white (89% and 90%, respectively).

In the titration-to-effect studies, the oxycodone/APAP patients were, on average, younger than BTDS patients (mean age = 49.0 years for oxycodone/APAP versus 55.9 years for BTDS), with a corresponding lower percentage of patients age 65 or over in the oxycodone/APAP group (18%) compared tot he BTDS group (29%). Placebo patients were, on average, slightly older than BTDS patients (mean age = 59.7 years in the placebo group), with 38% of patients age 65 years or over. Oxycodone/APAP patients weighed, on average, less than patients in the other treatment groups (mean in oxycodone/APAP group = 82 kg, means in other groups ranged from 86 kg to 89 kg.).

Gender and race distributions in the forced-titration studies were generally similar to those in the titration-to-effect studies. In the forced-titration studies, oxycodone/APAP and placebo patients were, on average, older than BTDS patients (mean ages: 62.0, 60.0, and 57.3 years, for oxycodone/APAP, placebo, and BTDS patients, respectively). As in the titration-to-effect studies, the oxycodone/APAP patients weighed less, on average, than patients in the other treatment groups (mean weight in the oxycodone/APAP group = 80 kg, mean weight in other treatment groups ranged form 84 to 86 kg).

Demographic characteristics of patients in the Phase 2 study BP96-0104 are presented in Sponsor's Table 10.4 in the BP96-0104 study report, which is reproduced below. Compared to the placebo group, higher proportions of patients in the BTDS groups were female and white. BTDS patients were, on average, slightly older than placebo-treated patients.

TABLE 10.4.
Study BP96-0104
Patient Demographics and Other Baseline Characteristics:
All Patients Enrolled, Intent-to-treat Population (N = 110

		TOTAL	Placebo	BTDS 5	BTDS 10	BTDS 20
		(N = 110)	(N = 11)	(N = 33)	(N = 33)	(N = 33)
		n (%)				
GENDER						
	Male	32 (29)	5 (45)	9 (27)	8 (24)	10 (30)
	Female	78 (71)	6 (55)	24 (73)	25 (76)	23 (70)
RACE						
	White	97 (88)	9 (82)	28 (85)	30 (91)	30 (91)
	Black	4 (4)	1 (9)	0 (0)	2 (6)	1 (3)
	Other	9 (8)	1 (9)	5 (15)	1 (3)	2 (6)
AGE GROUP (y)						
	18–49	20 (18)	4 (36)	6 (18)	6 (18)	4 (12)
	50–69	27 (25)	4 (36)	7 (21)	10 (30)	6 (18)
	70–79	28 (25)	0	9 (27)	7 (21)	12 (36)
	80–89	33 (30)	3 (27)	10 (30)	9 (27)	11 (33)
	>90	2 (2)	0	1 (3)	1 (3)	0
ANTIEMETICS						
	Present	36 (33)	3 (27)	8 (24)	13 (39)	12 (36)
	Absent	74 (67)	8 (73)	25 (76)	20 (61)	21 (64)
OPIOID-NAÏVE						
	No	107 (97)	11 (100)	32 (97)	33 (100)	31 (94)
	Yes	3 (3)	0	1 (3)	0	2 (6)
ANESTHETIC LOAD						
	Less than normal	13 (12)	0	0	4 (12)	9 (27)
	Normal	89 (82)	9 (100)	29 (88)	27 (82)	24 (73)
	More than normal	6 (6)	0	4 (12)	2 (6)	0
ORTHOPEDIC SURGERY*						
	Hip replacement	40 (35)	6 (55)	11 (31)	10 (29)	13 (39)
	Knee replacement	29 (25)	2 (18)	10 (29)	9 (26)	8 (24)
	Shoulder replacement	1 (1)	0	0	1 (3)	0
	Hip fixation	24 (21)	0	7 (20)	8 (23)	9 (27)
	Knee fixation	8 (7)	1 (9)	3 (9)	3 (9)	1 (3)
	Femur fixation	4 (4)	0 (0)	1 (3)	2 (6)	1 (3)
	Ankle fixation	2 (2)	0 (0)	1 (3)	1 (3)	0
	Shoulder fixation	3 (3)	2 (18)	1 (3)	0	0
	Other fixation	3 (3)	0	1 (3)	1 (3)	1 (3)
AGE						
	Mean	68	61	67	68	71
	Min, Max	18–94	43–85	18–94	36–90	20–88

(Cross-references: Tables 14.1.3E and 14.1.6E.)
*Patients could have had more than 1 type of surgical procedure.

Source: Table 10.4 in BP96-0104 study report

Demographic characteristics of the patients in open-label study BP96-0103 are presented in Sponsor Table 8.13.3.3C, which is reproduced below. As in the Phase 3 studies, the majority of patients were female (62%) and white (91%).

TABLE 8.13.3.3C. BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103) Demographic Characteristics All Patients Enrolled (N = 385)	
	No. (%) of Patients
GENDER	
Male	145 (38%)
Female	240 (62%)
RACE	
White	351 (91%)
Black	21 (6%)
Hispanic	13 (3%)
AGE (y)	
Mean	57.6
Range	22□89
AGE GROUP (y)	
18-49	126 (33%)
50-64	116 (30%)
65-74	95 (25%)
≥75	48 (12%)
WEIGHT (kg)	
Mean	82
Range	36-151
WEIGHT GROUP (kg)	
< 60	48 (13%)
60□74	106 (28%)
75□89	111 (29%)
90□104	60 (16%)
>104	59 (15%)
(Cross-reference: Table 8.14.3.1.3.)	
Source: Sponsor Table 8.13.3.3C in ISS	

The demographic characteristics of the subjects in the clinical pharmacology studies are presented in Sponsor's Appendix 8.13.A.2B in the ISS, which is reproduced below. Compared to patients in the Phase 2 and Phase 3 studies, the BTDS-treated subjects in the clinical pharmacology studies had a higher proportion of males (66%) and were more racially diverse. The mean age of subjects in clinical pharmacology studies (35.0 years) was notably lower than the mean age of patients in the Phase 2 and Phase 3 studies (approximately 56 years). The Sponsor notes in Section 8.13.3.3 of the ISS that " a preponderance of young adults of medium build reflects the inclusion/exclusion criteria" in the clinical pharmacology studies.

TABLE 8.13.A.2B.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Demographic Characteristics
All Subjects (N = 449)
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1204, and BP99-0204 Combined

	Any BTDS	BTDS 5	2 x BTDS 5	BTDS 10	BTDS 20	BIV	Duragesic®	Placebo	Any Treatment
	N = 377	N = 40	N = 26	N = 261	N = 102	N = 83	N = 24	N = 24	N = 449
GENDER[a]									
Male	247 (66%)	24 (60%)	14 (54%)	171 (66%)	66 (65%)	62 (75%)	17 (71%)	17 (71%)	297 (66%)
Female	130 (35%)	16 (40%)	12 (46%)	90 (35%)	36 (35%)	21 (25%)	7 (29%)	7 (29%)	152 (34%)
RACE[a]									
White	242 (64%)	29 (73%)	18 (69%)	150 (58%)	81 (79%)	53 (64%)	12 (50%)	14 (58%)	277 (62%)
Black	78 (21%)	4 (10%)	8 (31%)	66 (25%)	16 (16%)	18 (22%)	12 (50%)	10 (42%)	103 (23%)
Hispanic	46 (12%)	5 (13%)	–	37 (14%)	4 (4%)	12 (15%)	–	–	58 (13%)
Asian	4 (1%)	2 (5%)	–	2 (<1%)	–	–	–	–	4 (<1%)
Other	7 (2%)	–	–	6 (2%)	1 (1%)	–	–	–	7 (2%)
AGE (y)									
Mean	35.0	27.1	33.7	34.3	39.5	36.5	30.2	31.3	35.6
Range	18–80	18–43	23–44	21–77	21–80	21–70	21–44	21–44	18–80
AGE GROUP[a] (y)									
18–34	225 (60%)	34 (85%)	13 (50%)	149 (57%)	55 (54%)	48 (58%)	19 (79%)	16 (67%)	260 (58%)
35–49	113 (30%)	6 (15%)	13 (50%)	97 (37%)	23 (23%)	16 (19%)	5 (21%)	8 (33%)	131 (29%)
50–64	3 (<1%)	–	–	3 (1%)	–	15 (18%)	–	–	18 (4%)
65–74	31 (8%)	–	–	8 (3%)	23 (23%)	4 (5%)	–	–	35 (8%)
≥ 75	5 (1%)	–	–	4 (2%)	1 (1%)	–	–	–	5 (1%)
WEIGHT (kg)									
Mean	74	73	77	74	75	77	75	75	74
Range	42–98	48–98	62–95	42–98	50–95	49–103	51–92	54–95	42–103
WEIGHT GROUP[a] (kg)									
<45	1 (<1%)	–	–	1 (<1%)	–	–	–	–	1 (<1%)
45–59	39 (10%)	8 (20%)	–	25 (10%)	6 (6%)	3 (4%)	4 (17%)	3 (13%)	48 (11%)
60–89	318 (84%)	28 (70%)	25 (96%)	224 (86%)	91 (89%)	71 (86%)	19 (79%)	19 (79%)	373 (83%)
90–104	19 (5%)	4 (10%)	1 (4%)	11 (4%)	5 (5%)	9 (11%)	1 (4%)	2 (8%)	27 (6%)

(Cross-reference: Table 8.14.1.1.4.1.)
[a]Number (%) of subjects.
Source: Sponsor Table 8.12.A.2B

Baseline analgesic use was common in both the titration-to-effect and forced-titration studies. Proportions of patients using various classes of analgesics are presented in Sponsor's Tables 8.14.2.1.12.2 and 8.14.1.12.1 in the ISS for the titration-to-effect and forced-titration studies, respectively. These tables are reproduced below.

In the titration-to-effect studies, combination opioid use was highest in the hydrocodone/APAP group (81.5) and lowest in the placebo group (37.5%). Fifty percent or more of patients in each treatment group had had prior opioid exposure, either through combination opioid products or pure opioid products.

In the forced-titration studies, patients in the placebo group had less prior exposure to pure opioids (8%) than patients in the other treatment groups (range 16.3% - 23.8%). Among BTDS-treated patients, prior exposure to pure opioids was less in patients assigned to BTDS 20 (16.3%) than in patients assigned to BTDS 5 (23.8%) or BTDS 10 (23.3%). Use of non-opioids and combination opioids was similar among the treatment groups.

INTEGRATED SUMMARY OF SAFETY: PHASE II-III STUDIES
TABLE 8.14.2.1.12.2
BASELINE MEDICATION USE
POPULATION: All Patients Valid for Safety In Titration to Effect Studies

Analgesic Type	Placebo		Oxycodone/ APAP		Hydrocodone/ APAP		BTDS	
	(N=208)		(N=43)		(N=130)		(N=338)	
	N	(%)	N	(%)	N	(%)	N	(%)
Non-Opioids	181	(87.0)	43	(100.0)	68	(52.3)	256	(75.7)
Combination Opioids	78	(37.5)	23	(53.5)	106	(81.5)	185	(54.7)
Pure Opioids	26	(12.5)	2	(4.7)	37	(28.5)	63	(18.6)

NOTE: Placebo treatment group includes data from BP96-0604 and BP99-0203.
Oxy/APAP treatment group includes data from BP96-0604.
Hydro/APAP treatment group includes data from BP98-1201.
BTDS treatment group includes data from BP96-0604, BP98-1201 and BP99-0203.

Source: Sponsor Table 8.14.2.12.2 in ISS

INTEGRATED SUMMARY OF SAFETY: PHASE II-III STUDIES
TABLE 8.14.2.1.12.1
BASELINE MEDICATION USE
POPULATION: All Patients Valid for Safety In Forced-Titration Studies

Analgesic Type	Placebo		Oxycodone/ APAP		BTDS 5		BTDS 10		BTDS 20		Total BTDS	
	(N=100)		(N=107)		(N=105)		(N=103)		(N=104)		(N=312)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Non-Opioids	92	(92.0)	86	(80.4)	86	(81.9)	90	(87.4)	89	(85.6)	265	(84.9)
Combination Opioids	47	(47.0)	51	(47.7)	46	(43.8)	47	(45.6)	44	(42.3)	137	(43.9)
Pure Opioids	8	(8.0)	22	(20.6)	25	(23.8)	24	(23.3)	17	(16.3)	66	(21.2)

NOTE: Placebo, Oxy/APAP, BTDS 5, BTDS 10, and BTDS 20 include data from studies BP96-0101 and BP96-0102.

Source: Sponsor Table 8.14.2.12.1 in ISS

In the titration-to-effect studies, baseline medication use was collected for study BP96-0604, and not for BP98-1201 or BP99-0203. Apart from higher use of anti-inflammatory medications in the oxycodone/APAP group (93%) compared to the other groups (range 8 to 26%), the use of concomitant medications was similar among the treatment groups (see Sponsor Tables 8.14.2.1.11.2 and 8.14.2.1.13.2 in the ISS). In the forced-titration studies, use of concomitant medications was similar among all treatment groups (see Sponsor Tables 8.14.2.1.11.1 and 8.14.2.1.13.1 in the ISS).

7.6 Deaths

Three deaths have occurred in clinical studies of Norspan – two in trials sponsored by the NDA Sponsor, Purdue Pharma, LP (and reported in the ISS), and one in a trial sponsored by a Purdue-associated company, Napp Pharmaceuticals (and reported in the 120-day safety update). Each of these deaths, which all occurred in patients taking BTDS, is summarized below.

Patient 20304, a 76-year-old woman in open-label study BP96-0103, had originally participated in Study BP96-0102, a forced-titration study in patients with chronic back pain. Her patient number in Study BP96-0102 was 20209. Her medical history was notable for cardiovascular

disease (hypertension, angina, carotid artery disease, water retention, and a balloon angioplasty about four or five years prior to study entry). She also had gastroesophageal reflux disease and chronic depression. Concomitant medications included naproxen (Naprosyn®), azathioprine (Imuran®), furosemide (Lasix®), prednisone, folic acid, calcium carbonate (Tums®), metoprolol/hydrochlorothiazide (Lopressor HCT®), nifedipine (Procardia XL®), ticlopidine (Ticlid®), diazepam (Valium®), senna/docusate (Senokot S®), lansoprazole (Prevacid®), and propoxyphene napsylate/acetaminophen (Darvocet®) prn. In BP96-0102, the patient had been randomized to BTDS, which she received for 58 days (BTDS 20 for the last 44 days). In Study BP96-0103, she experienced intermittent drowsiness, intermittent dry mouth, intermittent itchiness, and an episode of fatigue, all of which were rated as severe. Intermittent upset stomach and an episode of itching were each rated as mild. One episode of an adverse event described as "weak" was rated as moderate. No serious adverse events were reported for her during Study BP96-0102. She completed this study on Day 58, at which time the BTDS 20 patch was removed. That same day, she entered into Study BP96-0103 (Study Day 0), and was started on a BTDS 5 patch. The dose was increased to BTDS 10 on Day 4, but was then decreased back to BTDS 5 on Day 65, because she reported that she did not think she needed the higher dose. She remained on BTDS 5 through Day 525. No adverse events were reported for the first 12 months of the open-label study. On Day 481, she fell at home and was hospitalized with shortness of breath and a lumbar fracture. She was taken to an emergency room that day, and was admitted to the hospital the next day. On Day 524 (day 42 of the hospitalization), she had a deterioration in her clinical course. An ECG showed atrial fibrillation, and an anteroseptal and inferior wall infarct. Chest X-ray showed cardiac enlargement, pulmonary edema, and bilateral infarcts. She was managed with "cardiopulmonary assist". She was weaned from bypass, but then developed a myopathy and required re-intubation. The BTDS 5 patch was removed on Study Day 525, with no change in her clinical status. She was extubated, but could not maintain ventilation. She died on Study Day 529. The investigator judged that this death was not related to study drug.

Review of the above narrative suggests that cardiopulmonary disease was the cause of the patient's death, though the reason for the in-hospital deterioration is not clear. In addition, the reason for the fall, which prompted the hospitalization, is not clear. While the buprenorphine in the BTDS patch could have contributed to her ventilatory insufficiency, it is certainly possible that her cardiopulmonary disease was extensive, and that it would have resulted in death regardless of the presence of an opiate. There are no details of her hepatic or renal function during her terminal acute illness. If she had concomitant extensive hepatic insufficiency, it is possible that buprenorphine levels would have been higher than during the period prior to her acute illness. Higher buprenorphine levels may have contributed to her inability to maintain ventilation.

Patient 79 in Study BP96-0104 was a 90-year-old woman who underwent a total right knee revision. The patient's medical history included cardiovascular disease (hypertension, chronic atrial fibrillation, and a soft systolic murmur) and neurologic disease (cerebrovascular accident in 1996, associated with weakness of the lower extremities, decreased sensation in both legs, and minimal aphasia). Preoperative medications included metoprolol, cefazolin, docusate, ranitidine, nifedipine, bacitracin, and polymyxin. The screening ECG revealed coarse atrial fibrillation with a ventricular response of 63 and probable left ventricular hypertrophy with ST-T abnormalities. The patient received BTDS 10 on (b) (6) at 8:00 AM (0 hour).

At 36 hours, the patient had a respiratory rate of 18 bpm, peak flow of 2.0 L/sec, FEV1 of 0.86 L, FVC of 1.36 L, and an O2 saturation of 98% while receiving 3 L/min nasal O2. During the study, the patient received hydrochlorothiazide and furosemide (Lasix®) for diuresis; enoxaparin (Lovenox®) for prevention of deep vein thrombosis; metoprolol (Lopressor®) for hypertension;

famotidine (Pepcid®) for dyspepsia; magnesium hydroxide (Milk of Magnesia®) and cascara for prevention of constipation; acetaminophen (Tylenol®) for fever; potassium chloride (K-dur®) for potassium replacement; and lorazepam (Ativan®) for sedation and agitation. At 38 hours, she had symptoms of severe hypoxia and developed severe, life-threatening respiratory failure (apnea) and ventricular tachycardia followed by asystole (cardiac arrest). She required cardioversion, converted to an atrial fibrillation rhythm, and was intubated; Swan-Ganz catheterization revealed evidence of congestive heart failure. She was treated with lidocaine for ventricular tachycardia; albuterol and normal saline by nebulizer for respiratory failure; and sodium chloride and dextrose 5%/0.45 normal saline for fluid replacement. The study medication was discontinued at 39 hours.

Abnormal laboratory results at the end of the study compared with screening (preoperative) values included hemoglobin, 8.0 g/dL (screening, 12.2 g/dL); hematocrit, 23.8% (screening, 37.5%); white blood cell count, 16.9 x 103/mm3, (screening, 7.4 x 103/ mm3); sodium, 131 mmol/L (screening, 134 mmol/ L); potassium, 3.2 mmol/L (screening, 3.8 mmol/L); and chloride, 94 mmol/L (screening, 92 mmol/L). The investigator did not consider these results to be significant.

Despite assisted ventilation, intravenous lidocaine, and potassium chloride, the patient died from respiratory failure on study Day 6, 5 days after system removal. The investigator judged the cardiac arrest to be possibly related to study medication, but did not consider the apnea or the tachycardia to be related to study medication.

In review of the above narrative, it is not clear if the hypoxia and apnea preceded the ventricular tachycardia, or if they followed it. If the initial event was the respiratory decompensation, then BTDS may certainly have played a role. The basis of the investigator's judgement that the apnea and tachycardia were not related to the study drug, but that the cardiac arrest may possibly have been related, is not clear. Of note, two other patients in post-operative study BP96-0104 had life-threatening serious adverse events of apnea. The Sponsor notes in Section 8.13.6.2 (Deaths) of the ISS that "BTDS is indicated for the management of pain in patients requiring continuous opioid analgesia, not for postoperative use.

A third death occurred in Study BUPN.CLIN0001, sponsored by Napp Pharmaceuticals. This study used a titration-to-effect design to compare the safety and efficacy of BTDS (5, 10, and 20) with buprenorphine sublingual tablets (200 mcg tid,qid, and 400 mcg tid) in patients with moderate to severe pain due to osteoarthritis of the hip or knee. Following a titration period of 21 days, patients were maintained on the optimum dose of study medication for 28 days. Paracetamol (1000 mg every 4 to 6 hours) was permitted throughout the study. Apart from the Sponsor's narrative in the 4-month safety update, no further information about this SAE is available. The Sponsor's narrative is reproduced below:

> **"UK/104/154** was a 66-year-old male patient who entered the trial with a diagnosis of osteoarthritis of the knees for >1 year. Significant medical history included impotence and smoking. Family history included a fatal coronary thrombosis in his father at age 53 years. The patient weighed 119 kg, and his height was 190 cm (BMI of 34.6). He had been receiving diclofenac for 2 years and sildenafil (Viagra) for 3 months. The patient began BTDS 5 on (b) (6) (Day 1). He was titrated to BTDS 10 on Day 8, to BTDS 20 on Day 15, and entered the assessment period on Day 21. On Day 16, the patient had an application site reaction (pruritus under the patch without erythema), which resolved by Day 21.

> On Day 25, while taking BTDS 10, the patient developed dyspnea attributed to a viral infection. On Day 30, his wife brought him to the emergency department where he was treated with nebulized drugs and was admitted to the hospital. The BTDS 10 was removed on the day of hospitalization. The patient died the following day (Day 31). Although the discontinuation page of the case report form stated myocardial infarction as the adverse event, the death certificate listed the cause of death as (a) left ventricular failure, (b) atrial fibrillation, and (c) septicemia and indicated evidence of underlying ischemic heart disease. The events were judged by the investigator to be improbably related to the study medication."

In review of the above narrative, it is not clear if the primary event was pulmonary (ie, dyspnea due to a pulmonary viral infection) or cardiac (eg, dyspnea due to left ventricular failure). It is also possible that he suffered a myocardial infarction after developing a primary pulmonary process, such as a pulmonary viral infection. In the absence of more detailed information about the patient's clinical course, no firm conclusions can be made about this death.

7.7 Non-Fatal Serious Adverse Events

Other serious adverse events were defined as serious adverse events other than death, including those temporally associated with or preceding death. In the adequate and well-controlled clinical trials, the degree of seriousness was classified as life-threatening, requiring hospitalization, resulting in disability, a congenital anomaly, or considered by the investigator to require intervention (procedural or concomitant therapy).

7.7.1 Other Serious Adverse Events in the Clinical Pharmacology Studies

In the clinical pharmacology studies, two serious adverse events occurred.

One subject in Study BP96-0501, a 33-year-old woman, received BTDS 10 on her upper chest for 48 hours (Period 1) without any reported adverse events. Pre-treatment blood pressure ranged from 90-101/52-55. Her lowest post-treatment blood pressure was 88/49 48 hours after BTDS application. After a 10-day washout period, she began Period 2 treatment with BTDS 10 application to her upper back. Her blood pressure immediately prior to BTDS 10 application was 90/62. The next morning, about 23 hours after patch application to her upper back, she experienced a syncopal episode and shortness of breath while showering. She exited the shower and sat down. She then became semi-conscious, unable to respond verbally, and appeared to be in respiratory distress. Her pulse was present but weak. She was treated with an ammonia inhalant, to which she responded only briefly (about 30 seconds). She again lost consciousness, and responded only to painful stimuli. She was pale and diaphoretic. She was placed in a supine position, and her legs were elevated. She was again administered ammonia inhalants. Two blood pressure recordings were 94/86 and 98/66, the pulse was 80 beats per minute, and respirations were 20 breaths per minute, though labored. She was afebrile. The BTDS 10 patch was removed about 5 minutes after the onset of the syncopal episode. Her blood pressure increased about 10 minutes after the onset of the syncope. By 20 minutes after the onset of the episode, she was alert. A tube of blood was drawn about 20 minutes after the onset of the episode (ie, about 15 minutes after the patch was removed) and revealed a buprenorphine level of 75.2 pg/mL. She remained well, except for an episode of mild weakness three days later which lasted for about 3.5 hours, at which times buprenorphine levels were below the limit of quantitation (25 pg/mL). This event was judged by the investigator to be probably related to the study drug. Review of this narrative indicates that the drug level (75.2 pg/mL) is about the expected level after 24 hours of wearing

the patch, and it is about one-half the expected steady state level (about 150 pg/mL). However, the patient was showering when the event occurred, and it is possible that the heat from the presumed hot shower water may have caused an increased release of buprenorphine, resulting in an increase in blood concentration of buprenorphine. Alternatively, the heat from the shower itself may have resulted in a vasovagal reaction, resulting in syncope. In this case, the exact causal role of the BTDS patch can not be definitively ascertained.

In Study BP97-0303, a 37-year-old woman (Patient No. 111) with a history of gallstones (last occurrence about 4 months prior to study entry), completed study BP97-0303. During the study, she reported a variety of adverse events after application of BTDS 5, including "feels weak", constipation, lower back pain, pain in the hips, numbness in the tips of the fingers, headache, double vision, dizziness, knee pain, nausea, blurred vision, stomach ache, vomiting, body aches, hot flashes, and chills. Each of these was rated as mild and non-serious. Approximately 11 hours after the removal of BTDS 20 on Day 14, she reported mild vomiting, body aches, hot flashes, and chills, as well as a moderate stomach ache. She was initially able to keep liquids down, but then began vomiting. Three days later, physical exam revealed right upper quadrant (RUQ) pain. Liver function tests and total bilirubin were elevated. A diagnosis of acute cholecystitis was made, and she underwent a cholecystectomy on Day 19, and was discharged on Day 24. She then developed evidence of continued common bile duct obstruction, and an endoscopic retrograde choledochopancreatoscopy (ERCP) was perfromed. A stent was placed in the common bile duct. This was to have been removed 3-5 weeks after placement, but there is no record if the removal occurred. The last contact with the patient, a little more than 4 months after she was discharged after the cholecystectomy, revealed that she was doing well. The investigator judged this event to be possibly related to study drug. The role of study drug can not be definitively ascertained, though the patient's prior history of gall bladder disease, as well as the occurrence of common bile duct obstruction after the cholecystectomy, suggest that others factors may also have been involved.

7.7.2 Other Serious Adverse Events in the Phase 2 and 3 Studies

In Phase 2/3 studies, the number and frequency of patients with at least one reported serious adverse events was as follows:

Frequency of Patients with at Least One Serious Adverse Event in Phase 2/3 Studies

	BTDS		Oxy/APAP		HCD/APAP		Placebo	
Study	N	%	N	%	N	%	N	%
BP96-0104	4	4/99 (4.0)	-	-	-	-	0	0/11 (0.0)
BP96-0101	2	2/163 (1.2)	1	1/55 (1.8)	-	-	3	3/52 (5.8)
BP96-0102	4	4/149 (2.7)	1	1/52 (1.9)	-	-	0	0/48 (0.0)
All Forced-Titration Studies	6	6/312 (1.9)	2	2/107 (1.9)	-	-	3	3/100 (3.0)
BP96-0604	2	2/46 (4.3)	4	4/43 (9.3)	-	-	2	2/45 (4.4)
BP98-1201	0	0/140 (0.0)	-	-	4	4/130 (3.1)	-	-
BP99-0203	0	0/152 (0.0)	-	-	-	-	2	2/163 (1.2)
All Titration-to-Effect Studies	2	2/338 (0.6)	4	4/43 (9.3)	4	4/130 (3.1)	4	4/208 (1.9)
BP96-0103	47	47/384 (12.2)	-	-	-	-	-	-
All Placebo Controlled Studies	12	12/609 (2.0)	6	6/150 (4.0)	-	-	7	7/319 (2.1)
All Controlled Studies	12	12/749 (1.6)	6	6/150 (4.0	4	4/130 (3.1)	7	7/319 (2.1)
All Phase 2/3	?60	60/919 (6.5)	6	6/150 (4.0)	4	4/130 (3.1)	7	7/319 (2.1)

Source: Study Reports for Studies BP96-0101, BP96-0102, BP96-0103, BP96-0104, BP96-0604, BP98-1201, and BP99-0203 in the NDA

Review of the above table indicates that, in general, the rate of patients with at least one serious adverse event in either placebo-controlled studies or all controlled studies was similar among the treatment groups. The rate of patients with at least one serious adverse event was higher in the long-term open label study (BP96-0103), though this higher rate is most likely the results of prolonged exposure.

Individual SAEs in the adequate and well-controlled studies are presented by treatment and subject in the tables below, taken from Sponsor's table 8.13.6.3.2 in the ISS.

TABLE 8.13.6.3.2. (Data for Placebo, Oxycodone/APAP, and Hydrocodone/APAP)
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Other Serious Adverse Events
Safety Population (N = 1344)
BP96-0101, BP96-0102, BP96-0604, BP98-1201, BP99-0203, and BP96-0104 Combined

Treatment/ Study No.	Patient/ Investigator No.[a]	Gender	Age (y)	Race	COSTART Term	Degree of Seriousness	Relationship to Study Drug	Day of Onset	Study Completion Status
Placebo									
BP96-0101	3017/1248	F	76	White	Injury accident, fractured clavicle	Hospitalization/ disability	None	17	Discontinued
BP96-0101	1001/1177	F	86	White	Right heart failure	Hospitalization	Possible	51	Completed
					Syncope	Hospitalization	None	51	
BP96-0101	11004/1740	M	80	White	Cholecystitis	Hospitalization	None	9	Discontinued
BP96-0604	16619/1820	F	72	White	Intestinal obstruction	Hospitalization	None	76	Discontinued
BP96-0604	11606/1740	F	39	White	Back pain	Hospitalization	None	61	Discontinued[b]
BP99-0203	2081/1995	M	78	White	Chest pain	Hospitalization	None	18	Discontinued
BP99-0203	2165/2063	F	59	White	Cerebrovascular accident[c]	Hospitalization	□[d]	21	Discontinued
Oxycodone/APAP									
BP96-0101	2024/1693	M	90	White	Arthralgia	Hospitalization	Possible	23	Discontinued
BP96-0102	8214/131	M	75	White	Chest pain	Hospitalization	None	31	Completed
BP96-0604	2604/100	F	52	White	Chest pain	Hospitalization	None	48	Discontinued
BP96-0604	4603/1627	F	79	White	Spontaneous bone fracture	Hospitalization	None	80	Discontinued[b]
BP96-0604	16604/1820	F	32	White	Paresthesia	Required intervention	None	27	Completed
BP96-0604	16613/1820	F	47	White	Uterine hemorrhage		None	60	Completed
Hydrocodone/APAP									
BP98-1201	4008/1820	M	38	White	Abdominal pain	Hospitalization	None	4	Discontinued
					Diarrhea	Hospitalization	None	4	
					Nausea	Hospitalization	None	4	
					Vomiting	Hospitalization	None	4	
BP98-1201	17118/2048	F	38	Black	Asthma	Hospitalization	None	30	Completed
					Asthma	Hospitalization	None	53	
BP98-1201	12287/1807	M	70	White	Colitis	Hospitalization	None	35	Discontinued
BP98-1201	11097/2035	F	77	White	Esophagitis	Hospitalization	None	35	Discontinued
					Anemia	Hospitalization	None	35	
					Stomach ulcer	Hospitalization	None	35	

(Cross-references: Table 8.14.2.2.24 of the Integrated Summary of Safety and Appendix 16.2.4.1 of the individual clinical study reports.)
[a]Patient number hyperlinked to narrative in clinical study report.
[b]Completed study according to protocol after early discontinuation of study medication.
[c]This adverse event was reported to the FDA, but was not included in the database.
[d]Relationship to study drug not established.
Source: Sponsor Table 8.13.6.3.2 in the ISS

TABLE 8.13.6.3.2. (Data for BTDS)
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Other Serious Adverse Events
Safety Population (N = 1344)
BP96-0101, BP96-0102, BP96-0604, BP98-1201, BP99-0203, and BP96-0104 Combined

Treatment/ Study No.	Patient/ Investigator No.[a]	Gender	Age (y)	Race	COSTART Term	Degree of Seriousness	Relationship to Study Drug	Day of Onset	Study Completion Status
BTDS 5									
BP96-0101	2005/1693	M	64	White	Chest pain	Required intervention	Probable	2	Discontinued
BP96-0102	22209/1574	F	75	White	Hypertension	Required intervention	Possible	9	Discontinued[b]
					Cerebral ischemia	Hospitalization	Possible	13	
BP96-0102	25201/1214	F	51	White	Migraine	Required intervention	None	12	Discontinued[b]
					Urticaria		None	12	
BP96-0104	64/1215	F	78	White	Cerebrovascular accident	Life threatening	Possible	1	Discontinued
BP96-0104	88/1215	F	84	His-panic	Apnea	Life threatening	Possible	1	Discontinued
					Asthma	Life threatening	Possible	1	
					Dyspnea	Life threatening	Possible	1	
					Sweating	Life threatening	Possible	1	
BTDS 10									
BP96-0104	79/1215	F	90	White	Heart arrest	Life threatening	Possible	1	Discontinued
					Tachycardia ventricular	Life threatening	None	1	
					Apnea	Life-threatening	None	1	
BTDS 20									
BP96-0101	2015/1693	M	83	White	Peripheral edema	Hospitalization	None	41	Discontinued
					Arthralgia	Hospitalization	None	39	
					Depression	Hospitalization	None	39	
BP96-0102	8204/131	F	88	White	Angina pectoris	Required intervention	None	15	Discontinued[b]
					Bradycardia	Hospitalization	None	15	
					Lung edema	Hospitalization	None	15	
BP96-0102	28201/302	F	50	White	Convulsion	Required intervention	None	48	Discontinued[b]
BP96-0604	7616/1215	M	39	White	Asthma	Hospitalization	None	72	Completed
BP96-0604	6612/1803	F	60	White	Syncope	Hospitalization	Possible	49	Discontinued[b]
BP96-0104	4/1215	F	71	White	Somnolence	Required	Possible	0	Discontinued
					Somnolence	interventionb	Possible	1	

(Cross-references: Table 8.14.2.2.24 of the Integrated Summary of Safety and Appendix 16.2.4.1 of the individual clinical study reports.)
[a]Patient number hyperlinked to narrative in clinical study report.
[b]Completed study according to protocol after early discontinuation of study medication.
[c]This adverse event was reported to the FDA, but was not included in the database.
[d]Relationship to study drug not established.

Source: Sponsor Table 8.13.6.3.2 in the ISS

In general, review of the SAEs in each treatment group reveals that the clinical spectrum of SAEs is comparable among the groups, and reflects events that can be expected to occur in a patient population of this age.

Review of the patient narratives is notable for the following:

Study/ Investigator/ Patient	Treatment	SAE COSTART/Verbatim	Reviewer Comments
B96-0101/ 1693/ 2005	BTDS	Chest Pain/Chest Pain	This event was part of a series of events, including sweating, fever, headache, lightheadedness, and nausea, which occurred about 18 hours after the application of the first BTDS 5 patch. The event was classified as a SAE because an ECG was performed. Though the ECG was unremarkable, the nature of these events and their temporal relationship to study drug application support a causal role for the BTDS.
B96-0101/ 1693/ 2015	BTDS	Depression/Depression Arthralgia/Pain Peripheral Edema/From baseline incr. in edema	This patient took BTDS for only 4 days. The SAEs had their onset 35 days later, and required hospitalization. It is not clear from the available data which of the three events prompted the hospitalization. CRF notes that the depression and edema were severe, while the pain was moderate The outcomes are not known.
BP96-0102/ 0131/ 8204	BTDS	Angina Pectoris/Angina Bradycardia/Bradyarrhthmia Pulmonary Edema/Lung Edema	This patient had an extensive cardiovascular history, including prior angina, myocardial infarction, and balloon angioplasty. Of note, these events occurred after one day of exposure to BTDS 20. The angina lasted about 10 minutes, though she required a five-day hospitalization for the bradyarrythmia. Of note, PVCs were recorded as an "intercurrent illness" at the same time, but were not recorded as an adverse event.
BP96-0102/ 0302/ 28201	BTDS	Convulsions/Seizures	This patient had a history of "petit mal seizures". She discontinued BTDS 10 after 10 days on study drug, due to vomiting, headache, and chills, all of which were judged to be related to the study drug. Her seizure occurred 38 days after study drug was discontinued, and was treated with phenytoin.
BP96-0102/ 1574/ 22209	BTDS	Hypertension/Elevated BP Cerebral Ischemia/TIA (Transient Ischemic Attack)	Patient had no history of cardiovascular or neurological problems. BP on Day 9 was 290/92 (judged possibly related to BTDS by the investigator), and was treated with amlodipine. She also experienced a TIA (no details available), and evaluated with multiple tests in hospital. Study medication was stopped.
BP96-0102/ 1214/ 25201	BTDS	Urticaria/Hive welts on face Migraine/Migraine headache	Patient has prior history of migraine, as well as allergies to several medications. Facial hives and welts developed on Day 12, 4 days after stopping BTDS on Day 8 due to lack of efficacy. Migraine occurred on same day as welts, and was treated with Midrin. Benadryl was used for hives and welts.
BP96-0104/ 1215/ 64	BTDS	Cerebrovascular Accident/CVA	Patient has a medical history notable for cardiovascular disease (hypertension, angina, myocardial infarction, cardiomegaly, and coronary artery disease) and was judged to be ASA III. Post-op, she received BTDS 5. One hour later she developed angina. At 25 hours after BTDS was applied, she developed a non-productive cough, and at 33 hours wheezing. At 40 hours, she developed a life-threatening cerebrovascular accident (no details). This was judged possibly related to study medication, for which she received heparin and was transferred to an intensive care unit. No further outcome information is available.

Study/ Investigator/ Patient	Treatment	SAE COSTART/Verbatim	Reviewer Comments
BP96-0104/ 1215/ 79	BTDS	Heart Arrest/ Tachycardia ventricular/ Apnea/	Patient died. Event is summarized in section on Deaths above.
BP96-0104/ 1215/88	BTDS	Apnea/Respiratory Failure Asthma/Wheezing Dyspnea/Shortness of Breath Sweating/Diaphoretic	84 year-old woman with a fractured hip and poor post-operative pulmonary function (FEV1 = 44% and FVC = 32% (both well below the protocol-specified >80% but not much different from pre-op values, necessitating permission from the Sponsor to enroll the patient). She had a history of multiple medical problems, including cardiovascular, cerebrovascular and peripheral vascular disease. 22 hours after the patch was applied, she became diaphoretic, dyspneic, developed wheezing and became apneic. Study treatment was prematurely discontinued. Hypoxia continued for 6 hours after system removal. Pulmonary edema and ECG changes consistent with myocardial ischemia also developed.
BP96-0104/ 1215/ 64	BTDS	Somnolence/Lethargy Somnolence/Lethargy (Note there were two occurrences of this SAE)	71 year-old woman with a fractured left hip with pre-operative history of hypertension, hypothyroidism, seizures, and anxiety. Lethargy was noted at 8 hours after BTDS 20 application (moderate severity) and again at 24 hours after application (mild severity). At 12 hours after application, the BTDS patch was removed, and she was discontinued from the study.
BP96-0604/ 1215/ 7616	BTDS	Asthma/Status Asthmaticus	39 year-old man with asthma was enrolled in study BP96-0604 for myofascial pain. He was started on BTDS 5 on Day 1, and had been receiving BTDS 20 since Day 73, when he developed an asthma attack requiring hospitalization. His asthma medications were changed, the attack resolved, and he resumed study medication (BTDS 20) on Study Day 76.
BP96-0604/ 1803/ 6612	BTDS	Syncope/Syncope	61-year-old woman with a prior history of vasopressor syncope, for which she was taking Inderal LA. On Study Day 50, while taking BTDS 20, she developed "syncope for 3 hours", for which she was hospitalized. Further details are not available, including the reason for the prolonged duration of the event. Of note the CRF simply indicates a start date (b) (6) and an end date (b) (6)). A duration of 3 hours is not listed, though a duration of 3 hours is listed for a separate AE ("heartburn") recorded above the AE "syncope". The "heartburn" AE occurred on (b) (6).

Review of the SAEs in the controlled clinical studies suggests the following conclusions:

- The use of BTDS in the post-operative is associated with apnea and therefore, as the Sponsor has noted, is not indicated for post-operative use. This association with apnea in post-operative patients raises the possibility that use of BTDS in patients with chronic pain may not be appropriate when these patients experience acute changes in cardiac or pulmonary function (eg, myocardial infarct, pulmonary edema, pneumonia, exacerbation of COPD, etc).

- Apart from the cases of apnea, the clinical spectrum of SAEs in BTDS-treated patients is similar to the clinical spectrum of SAEs in patients in the other treatment groups, including the placebo group. In general, these SAEs are typical of what might be expected in patients in this age group. Apart from the cases of apnea, the causal role of BTDS in the above SAEs is not definitive, and generally can not be ascertained.

In open-label study BP96-0103, 47 (12%) patients had 92 serious adverse events other than death. Thirty-one of these 47 patients discontinued study medication prematurely, and 16 completed the study.

The Sponsor has listed all SAEs in Study BP96-0103 in Table 12.3.1.2 of the BP96-0103 study report. Of note, nine patients had 17 SAEs that were related to intercurrent illnesses that were identified after review of source documents, but had not been reported as adverse events on the AE CRF, and thus were not in the AE database. Sponsor's Table 12.3.1.2 in the BP96-0103 study report identifies the SAEs by the COSTART Body System and COSTART Term, but does not provide the investigator term.

Review of Table 12.3.1.2, in conjunction with the SAE narratives contained in Sponsor's Section 14.3.3.2 of the BP96-0103 study report, reveals the following:

- Two of the three cases of COSTART term "abdominal pain" were cases of cholecystitis (Patients 7319 and 21323), while the etiology of the third case (Patient 21314) was not clear. The two cases of cholesystitis in the COSTART Body System category are in addition to one case of "cholecystitis" and one case of "cholelithiasis".
- There were two falls among the SAEs – the one case of "accidental injury" (Patient 7302) and one fall due to syncope (Patient 22302), who later was hospitalized and suffered a "cerebrovascular accident", though the relationship of the fall, the syncope, and the CVA are not clear.
- Three cases of "chest pain" appear to be of cardiac origin (Patients 7304, 21314, 24301), one appears related to pneumonia (Patient 7307), one appears to be non-cardiac in origin (Patient 6318), and the etiology of one case could not be determined (Patient 29301).
- The one case of "allergic reaction" appears to have been a reaction to eyedrops (Patient 21308).
- One case of "fever" (Patient 26311) was recorded as "fever of unknown origin" for which the patient was hospitalized, but no details are available. Specifically, the patient did not have a final hematology evaluation to evaluate for neutropenia or other abnormalities.
- Many of the SAEs in the Cardiovascular system were in patients who had histories of cardiovascular disease. There was no pattern of abnormalities in this group of SAEs that raised any significant safety concerns about the study drug.
- Twenty SAEs were reported in the Digestive body system. Six of these were judged by the investigator to be related to study drug – one case of "colitis" (Patient 21364, who had diverticulits), three cases of constipation (Patients 7301, 8313, and 25303), one cases of "dyspepsia" (Patient 25303, who also had bile acid reflux), and one case of nausea (Patient 7301). These cases share in common the feature that each may be related to opiate-related slowing of gastrointestinal transit. While none of the other Digestive SAEs was judged to be related to BTDS, some of them are known to be associated with opiate use, such as vomiting.

- The one case of "anemia" appears to have developed in-hospital, in the setting of acute illness in Patient 2302, who was hospitalized for cardiovascular disease, and developed *C. difficile* colitis and diarrhea.
- All six cases of "joint disease" (patients 6315, 7304, 7309, 7312, 7324, and 26312) involved patients having joint replacement.
- One patient (7307) has three Musculoskeletal SAEs. This patient, an 88-year-old woman, had previous flares of rheumatoid arthritis judged to be non-serious. On Study Day 131, she was hospitalized for increasing RA pain. This SAE lasted 6 days and was judged to be unrelated to study medication. She was again hospitalized for increased RA pain on Study Day 157. This event was judged to be possibly related to study medication, though the reason for this attribution is not clear. This event also lasted 6 days. A third RA flare started on Study Day 256, which was associated with diarrhea, required hospitalization, but was judged not related to study medication. Of note, this patient had other SAEs, including a hospitalization for vomiting (which started on Day 166) and dehydration due to vomiting (which started on day 168), as well as a hospitalization for chest pain and pneumonia, both of which started on Day 216. None of these other SAEs was judged to be related to study drug.
- One cases of "arthritis" (Patient 2302) was actually a case of septic arthritis, which required antibiotics.
- One patient (21348) is reported in Table 14.3.2.2 of Study Report BP96-0103 as having had 8 SAEs with onset on Day 52 (rhinitis, diarrhea, vomit, headache, abdominal pain, chills, fever, and dehydration), though these SAEs were omitted from Sponsor's Table 12.3.1.2. These SAEs required hospitalization, antibiotics (cefaxolin and ciprofloxacin), intravenous fluids, loperamide, and ranitidine. Echograms, hepatobiliary scan, abdominal ultrasound, and abdominal and chest X-rays were all normal. All symptoms resolved by Day 56, with the exception of the stuffy nose and diarrhea, which resoled by Day 60. All events were judged to be possibly related to study medication. The patient discontinued BTDS on Study Day 168 due to lack of efficacy. On Day 185 (17 days after study medication discontinuation), final laboratories showed AST 78 U/L and ALT 141 U/L. (Baseline values were 23 U/L and 47 U/L, respectively). Alkaline phosphatase and total bilirubin were within normal ranges. The abnormalities were judged to be of uncertain significance by the investigator. Repeat laboratory tests were not performed. The Sponsor noted that a possible cause of the elevated liver function tests was concomitant treatment with cefazolin (Ancef®) and ranitidine hydrochloride (Zantac®)
- The one case of "diabetic coma" (Patient 1314) occurred in a patient without a previous diagnosis of diabetes.
- The cases of "cerebrovascular accident" were varied in nature, though one (Patient 22302) was diagnosed after he was evaluated from a fall due to syncope.
- For one case of "rash" and "pruritus" on Day 66 (Patient 5315) at the patch site that was definitely associated with study drug, the event resolved after the patch was removed.
- One case of "skin ulcer" on the right foot (Patient 20306, which developed on Day 237), required hospitalization due to failure of antibiotics (cephalexin). BTDS was stopped on Study Day 238, and she received intravenous antibiotics and underwent a left femoral-popliteal bypass graft.
- One case of "rash" involved a severe, full body rash on Study Day 98. The Sponsor's narrative of this event, which is reproduced below, implicates both the study drug as well as the concomitant medication nambumetone:

> *Patient 07311* was a 76-year-old male with a diagnosis of osteoarthritis of the left spine [sic].

Medical history included dermatitis, constipation, and Paget's disease. In BP96-0101, the patient was exposed to placebo TDS for 47 days. Reported adverse events during BP96-0101 were nonserious and mild and included constipation, itchiness, rash at site, and vomiting. The patient completed the study. The last dose of BP96-0101 was removed on (b) (6), at which time he enrolled in BP96-0103, receiving the first dose of study medication for BP96-0101 (BTDS 5) on that same day (Day 0). The patient increased the dose to BTDS 10 on Day 28 and to BTDS 20 on Day 98. On Day 14, while taking BTDS 5, the patient reported moderate constipation and took senna/docusate sodium (Senokot-S). On Day 28, while taking BTDS 10, the patient reported mild constipation and a scab on the left arm BTDS site, both judged not to be related to study medication. The scab resolved without treatment by (b) (6) On Day 90, the patient reported moderate itchiness and severe constipation, judged possibly related to study medication. He continued to take senna/docusate sodium for his constipation. On Day 98, the patient's dose was increased to **BTDS 20,** and he was given topical betamethasone for itchiness and rash at site. On Day 166, the patient started taking nambumetone (Relafen) 750 bid for pain. On Day 170, the patient was hospitalized with a severe full body rash, fever (102°F), chills, and generalized weakness reported to have begun approximately 24 hours before. The event was judged probably related to study medication. As instructed by the investigator, study medication was stopped before admission on Day 168. Nambumetone was stopped on Day 170. The rash was treated with topical hydrocortisone cream and IV steroids. The patient underwent inpatient observation for 24 hours, was released on Day 171, and began a 12-day course of prednisone. Study medication was discontinued on and the patient did not complete the study. The body rash resolved by Day 175. On Day 186, upon final follow-up, the patient reported no adverse events, and all symptoms were resolved.

Review of the narratives of the other SAEs raises no significant safety concerns regarding the study drug.

7.8 Other Significant Adverse Events

7.8.1 Adverse Events That Led to Discontinuation of Study Drug

The incidence of adverse events by body system that led to study drug discontinuation were summarized in Sponsor Table 8.13.6.3.1A in the 4-month safety update, which is reproduced below:

Table 8.13.6.3.1A.
BTDS Four-Month Safety Update
Overall Incidence of Discontinuations Due to Adverse Events or Laboratory Abnormalities and Discontinuations Due to Adverse Events or Laboratory Abnormalities by Body System:
All Patients Enrolled, Phase 3 Adequate and Well-Controlled Studies (N = 1238)
BP96-0604, BP98-1201, BP99-0203, BP96-0101, and BP96-0102

	Placebo	HCD/APAP	Oxy/APAP	BTDS
	(N = 308)	(N = 130)	(N = 150)	(N = 650)
Body System	n (%)			
Total no. of patients	37 (12%)	34 (26%)	27 (18%)	160 (24%)
Digestive	14 (5%)	17 (13%)	12 (8%)	80 (12%)
Nervous	11 (4%)	11 (8%)	12 (8%)	73 (11%)
Body as a whole	15 (5%)	11 (8%)	6 (4%)	50 (8%)
Skin and appendages	10 (3%)	5 (4%)	10 (7%)	34 (5%)
Cardiovascular	2 (<1%)	5 (4%)	3 (2%)	12 (2%)
Respiratory	2 (<1%)	3 (2%)	2 (1%)	11 (2%)
Metabolic and nutritional	0	5 (4%)	0	5 (<1%)
Special senses	2 (<1%)	0	1 (<1%)	5 (<1%)
Musculoskeletal	4 (1%)	1 (<1%)	2 (1%)	3 (<1%)
Urogenital	0	2 (2%)	1 (<1%)	2 (<1%)
Hemic and lymphatic	1 (<1%)	1 (<1%)	0	0

(Cross-reference: Four-Month Safety Update, Table 8.14.2.2.20.4.)
Source: Sponsor Table 8.13.6.3.1A in 4-Month Safety Update

Review of the above table indicates that, in general, discontinuations due to adverse events within a given body system occurred at similar frequencies for BTDS and its two active comparators (Oxy/APAP and HCD/APAP), and that these frequencies were notably higher than the corresponding frequencies in the placebo group.

The incidence of adverse events that led to study discontinuation in the titration-to-effect studies is summarized in Sponsor Table 8.13.6.4.1A in the ISS, which is reproduced below:

TABLE 8.13.6.4.1A.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Incidence of Adverse Events That Led to Discontinuation of Study Drug in ≥ 2% of Patients in BTDS Group by Treatment:[a] Titration-to-Effect Studies
Safety Population (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

	No. (%) of Patients			
	BTDS	Oxycodone/APAP	Hydrocodone/APAP	Placebo
COSTART Term	N = 338	N = 43	N = 130	N = 208
Any adverse event	83 (25%)	12 (28%)	34 (26%)	25 (12%)
Nausea	26 (8%)	6 (14%)	11 (9%)	4 (2%)
Vomiting	20 (6%)	3 (7%)	5 (4%)	3 (1%)
Dizziness	19 (6%)	6 (14%)	5 (4%)	4 (2%)
Headache	17 (5%)	1 (2%)	5 (4%)	4 (2%)
Somnolence	10 (3%)	1 (2%)	2 (2%)	2 (<1%)

(Cross-reference: Table 8.14.2.2.20.2.)
[a]By descending order of frequency in BTDS group.
Source: Sponsor Table 8.13.6.4.1A in the ISS

Review of the above table indicates that the most frequent adverse events leading to drug discontinuation are those that are typical of opiate-related side effects. Thus, the rates among the three active groups (BTDS, Oxy/APAP, and HCD/APAP) are generally similar, with the exception of nausea, which is higher in the Oxy/APAP group than in the other two groups. For each of the adverse events in the above table, the rates in the BTDS groups are notably higher than the corresponding rates in the Placebo group.

The incidence of adverse events that led to study drug discontinuation in ≥ 2% of patients was summarized for the forced-titration studies in Sponsor Table 8.13.6.4.1B in the ISS, which is reproduced below:

TABLE 8.13.6.4.1B.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Incidence of Adverse Events That Led to Discontinuation of Study Drug in ≥ 2% of Patients in Total BTDS Group by Treatment:[a] Forced-Titration Studies
Safety Population (N = 519)
BP96-0101 and BP96-0102 Combined

	No. (%) of Patients					
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo
COSTART Term	N = 312	N = 105	N = 103	N = 104	N = 107	N = 100
Any adverse event	73 (23%)	21 (20%)	18 (18%)	34 (33%)	15 (14%)	12 (12%)
Nausea	26 (8%)	7 (7%)	5 (5%)	14 (14%)	3 (3%)	2 (2%)
Dizziness	17 (6%)	4 (4%)	2 (2%)	11 (11%)	1 (<1%)	2 (2%)
Somnolence	16 (5%)	4 (4%)	2 (2%)	10 (10%)	2 (2%)	1 (1%)
Vomiting	14 (5%)	3 (3%)	4 (4%)	7 (7%)	1 (<1%)	1 (1%)
Headache	8 (3%)	3 (3%)	1 (<1%)	4 (4%)	1 (<1%)	2 (2%)
Constipation	7 (2%)	2 (2%)	1 (<1%)	4 (4%)	1 (<1%)	1 (1%)
(Cross-reference: Table 8.14.2.2.20.1.)						
Source: Sponsor Table 8.13.6.4.1B in the ISS						

Review of the above table indicates that the proportion of BTDS-treated patients who discontinued due to an adverse event was similar between the titration-to-effect and forced-titration studies. As in the titration-to-effect studies, the proportion of BTDS-treated patients who discontinued due to an adverse event was notably higher than the corresponding proportion in the Placebo group. The rate in the Oxy/APAP group is closer to the rate in the Placebo group than to the rate in the BTDS group. The adverse events that frequently resulted in discontinuation are typical opiate-related side effects. The above table does not shed light on a dose-response relationship of these AEs, since the column headings for BTDS 5, BTDS 10, and BTDS 20 refer to the dose to which the patient was randomized, not to the dose that the patient was receiving at the time the AE developed or at the time discontinuation occurred.

The incidence of adverse events that led to study drug discontinuation in ≥ 1% of patients was summarized for the open-label study BP96-0103 in Sponsor Table 8.13.6.4.1D in the ISS, which is reproduced below:

TABLE 8.13.6.4.1D. BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103) Incidence of Adverse Events That Led to Discontinuation of Study Drug in ≥ 1% of Patients Intent-to-Treat/Safety Population (N = 384)	
COSTART Term[a]	No. (%) of Patients
Nausea	37 (10%)
Rash	34 (9%)
Dizziness	24 (6%)
Pruritus	24 (6%)
Vomiting	15 (4%)
Somnolence	15 (4%)
Application site reaction	15 (4%)
Headache	11 (3%)
Constipation	10 (3%)
Depression	4 (1%)
Dyspnea	4 (1%)
(Cross-reference: Table 8.14.3.2.15.)	
[a]By descending order of frequency.	
Source: Sponsor Table 8.13.6.4.1D in the ISS	

Review of the above table indicates that, as in the titration-to-effect and forced-titration studies, many of the adverse events leading to discontinuation are those typical of opiate-related side effects. However, “rash”, “pruritus”, and “application site reaction” may be related to the patch itself, and not to the opioid activity of the product. Many of the investigator verbatim terms corresponding to “rash” appear to be patch site rashes, even though they were not coded to “rash at site.” To a lesser extent, many of the cases of “pruritus” appear to be pruritis at the patch site, even though they were not coded as such.

Dyspnea that required study medication discontinuation occurred in 4 patients. Features of these cases are summarized in the table below:

INO/PNO	Age	Study Day	Duration	Severity	Relationship	Reviewer's Comment
100/4306	63	16	4	Moderate	None	Occurred on second day of BTDS 20, but attributed to "fluid in the lungs", for which furosemide was given.
100/4312	53	14	19	Moderate	Definite	Developed on Day 14, medication discontinued on Day 30, event resolved on Day 32. No other etiology provided in narrative.
100/4315	74	30	2	Severe	Possible	No narrative provided. Began two days after constipation began. Judged to be non-serious.
1215/21317	42	65	1	Mild	Possible	Occurred in conjunction with hypertension, diaphoresis, pallor, and chest pain, each of which was judged to be possibly realted to study drug. An evaluation in an ER was "negative". Patient recovered.
Source: Sponsor Table 14.3.2.3 in BP96-0103 Study Report, Narratives on BP96-0103 Study Report (Table 14.3.3) and Data Listing 16.2.7.1 in BP96-0103 Study Report.						

As with the controlled clinical trials, the data from the open-label trial do not shed light on the dose-response relationship of adverse events resulting in study drug discontinuation.

Discontinuations in the Phase 2, single-dose, post-operative study occurring in 2% or more of patients are summarized in Sponsor's Table 8.13.6.4.1C in the ISS, whichis reproduced below:

TABLE 8.13.6.4.1C.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Incidence of Adverse Events That Led to Discontinuation of Study Drug in ≥ 2% of Patients in Total BTDS Group by Treatment:[a] Phase 2 Study (BP96-0104)
Safety Population (N = 110)

	No. (%) of Patients				
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Placebo
COSTART Term	N = 99	N = 33	N = 33	N = 33	N = 11
Any adverse event	12 (12%)	6 (18%)	1 (3%)	5 (15%)	1 (9%)
Confusion	5 (5%)	2 (6%)	0	3 (9%)	0
Somnolence	3 (3%)	0	0	3 (9%)	0
Hostility	2 (2%)	2 (6%)	0	0	0
Apnea	2 (2%)	1 (3%)	1 (3%)	0	0

(Cross-reference: Table 8.14.2.2.20.3.)
[a]By descending order of frequency in total BTDS group.
Source: Sponsor Table 8.13.6.4.1C in the ISS

Review of the above table is notable for the cases of apnea, which were discussed in the Deaths and Serious Adverse events sections above. As noted in those sections, the Sponsor has indicated that BTDS is not indicated for post-operative use.

Adverse events leading to discontinuation in the Phase 1 clinical pharmacology studies are summarized in Sponsor Table 8.13.A.5A in the ISS, which is reproduced below:

TABLE 8.13.A.5A.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Other Significant Adverse Events That Led to Discontinuation of Study Drug
Safety Population (N = 449)
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202,
BP98-1204, BP99-0204 Combined

Study No.	Subject/ Investigator No.	Gender	Age (y)	COSTART Term	Serious/ Nonserious	Relationship to Study Drug	Days Treated	Study Completion Status
BTDS 10								
BP98-0201	14/1925	Female	21	Vomiting	Nonserious	Definite	1	Discontinued
BP98-1204	20/2099	Male	40	Genital lice	Nonserious	None	3	Discontinued
				Urethral discharge	Nonserious	None	3	
BP96-0501	7/1672	Female	33	Syncope	Serious	Probable	1	Discontinued
				Dyspnea	Nonserious	Probable	1	
BTDS 20								
BP95-0901	6/1544	Female	44	Vomiting	Nonserious	Definite	2	Discontinued
BP96-0304	1/1277	Male	40	Hypoventilation	Nonserious	Definite	1	Discontinued
				Hypoventilation	Nonserious	Definite	1	
BP96-0304	5/1277	Male	44	Anxiety	Nonserious	Probable	1	Discontinued
				Confusion	Nonserious	Definite	1	
				Dizziness	Nonserious	Definite	1	
BP97-0303	109/1695	Male	25	Vomiting	Nonserious	Definite	3	Discontinued
BP97-0303	908/1695	Female	65	Hypotension	Nonserious	Definite	9	Discontinued
BIV								
BP97-0501	16/1695	Male	31	Vomiting	Nonserious	Probable	0	Discontinued

(Cross-reference: Table 8.14.1.2.9.1.)

Review of the above adverse events leading to drug discontinuation is notable for the following:

Subject 0001 at site 1277 in Study BP96-0304 had received BTDS 10 for 72 hours in the first phase of the study, and 24 hours after application of the BTDS 10 patch he began to complain of nausea and vomiting, which required metoclopramide 5 mg IM. The nausea persisted until 2 hours after the patch was removed after 72 hours of wear. After a 10-day washout, two BTDS 5 patches were applied. He again developed nausea after about 5 hours, followed by dizziness and moderately severe nausea and vomiting about 24 hours after application. Promethazine 25 mg IM and metoclopramide 5 mg IM were applied. After a second 10-day washout period, a BTDS 20 patch was applied. He again developed nausea and vomiting 10 hours after the patch was applied, which required treatment with promethzine 12.5 mg IV. Thirteen hours after the patch was applied, he reported a sensation of paresthesia of his chest, with the subjective feeling of a decreased respiratory rate. Oxygen saturation by pulse oximetry was normal (96%, normal range 94-100%). The Sponsor's narrative continues as follows: "The subject was under continuous observation for the remainder of the night. His SaO2 remained at 96% or greater, with a respiratory rate of 10 to 14 breaths per minute, until 24 hours. At that time, he was noted to have 15-second periods of apnea when he was sleeping, with a decrease in his SaO2 to 92%. By 25 hours the subject was having 20- to 30-second periods of apnea with a SaO2 of 93–97% when he was not being aroused and coached by the staff to take deep breaths. He was placed on continuous EKG and pulse oximetry monitoring at 25.5 hours. At 27 hours, the subject was not coached to breathe, and his SaO2 decreased to 87%. The subject was continually aroused after that. The BTDS 20 was removed at 28.5 hours, and the site was flooded with alcohol to remove

any residual buprenorphine on the skin and allowed to air-dry. Respiratory depression completely by 33 hours without further intervention."

The case of syncope in Subject 0007 (Investigator 1627) in Study BP96-0501 was discussed in the review of other serious adverse events above.

Subject 0005 (Investigator 1277) on Study BP96-0304 complained of disorientation with each application of the patch (Two BTDS 5 patches, one BTDS 10 patch, and one BTDS 20 patch, each separated by a 10-day washout period). He also experienced nausea with each application of the patch. With the BTDS 20 patch, he also complained of dizziness and anxiety, and required that the patch be removed early, at about 29 hours after its application. These events were not associated with respiratory depression. The Sponsor's narrative notes that the subject "complained of" confusion, while the CRFs note "confusion." It is not clear if any confusion or other abnormality of mental state was formally documented.

Subject 0908 (Investigator 1695) in Study BP97-0303 was a 65 year-old healthy woman whose treatment with BTDS 5 was complicated by mild constipation (Day 2) and mild fever (Day 3). BTDS 10 treatment was complicated by vomiting (Day 4, first day of BTDS 10). On BTDS 20, she had mild nausea (Day 7, second day of BTDS 20), and began vomiting the next day. On Day 9, she was mildly disoriented, and was unable to recognize other subjects in her group. A urinary tract infection was diagnosed (100-150 WBC/hpf; 5-10 RBC/hpf, and no casts). She received ciprofloxacin 5000 mg bid and acetaminophen. On Day 10, she was pale and had mild low blood pressure (146/95 supine at 6:00 am; 109/65 supine at 7:00 pm that dropped to 90/63 upon standing). Here legs were elevated, and she felt better. The BTDS 20 was removed. The next morning, supine BP was 114/82 and standing BP was 109/75. Nausea returned on Day 14, for which she was given prochlorperazine 10 mg po. Discharge evaluation was notable for urinalysis abnormalities.

7.8.2 Adverse Events That Led to Drug Interruption or Dose Reduction

Drug interruptions were those cases in which the drug was stopped, but later resumed.

The incidence of adverse events that led to drug interruptions in the titration-to-effect studies ranged between 2.3% and 2.4% for the BTDS, Oxy/APAP and HCD/APAP groups, and 1.4% for the Placebo group (see Sponsor Table 8.14.2.2.21.2 in the ISS). The incidence of individual adverse events that led to drug interruption was <1% for all such adverse events. Adverse events leading to drug interruption occurred in eight BTDS-treated patients, and included: anorexia (n=1), dyspepsia (n=1), nausea (n=2), vomiting (n=1), confusion (n=1), dizziness (n=1), insomnia (n=1), asthma (n=1), other site reaction (n=1), pruritus (n=1), and pruritis at site.

The incidence of adverse events that led to drug interruptions in the forced-titration studies was 2.9% in the BTDS 5 group, 6.8% in the BTDS 10 group, 3.9% in the BTDS 20 group, and 3.7% in the Oxy/APAP group (see Sponsor Table 8.14.2.2.21.1 in the ISS). The incidence of individual adverse events that led to drug interruption was between 1% and 2% for all such adverse events. Adverse events leading to drug interruption occurred in two BTDS 5-treated patients, and included: edema at three different sites (n=1), erythema at three different sites (n=1), and rash (n=1). Adverse events leading to drug interruption occurred in four BTDS 10-treated patients, and included: nausea (n=2), vomiting (n=2), dizziness (n=1), sweating (n=1) and erythema at site (n=1). Adverse events leading to drug interruption occurred in four BTDS 20-treated patients, and included: dizziness (n=1), vomiting (n=1), and headache (n=1).

Review of the above data indicates that the incidence of adverse events that led to drug interruption was generally similar between the titration-to-effect studies and the forced-titration studies, though the rate in the BTDS 10 group (6.8%) in the forced-titration studies was higher than other rates. The adverse events leading to drug interruption are typical of opiate-related adverse reactions, except for the local reaction, which, as will be discussed in the section on adverse events, may be related to the patch itself.

TABLE 8.13.A.5B. BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103) Incidence of Adverse Events That Led to Drug Interruption in ≥ 1% of Patients Intent-to-Treat/Safety Population (N = 384)	
COSTART Term[a]	No. (%) of Patients
Nausea	14 (4%)
Rash	10 (3%)
Vomiting	8 (2%)
Pruritus	7 (2%)
Joint disorder	4 (1%)
Headache	4 (1%)
Abdominal pain	4 (1%)
Application site reaction	4 (1%)
(Cross-reference: Table 8.14.3.2.16.) [a]By descending order of frequency.	
Source: Sponsor Table 8.13.A.5B in ISS Appendix	

As in the controlled clinical trials, the adverse reactions commonly leading to drug interruption are those typically associated with opiate-related side effects, or those related to local site reactions.

There were no adverse events leading to drug interruptions in the Phase 2 study or in the clinical pharmacology studies.

In the titration-to-effect studies, the incidence of any adverse events that led to dose reduction was 11.8% in the BTDS group, 6.2% in the HCD/APAP group, 4.7% in the Oxy/APAP group, and 1.9% in the placebo group (see Sponsor Table 8.14.2.2.22.2 in the ISS). Among BTDS-treated patients, 22/338 (6.5%) required dose reduction due to an adverse event in the digestive system, including anorexia (n=1), constipation (n=3), dry mouth (n=3), nausea (n=17, 5%), and vomiting (n=6, 1.8%). The rates of nausea requiring dose reduction was notably higher in the BTDS group (5%) than in the HCD/APAP group (0.8%), the Oxy/APAP group (2.3%), or the placebo group (0%). Twenty-four of 338 BTDS-treated patients (7.1%) required dose reduction due to an adverse event in the nervous system, including confusion (n=1), depression (n=1), dizziness (n=7, 2.1%), insomnia (n=1), nervousness (n=1), paresthesia (n=2), somnolence (n=13, 3.9%), speech disorder (n=1), stupor (n=1), thinking abnormal (n=1), and tremor (n=1). The rate of somnolence leading to dose reduction in the BTDS group (3.9%) was higher than the corresponding rates in the HCD/APAP group (0.8%), the oxy/APAP group (2.3%), or the Placebo group (0%).

In the forced-titration studies, one patient in the Oxy/APAP group, and none in the BTDS group, required dose reduction due to an adverse event.

There were no adverse events leading to dose reductions in the Phase 2 study or in the clinical pharmacology studies.

7.9 Overall Evaluation of Adverse Events

7.9.1 Approach to Eliciting Adverse Events in the Development Program

In all studies, adverse events were reported by the patient or subject in an ongoing manner throughout the study. These events, whether recorded in a diary or reported directly to the study staff, were transcribed by the study staff onto the case report form. Severity and causality assessments were made by the investigator using standard definitions.

The Sponsor notes in the ISS (Section 8.13.A.1.1) that in the ISS "an adverse event was defined as an untoward medical occurrence, whether or not related to the study drugs, in a subject or patients during a clinical trial." Review of the data and the CRFs indicates that some of the clinical studies used a CRF for Intercurrent Diseases or Conditions, as well as a CRF for adverse events. In response to a question from the Agency (sent on June 12, 2001) asking about this distinction, as well as about the extent of use of Intercurrent Disease or Condition CRFs, the Sponsor noted that prior to 1997 it used Intercurrent Illness or Condition CRF pages as well as Adverse Event CRF pages. This practice was discontinued for all protocols initiated after 1997. Protocols BP06-0803, BP95-09-1, BP96-0304, BP96-0104, BP96-0101, BP96-0102, and BP96-0103 each used both CRFs. The definition of adverse events varied among these protocols. For instance, the definition used in BP96-0803, BP95-0901, BP96-0304 was "an adverse experience is defined as any adverse events associated with these use of a drug in humans, whether or not considered drug related." In these protocols, no definition was provided for an intercurrent disease or condition. In BP96-0104, on the other hand, an adverse event was "any event that was clearly related or suspected to be related to the study medication (BTDS)", while and intercurrent illness was "any event that was clearly not related to the study medication (BTDS), such as common post-operative conditions, and events that were not consistent with opioid medications." In this case, the investigator must make a judgement about the nature and causality of the event before determining if it is an adverse event or an intercurrent illness. The definitions used in BP96-0104 are therefore not consistent with the Sponsor's definition of an adverse event in the ISS, which defines adverse events regardless of their causal relationship to the study drug. For studies BP96-0101, BP96-0102, and BP96-0103, adverse event were "all adverse drug experiences reported by the patient or observed by the investigator/research assistant throughout the study." For these three studies, intercurrent illnesses or conditions were "all illnesses, disease, or conditions which are not adverse events and are new onset during the study." Because the definition of adverse events in these studies is broad and implies no limitations, the distinction between and adverse event and an intercurrent illness is not clear. The Sponsor notes in its response that investigators were allowed to use their judgement as to whether an event was an adverse event or an intercurrent illness or condition. If in doubt, they were instructed to characterize the event as an adverse event. At least one intercurrent illness or condition was reported in 364 patients/subjects. A total of 750 intercurrent illnesses or diseases were reported in these 364 individuals.

In some cases, additional information, including events that could be considered as adverse events or serious adverse events, was available to the Sponsor during the preparation of narratives for serious adverse evens. Such information includes a Serious Adverse Event Form (not part of the CRF) and patient source documents. However, only information recorded on the CRF was listed as an adverse event in the study database.

In response to an Agency question, the Sponsor noted in a correspondence to the Agency on May 4, 2001 that both treatment-emergent adverse events and adverse events present at baseline were in included in the adverse events tables and listings. The exception to this practice was for the two studies with ibuprofen run-in periods, BP98-1201 and BP99-0203. For these studies, only treatment-emergent adverse events were included in the summary tables. For all studies, including these two studies, all adverse events are included in the listings. No treatment-emergent algorithm was used.

7.9.2 Appropriateness of Adverse Event Categorization and Preferred Terms

Review of the pooled Phase2/3 adverse event database was notable for the fact that several clinically similar investigator terms were coded to more than one coded term. For example, some cases of edema coded to PERIPHERAL EDEMA, while other were coded to EDEMA, regardless of whether the body site was included in the verbatim terms. Investigator verbatim terms suggestive of a common cold, were variably coded to CHILLS, FLU SYNDROME, INFECTION, or PHARYNGITIS. The investigator term "blurred vision" and other related terms were variably coded to ABNORML VISION or to AMBLYOPIA. Some cases of numbness were coded to PARESTHSIA, while others were coded to HYPESTHESIA. These and other examples were sent to the Sponsor in a letter dated June 11, 2001 for an explanation of the coding process. The Sponsor responded that all terms are manually coded and added to an autoencoding capability that retains a history of all previously coded terms across all protocols and projects. Any term that fails to autoencode is reviewed and manually coded. These new terms are then added to the autoencoder dictionary for future use. The Sponsor noted that minor inconsistencies in the above process may have resulted in the observed inconsistencies. Minor differences in verbatim terms could have resulted in individual coding decisions that are different from previous decisions.

7.9.3 Analyses and Explorations

In the initial NDA submission, the Sponsor analyzed adverse event frequency separately for the titration-to-effect studies and the forced-titration studies. In the titration-to-effect studies, adverse event frequency rates were not broken down by doses at which the adverse event occurred. In the forced-titration studies, the adverse events frequencies were reported separated by the dose group to which the patients was assigned (ie, BTDS 5, BTDS 10, or BTDS 20), but not by the dose at which they occurred. The Agency therefore asked for a pooled analyses is of adverse event frequencies in the five Phase 3 studies, with frequency rates for any BTDS regimen, as well as frequencies rates for each dose, based on the dose at which the adverse event occurred. The Agency also asked for a pooled analysis of the four placebo-controlled Phase 3 studies, but this was received too late in the review cycle to be included in this review.

The Sponsor has reported adverse event frequency by severity in two ways. First, adverse events rates are presented "as reported" for each severity. For example, it a patients has a case of nausea of "mild" severity and then develops a cases of nausea of "moderate" severity, this case is tabulated both in the frequency of "mild" cases and in the frequency of "moderate" cases. The other approach used is the "worst case" method, in which each patient's most severe case only is presented in the tabulations. In the example, the frequency calculation of the "mild" cases would not include this patient's case, since the patients also had a more severe case.

In the five Phase 3 studies, 548 of 650 BTDS-treated patients (84.3%) had at least one adverse event. A total of 3378 adverse events were reported in these patients. Of 650 patients treated with BTDS 5, 417 (64.2%) had at least one adverse event. Of 478 patients treated with BTDS 10, 258 (54.0%) had at least one ad verse event. Of 307 patients treated with BTDS 20, 203 (66.1%) had at least one adverse event. Of 308 Placebo-treated patients, 197 (64.0%) had at least one adverse event.

The frequency of selected adverse event in the five pooled Phase 3 studies is presented in the table below.

Frequency Rates of Selected Adverse events in the Five Pooled Phase 3 Studies						
Body System	Adverse Event	Any BTDS	BTDS 5	BTDS 10	BTDS 20	Placebo
Body as a Whole	Asthenia	9.7	5.4	5.0	3.3	5.2
Body as a Whole	Face Edema	0.6	0.2	0.2	0.7	0.0
Body as a Whole	Headache	28.0	20.9	10.0	7.5	18.2
Cardiovascular	Vasodilation	2.6	1.7	0.4	1.3	0.3
Digestive	Anorexia	2.8	1.4	1.0	1.3	0.6
Digestive	Constipation	26.8	14.5	10.9	12.1	10.7
Digestive	Dry Mouth	22.6	14.0	7.1	8.1	13.3
Digestive	Nausea	34.8	20.0	14.0	16.6	14.0
Digestive	Vomiting	15.1	6.6	6.3	10.1	3.9
Metabolic and Nutritional	Edema	2.2	0.5	1.0	2.0	1.3
Metabolic and Nutritional	Peripheral Edema	6.2	1.4	3.3	6.2	1.3
Nervous	Anxiety	2.3	0.8	0.8	2.0	1.0
Nervous	Confusion	3.1	1.4	1.7	1.3	0.3
Nervous	Depression	2.3	1.2	1.3	0.3	0.6
Nervous	Dizziness	31.2	19.1	13.4	13.0	14.6
Nervous	Nervousness	5.1	3.2	1.7	2.0	1.3
Nervous	Paresthesia	2.6	1.1	0.8	2.3	0.6
Respiratory	Dyspnea	2.8	0.9	0.8	2.9	1.0
Skin	Erythema at Site	7.5	2.3	3.1	6.8	5.2
Skin	Other Stie Reaction	4.0	1.7	2.3	1.6	3.2
Skin	Pruritus	18.2	11.7	7.1	5.9	13.6
Skin	Pruritus at Site	19.8	11.7	7.9	11.4	14.9
Skin	Rash	3.8	1.5	1.9	2.9	1.9
Skin	Rash at Site	8.6	2.9	4.4	7.2	10.7
Skin	Sweating	6.6	3.2	2.5	3.3	2.9
Special Senses	Abnormal Vision	1.1	0.6	0.2	0.7	0.6
Special Senses	Amblyopia	0.9	0.5	0.2	0.2	0.0
Source: Sponsor Table 2 in May 4, 2001 General Correspondence in reply to Agency question						

In the Body as a Whole system, the most common adverse event in any BTDS-treated patients was headache, which occurred 28.0% of BTDS-treated patients and 18.2% of placebo-treated patients. The frequency of headache decreases with increasing BTDS dose, and the distribution of severe cases is similar for the three dose groups and for the Placebo group.

The second most common AE in this body sytsem is asthenia, which occurred in 9.7% of BTDS-treated patients and in 5.2% of placebo-treated patients. There was no relationship of dose to the

frequency of asthenia, and the distribution of severities was generally similar across the three dose groups.

Face edema occurred in 0.6% of BTDS patients and in no placebo patients. In two patients, the cases were rated as severe (one was reported as “swelling of right lip and face” and the other patient, in whom study medication was discontinued, had “swelling left lower lip” and “swelling of upper lip”).

Pain was reported in 4.3% of BTDS patients and in 5.2% of placebo-treated patients. No case was serious, and the frequency of severe cases was similar for the BTDS group (0.5%) and the Placebo group (0.6%). In most cases, the pain, based on review of the investigator verbatim terms, was unrelated to the underlying pain condition for which the patients was being given study drug.

The overall frequency of adverse events in the Cardiovascular body system was more frequent for BTDS patients (8.2%) than for placebo patients (3.9%). The frequency of serious cardiovascular events was 0.6% (n=4) for BTDS patients and 0.3% (n=1) for placebo patients. These have been reviewed in the section on serious adverse events. Cardiovascular adverse events related to heart rate and blood pressure are discussed below in the section on vital signs. Apart from these event, no specific event was responsible for the increased frequency of cardiovascular events in the BTDS group. Vasodilation was notably more common in the BTDS patients (2.6%) compared to placebo patients (0.3%). A heterogenous group of investigator terms corresponding to this COSTART term include “flushing”, “hot flashes”, “Warm hands”, “heat sensitivity”, “hot”, “face flushed and hot”, “heat sensation”, “flushes”, “hot/cold body”, “hot/cold body temperature”, “severe leg and feet burning” and other similar terms. No case was serious, and only one case in the BTDS 5 group was severe (Patient 1190 in BP99-0203, who developed hot flashes on Day 15 [first day of BTDS 20], which lasted for 10 days and required no action with regard to the study drug).

Adverse events in the Digestive system were more common in BTDS patients (58.8%) than in the Placebo patients (32.5%). Constipation was reported in 26.8% of BTDS patients, and in 10.7% of Placebo patients. No case was serious, and the frequency of severe cases was similar in the BTDS group (0.9%) and the Placebo group (0.6%). Increasing BTDS strength did not results in an increased frequency of constipation. Dry mouth occurred in 22.6% of BTDS patients, and in 13.3% of Placebo patients. Nausea occurred in 34.8% of BTDS patients and in 14.0% of Placebo patients. Vomiting occurred in 15.1% of BTDS patients and in 3.9% of Placebo patients. While the frequency of common adverse events in this body sytem was not notably higher for the BTDS 20 group compared to the two lower strengths, the frequency of vomiting at the BTDS 20 strength (10.1%) was higher than the frequency at the BTDS 5 strength (6.6%) and at the BTDS 10 strength (6.3%).

Only one adverse event was reported in the Endocrine system in the Phase 3 studies, a non-serious, mild case of hyperthyroidism in a patient treated with BTDS 20.

Adverse events in the Hemic/Lymphatic system were relatively rare, occurring in 0.9% of BTDS patients and in 1.0% of Placebo patients. Abnormal platelets were reported in one patient (12074 in Study BP981201, who had a screening platelet count of 208,000/mm3 and an end-of-study platelet count of 196,000. The latter count was judged to be clinically significant, though the adverse event listing notes that the “abnormal platelets” resolved.

In the Metabolic system, adverse events were more common in the BTDS group (10.%) than in the Placebo group (4.9%). The most common adverse event in this system, Peripheral Edema, occurred in 6.2% of BTDS patients and in 1.3% of Placebo patients. The investigator verbatim terms in this category were generally indicative of lower extremity edema. In some cases, a causal relationship with the study drug was suspected. In most cases, however, no action with regard to study drug was taken. Two cases in the BTDS group were severe – one at the BTDS 5 level and one at the BTDS 10 level. One case at the BTDS 10 level was a serious adverse event because it required hospitalization.

Adverse events in the Musculoskeletal system occurred with near equal frequency in the BTDS group (5.1%) and in the Placebo group (5.5%). Apart from events that occurred only in one patient, no adverse event in this body system was more common in BTDS patients compared to Placebo patients.

Though adverse events in the Nervous system were common in all groups of patients, the frequency of BTDS patients with at least one nervous system adverse event (53.1%) was notably higher than the frequency of Placebo patients with at lest one nervous system adverse event (25.0%). Nervous system adverse events occurring in more than 2.0% of all BTDS patients is presented in the table below.

Nervous System Adverse Events Occurring in at Least 2% of All BTDS-treated Patients
Population: All Phase 3 Controlled Studies (BP96-0101, BP96-0102, BP96-0604, BP98-1201, and BP99-0203)

Adverse Event	Any BTDS (N=650)		BTDS 5 (N=650)		BTDS 10 (N=478)		BTDS 20 (N=307)		Placebo (N=308)	
	N	%	N	%	N	%	N	%	N	%
Any Nervous System AE	345	5.3.1	228	35.1	121	25.3	92	30.0	77	25.0
Anxiety	15	2.3	5	0.8	4	0.8	6	2.0	3	1.0
Confusion	20	3.1	9	1.4	8	1.7	4	1.3	1	0.3
Depression	15	2.3	8	1.2	6	1.3	1	0.3	2	0.6
Dizziness	203	31.2	124	19.1	64	13.4	40	13.0	45	14.6
Hypertonia	13	2.0	8	1.2	3	0.6	2	0.7	3	1.0
Insomnia	37	5.7	26	4.0	6	1.3	6	2.0	15	4.9
Nervousness	33	5.1	21	3.2	8	1.7	6	2.0	4	1.3
Paresthesia	17	2.6	7	1.1	4	0.8	7	2.3	2	0.6
Somnolence	199	30.6	116	17.8	64	13.4	39	12.7	32	10.4

Source: Table 2 (Attachment 4) in Sponsor submission on May 4, 2001

Review of the above table reveals that all nervous system adverse events that occurred in 2.05 or more of BTDS patients were more common in BTDS patients compared to placebo patients. The majority of these above events, as well as the most common events, are related to the central nervous system. Many of the COSTART terms used (eg, confusion, dizziness, somnolence) are somewhat non-specific. The most common investigator terms corresponding to Confusion were either “confusion” or “disorientation”. The most common investigator terms corresponding to Dizziness were “dizziness” or, less commonly, “lightheadedness.” The most common investigator terms corresponding to Somnolence were either “drowsiness” or “sleepy”. Despite some minor lack of specificity in coding the investigator verbatim terms, central nervous system events are much more common in BTDS-treated patients, regardless of dose, compared to Placebo patients. The high frequency of dizziness (31.2%) and somnolence (30.6%) in the Phase 3 controlled studies are an indication of the central nervous system side effects of the product, which will need to be addressed in the labelling.

Among the adverse events in the table above, most were not rated as severe. Among BTDS-treated patients, severe cases included one case of anxiety (BTD 20 group), three cases of confusion (two at BTDS 10 and one at BTDS 20), one case of depression (BTDS 5), twelve cases of dizziness (7 at BTDS 5, 3 at BTDS 10, and 4 at BTDS 20), one case of hypertonia (BTDS 10), three cases of insomnia(one at BTDS 5 and two at BTDS 20), one case of nervousness (BTDS 5), no cases of paresthesia, eighteen cases of somnolence (8 at BTDS 5, 6 at BTDS 10, and 5 at BTDS 20). Among Placebo patients with the above adverse events, there were two severe case of dizziness and one severe case of somnolence. Thus, common nervous system adverse events were not only notably more frequent in BTDS-treated patients compared to Placebo patients, but were also more likely to be severe in BTDS-treated patients compared to Placebo-treated patients.

Respiratory system adverse events were slightly more common in BTDS-treated patients compared to Placebo-treated patients, with 10.6% BTDS-treated patients having at least one adverse event in this body system compared to 7.1% Placebo-treated patients. The clinically important adverse events of dyspnea, hyperventilation, and hypoventilation are discussed in the review of vital signs (see Section 7.11.3 of this review). Severe adverse events in this body system included one case of asthma (BTDS 20), one case of cough increased (Placebo), one case of hiccup (BTDS 20), and one case of pharyngitis (BTDS 20). In this body system, two serious adverse events were reported – one case of asthma BTDS 20) and one case of lung edema (BTDS 20).

The proportion of BTDS-treated patients with at least one adverse event in the Skin body system (48.3%) was higher than the corresponding proportion among Placebo-treated patients (37.7%). Among skin-related adverse events that were not related to local (ie, patch site) reactions, pruritus was reported in 18.2% of BTDS-treated patients and in 13.6% Placebo-treated patients. While there were no severe cases of pruritus among Placebo-treated patients, there were seven severe cases among BTDS-treated patients – three at the BTDS 5 level, three at the BTDS 10 level, and one at the BTDS 20 level. There were no serious cases of pruritus. Rash was reported in 3.8% of BTDS-treated patients and in 1.9% of Placebo-treated patients. There was one severe case of rash at the BTDS 5 level, one at the BTDS 10 level, and one in the Placebo group. Sweating was reported in 6.6% of BTDS patients and in 2.9% of Placebo patients. There was one severe case in the BTDS group (BTDS 5) and one severe case in the Placebo group.

Adverse events in the Skin body system related to application site reactions include those in the following table.

Adverse Events in the Skin Body System Relating to Application Site Reactions
Population: All Phase 3 Controlled Studies (BP96-0101, BP96-0102, BP96-0604, BP98-1201, and BP99-0203)

Adverse Event	Any BTDS (N=650)		BTDS 5 (N=650)		BTDS 10 (N=478)		BTDS 20 (N=307)		Placebo (N=308)	
	N	%	N	%	N	%	N	%	N	%
Application Site Reaction	1	0.2	0	0	0	0	1	0.3	0	0
Edema at Site	2	0.3	1	0.2	1	0.2	0	0	2	0.6
Erythema at Site	49	7.5	15	2.3	15	3.1	21	6.8	16	5.2
Other Site Reaction	26	4.0	11	1.7	11	2.3	5	1.6	10	3.2
Pruritus at Site	129	19.8	76	11.7	38	7.9	35	11.4	46	14.9
Rash at Site	56	8.6	19	2.9	21	4.4	22	7.2	33	10.7

Source: Table 2 (Attachment 4) in Sponsor submission on May 4, 2001

Review of the above table indicates that "pruritus at site" was more common in BTDS-treated patients compared to Placebo-treated patients. Rash at site, which was less common overall among BTDS-patients compared to Placebo patients, appeared nonetheless to be dose-related. Overall, however, these events may be more related to the application of the patch itself, and not to the buprenorphine content of the patch. It is important to note that the designation of a skin reaction (ie, erythema, pruritus, and rash) as a site reaction as opposed to a non-site reaction was made retrospectively by the Sponsor for Studies BP96-0101, BP96-0102, BP96-0103, BP96-0104, and BP96-0604 based on review of the investigator verbatim term and other comments. In some cases, the comments were not available to the physician doing the coding, so erroneous codes were assigned in at least 11 cases. In studies BP98-1201 and BP99-0203, additional information was captured on the CRF to distinguish between a local site reaction versus a non-site reaction. In some cases, illogical coding still appears (eg, Study BP98-1201, Patient No. 18131, had two adverse events coded to PRURITUS AT SITE – a case of "facial itchiness" and a case of "itchy all over body." In both cases, the information about patch site was listed as "not applicable."

To assess further skin reactions at the patch application site, the Sponsor incorporated periodic standardized assessments of patch-site erythema and edema in the Phase 3 controlled studies, in the open-label study BP96-10103, and in the clinical pharmacology studies. Both edema and erythema were rated on 0- to 4-point scales, wit "0" indicating no reaction and "4" indicating a severe reaction. In the forced-titration studies, moderate-to-severe erythema score were recorded for about 2-3% of BTDS patients and for about 1% of Placebo patients at any time point. In these studies, moderate or severe edema was recorded in no BTDS patients, and in less than 1% of Placebo patients. In the open-label study, moderate application-site erythema was recorded in up to 14% of patients at any time point, while severe application site erythema was recorded in up to 4% of patients at any time point. Moderate edema was recorded in up to 2% of patients and any time point, and severe edema was recorded in less than one percent of patients at any time point. In these analyses, the Sponsor has not summarized the proportion of patients with at least one episode of moderate or severe erythema or edema (see Section 8.13.5.6 of the ISS).

In the clinical pharmacology studies, severe application site erythema was not reported in any subjects. The Sponsor notes in Section 8.13.5.6 of the ISS that the proportion of subjects in the clinical pharmacology studies with application site erythema or edema was similar among those treated with BTDS and those treated with Placebo. However, the supporting tables (8.13.A.4H and 8.13.A.4I) are confusing, in that the total proportion of patients is much greater than 100%, making interpretation of the individual percentage values impossible. Tables 8.13.A.4H and 8.13.A.4I do not match source tables 8.14.1.6.1 and 8.14.1.6.2.

Adverse events in the Special Senses system occurred in 6.2% of BTDS-treated patients and in 5.2% of Placebo-treated patients. Abnormal vision occurred in 1.1% BTDS-treated patients and in 0.6% Placebo-treated patients. Amblyopia occurred in 0.9% BTDS-treated patients and in no Placebo-treated patients. Review of the investigator verbatim terms for both of these COSTART terms reveals that nearly all were cases of either "blurry vision" or "blurred vision". No cases were severe and no cases were serious. Taste perversion occurred in 1.8% of BTDS-treated patients and in 1.6% of Placebo-treated patients.

Adverse events in the Urogenital body system occurred in 4.5% of the BTDS-treated patients and in 2.6% of the Placebo-treated patients. No single adverse event accounted for the majority of these adverse events. Urinary frequency was reported in 0.9% of BTDS-treated patients and in no Placebo-treated patients. Urinary tract infection was reported in 1.5% of BTDS-treated patients and in 1.0% of Placebo-treated patients.

In the Phase 2 post-operative study (BP96-0104) the most common adverse events were those typically associated with opiates, though the frequency of many of these event is confounded by the use of concomitant morphine PCA use. Adverse events occurring in 10% or more of patients in any treatment group are summarized in Table 12.2.2B of the BP96-0104 Study Report, which is reproduced below.

TABLE 12.2.2B.
Study BP96-0104
Adverse Events With ≥10% Incidence in Any Treatment Group, by Treatment:
Intent-to-treat/Safety Population (N = 110)

		TOTAL (N = 110)	Placebo (N = 11)	BTDS 5 (N = 33)	BTDS 10 (N = 33)	BTDS 20 (N = 33)
Body System	Adverse Event	n (%)				
Body as a whole	Asthenia	7 (6%)	1 (9%)	1 (3%)	0	5 (15%)
Digestive	Nausea	29 (26%)	2 (18%)	7 (21%)	12 (36%)	8 (24%)
	Constipation	28 (26%)	3 (27%)	11 (33%)	7 (21%)	7 (21%)
	Dry mouth	15 (14%)	0	4 (12%)	5 (15%)	6 (18%)
	Vomiting	10 (9%)	0	5 (15%)	3 (9%)	2 (6%)
Nervous	Dizziness	19 (17%)	3 (27%)	3 (9%)	7 (21%)	6 (18%)
	Somnolence	13 (12%)	1 (9%)	2 (6%)	5 (15%)	5 (15%)
	Confusion	12 (11%)	0	2 (6%)	2 (6%)	8 (24%)
Skin	Sweating	8 (7%)	0	3 (9%)	5 (15%)	0
	Erythema at site	8 (7%)	2 (18%)	2 (6%)	3 (9%)	1 (3%)

(Cross-reference: Table 14.3.1.1.C2.)
N = Number of patients analyzed in each treatment group.
n = Number of patients reporting the adverse event.

Source: Sponsor Table 12.2.2B in the BP96-0104 Study Report

Review of the above table indicates that the incidence of dizziness, somnolence, and confusion was higher with higher doses of BTDS. Many opioid-related adverse events were more frequent in the BTDS-treated groups than in the placebo-treated group. Dizziness, however, was more common in placebo-treated patients than in BTDS-treated patients. Review of Table 12.2.2D in the BP96-0104 study report indicates that the majority of the adverse events in the table above, with the exception of sweating, were judged to be related to study medication.

Adverse events in the open-label study BP96-0103 occurring in 10% or more of the study population are summarized in Table 8.13.5.3E in the ISS. The adverse event profile in the open-label study BP96-0103 was similar to that in the controlled Phase 3 studies. Adverse events occurring with a frequency of 5% or higher at any BTDS dose are summarized in the table below.

Frequency of Adverse Events Occurring in More than 5% of BTDS-treated Patients in the Open-label Study BP96-0103	
Adverse Event (COSTART Term)	Any BTDS Dose
Pruritus	35.9
Nausea	35.7
Consipation	34.9
Somnolence	28.4
Dry Mouth	27.9
Dizziness	24.7
Rash	20.1
Application Site Reaction	18.8
Vomiting	14.3
Headache	13.5
Insomnia	5.5
Source: Table 4 in Sponsor Submission o f July 26, 2000	

The above adverse events are similar in nature to the adverse events in the controlled Phase 3 studies.

Adverse events occurring in at lest 10% of subject in the clinical pharmacology studies are summarized on Table 8.13.5.3F in the ISS, which is reproduced below.

TABLE 8.13.5.3F.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Incidence of Adverse Events Reported by ≥ 10% of Subjects[a] in at Least 1 BTDS Treatment
Safety Population (N = 449[b])
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1204, and BP99-0204 Combined

	No. (%) of Subjects							
	Any BTDS	BTDS 5	2 x BTDS 5	BTDS 10	BTDS 20	BIV	Duragesic®	Placebo[c]
COSTART Term	N = 377	N = 40	N = 26	N = 261	N = 102	N = 83	N = 24	N = 24
Headache	153 (41%)	17 (43%)	12 (46%)	106 (41%)	38 (37%)	11 (13%)	4 (17%)	3 (13%)
Nausea	150 (40%)	7 (18%)	13 (50%)	102 (39%)	53 (52%)	26 (31%)	11 (46%)	1 (4%)
Dizziness	133 (35%)	3 (8%)	10 (39%)	82 (31%)	56 (55%)	39 (47%)	7 (29%)	2 (8%)
Vomiting	104 (28%)	6 (15%)	8 (31%)	66 (25%)	39 (38%)	41 (49%)	5 (21%)	0
Constipation	86 (23%)	3 (8%)	1 (4%)	48 (18%)	34 (33%)	2 (2%)	3 (13%)	1 (4%)
Somnolence	60 (16%)	10 (25%)	1 (4%)	35 (13%)	14 (14%)	24 (29%)	2 (8%)	0
Asthenia	50 (13%)	10 (25%)	1 (4%)	27 (10%)	13 (13%)	1 (1%)	2 (8%)	0
Pruritus	43 (11%)	9 (23%)	0	18 (7%)	16 (16%)	16 (19%)	1 (4%)	2 (8%)
Pruritus at site	37 (10%)	0	3 (12%)	24 (9%)	14 (14%)	0	0	1 (4%)
Pruritus (nonsite)	33 (9%)	0	5 (19%)	23 (9%)	14 (14%)	18 (22%)	1 (4%)	0
Abdominal pain	20 (5%)	0	1 (4%)	3 (1%)	16 (16%)	2 (2%)	1 (4%)	1 (4%)
Rash at site	25 (7%)	6 (15%)	0	12 (5%)	7 (7%)	0	0	1 (4%)
Vasodilation	17 (5%)	0	3 (12%)	7 (3%)	10 (10%)	4 (5%)	0	0

(Cross-reference: Table 8.14.1.2.3.1.)
[a]Based on the population valid for safety in all clinical pharmacology studies combined.
[b]Of the total of 449 subjects, 377 unique subjects received BTDS, 24 BIV, 24 Duragesic®, and 24 placebo.
[c]There was no true placebo group. All subjects who received placebo TDS during BP97-1001 or BP98-0202 received either midazolam or prochlorperazine.

Source: Sponsor Table 8.13.5.3F in the ISS

7.9.4 BTDS-Placebo Differences in Adverse Event Rates

To compare the frequency of common adverse events between BTDS-treated patients and Placebo-treated patients, the Agency asked the Sponsor to analyze adverse event frequency rates for the pooled four Phase 3 placebo-controlled trials. This analysis was submitted to the Agency on July 26, 2001. These data indicate that with one exception (rash at site) all adverse events that occurred in more than 5% of BTDS-treated patients were more common in BTDS-treated patients than in Placebo-treated patients. These data are summarized in the table below.

BTDS-Placebo Difference for All Adverse Events Occurring in More than 5% of BTDS-treated Patients in the Four Phase 3 Placebo-Controlled Trials			
Adverse Event (COSTART Term)	Any BTDS Dose	Placebo	Difference (BTDS-Placebo)
Nausea	37.5	14.0	23.5
Dizziness	35.7	14.6	21.1
Somnolence	34.5	10.4	24.1
Headache	30.8	18.2	12.6
Consipation	29.6	10.7	18.9
Dry Mouth	27.1	13.3	13.7
Pruritus	23.1	13.6	9.5
Pruritus at Site	18.2	14.9	3.3
Vomiting	16.7	3.9	12.8
Asthenia	10.4	5.2	5.2
Dyspepsia	6.9	5.5	1.3
Erythema at Site	6.9	5.2	1.7
Sweating	6.9	2.9	3.9
Diarrhea	6.7	6.2	0.5
Insomnia	6.3	4.9	1.4
Rash at Site	6.1	10.7	-4.6
Nervousness	5.7	1.3	4.4
Source: Table 3 in Sponsor Submission o f July 26, 2000			

Review of the above table is notable for the fact that many of the above adverse events are those that can be expected to occur in patients treated with opioid analgesics.

7.9.5 Adverse Events by Severity

Severity of adverse events was rated by the investigator as mild, moderate, or severe. In the titration to effect studies, adverse events whose incidence in the BTDS groups was 3% or higher included nausea, headache, dizziness, somnolence, peripheral edema, vomiting, constipation, pruritus at site, and asthenia. The incidence rates in the BTDS group for these events were generally similar to the corresponding rates in the Oxy/APAP and HCD/APAP groups, and were generally higher than the rates in the Placebo group (see Table 8.13.5.5A in the ISS). The same general pattern was seen in the forced-titration studies (see Table 8.13.5.5B in the ISS). Most of the adverse events whose frequency of moderate or severe events was 3% or higher are those generally associated with opioid usage.

Adverse events whose frequency of moderate or severe events was 3% or higher in the clinical pharmacology studies included headache (13% moderate, 3% severe), nausea (13%, 2%), vomiting (9%, 1%), dizziness (7%, 1%), constipation (7%, 1%), somnolence (5%, <1%), asthenia (3%, 1%), and non-site pruritus (3%, 1%). These rates were higher than the corresponding rates

among Placebo-treated subjects, whose rate of moderate or severe adverse events was low (see Table 8.13.5.5C in the ISS).

7.9.6 Adverse Events Judged to be Related to Treatment

Investigators assessed the relationship of study drug to an adverse event as none, possibly, probably, or definitely related to study drug. For both the titration-to-effect studies and the forced-titration studies, the body systems with the highest frequencies of adverse events judged to be related (ie, either possibly, probably, or definitely) were the digestive, nervous, skin, and body as a whole systems. The same pattern was seen in the open-label study. In the Phase 2 study, the respiratory body system had a high frequency of treatment-related adverse events, in addition to the other body systems. These body systems contain nearly all of the adverse events commonly associated with opioids.

7.9.7 Time Course of Adverse Events

To characterize the time course of onset for common adverse events, the Sponsor used Kaplan-Meier methodology and calculation of hazard rate per day measure the proportion of patients with the event over time and the rate of new events over time. These analyses were performed for nausea, vomiting, dry mouth, dizziness, somnolence constipation, and headache.

For the titration-to-effect studies, the Sponsor claims that the highest rates for nausea and headache occurred in the first five days, while the highest rates for the other adverse events occurred in the first 10 days.

For the forced-titration studies, the Sponsor claims that the highest rates for all analyzed adverse events except constipation were in the first five days. The highest rates for constipation were at about 12 days. These analyses were not further analyzed by the Agency.

7.9.8 Relationship of BTDS Dose to Adverse Events

The Sponsor's analyses of adverse events and the presentation of adverse event data did not consider BTDS dose level. Specifically, the number and frequency of adverse events was not specified by dose level. At the request of the Agency, the Sponsor provided frequency tables of adverse events by the dose at which the event occurred. The table below summarizes the frequency of adverse common adverse events by dose in the pooled four Phase 3 placebo-controlled studies.

Adverse Event	Any BTDS (N=510)	BTDS 5 (N=510)	BTDS 10 (N=351)	BTDS 20 (N=200)	Placebo (N=308)
	%	%	%	%	%
Asthenia	10.4	6.1	5.7	4.0	5.2
Headache	30.8	23.3	11.7	9.5	18.2
Pain	4.5	2.5	2.0	2.0	5.2
Constipation	29.6	17.3	12.0	14.0	10.7
Diarrhea	6.7	4.9	2.0	2.5	6.2
Dry Mouth	27.1	17.1	9.1	11.0	13.3
Dyspepsia	6.9	4.5	2.8	2.5	5.5
Nausea	37.5	22.0	16.5	19.5	14.0
Vomiting	16.7	7.5	8.0	12.5	3.9
Peripheral Edema	4.1	1.4	2.3	4.0	1.3
Dizziness	35.7	22.2	16.2	16.5	14.6
Insomnia	6.3	4.7	1.1	2.5	4.9
Nervousness	5.7	3.5	1.7	3.0	1.3
Somnolence	34.5	21.8	14.5	16.0	10.4
Erythema at Site	6.9	2.9	3.4	5.0	5.2
Other Site Reaction	4.3	2.0	2.6	2.0	3.2
Pruritus	23.1	14.9	9.7	9.0	13.6
Prutitus at Site	18.2	12.7	7.7	6.5	14.9
Rash	4.1	2.0	2.0	3.0	1.9
Rash at Site	6.1	2.9	3.1	3.0	10.7
Sweating	6.9	3.5	2.6	4.0	2.9
Source: Table 2 in Sponsor Submission of July 26, 2001					

Review of the above table indicates that there is not a trend of increasing frequency of common adverse events with increasing dose of BTDS. In fact, many adverse events have a higher frequency at the BTDS 5 dose level than at any other dose level. Because patients spent variable amount of time at the different dose levels (eg, all patients wore the BTDS 5 patch for at least a few days, while many never wore the BTDS 20 patch), a simple calculation of rates may not be sufficient to analyze the relationship of dose to development of adverse events. At the request of the Agency, the Sponsor provided person-time exposure for all studies. The table below uses the number of reported adverse events at each dose level (not the number of patients with the adverse event at each dose level) to characterize the number of event per person-year of exposure.

Rates of Common Adverse Events Based on Person-Years of Exposure in the Four Phase 3 Placebo-Controlled Trials Studies BP96-0101, BP96-0102, BP96-0604, and BP99-0203										
	Any BTDS (47.5 Person-yrs)		BTDS 5 (18.3 Person-yrs)		BTDS 10 (16.9 Person-yrs)		BTDS 20 (12.0 Person-yrs)		Placebo (25. 9 Person-yrs)	
	# Events	Events/yr	# Events	Events/yr	# Events	Events/yr	# Events	Events/yr	# Events	Events/yr
Asthenia	81	1.71	40	2.19	32	1.90	9	0.75	23	0.89
Headache	257	5.41	164	8.98	67	3.97	26	2.16	78	3.01
Pain	31	0.65	20	1.09	7	0.42	4	0.33	20	0.77
Constipation	178	3.75	101	5.53	46	2.73	31	2.58	31	1.20
Diarrhea	45	0.95	33	1.81	7	0.42	5	0.42	20	0.77
Dry Mouth	151	3.18	95	5.20	33	1.96	23	1.91	41	1.58
Dyspepsia	49	1.03	32	1.75	12	0.71	5	0.42	18	0.69
Nausea	262	5.52	133	7.28	72	4.27	57	4.74	57	2.20
Vomiting	98	2.06	40	2.19	31	1.84	27	2.24	12	0.46
Peripheral Edema	24	0.51	7	0.38	9	0.53	8	0.67	4	0.15
Dizziness	251	5.29	140	7.66	69	4.09	42	3.49	54	2.08
Insomnia	42	0.88	28	1.53	7	0.42	7	0.58	19	0.73
Nervousness	36	0.76	24	1.31	6	0.36	6	0.50	5	0.19
Somnolence	236	4.97	131	7.17	62	3.68	43	3.57	42	1.62
Erythema at Site	45	0.95	20	1.09	15	0.89	10	0.83	19	0.73
Other Site Reaction	27	0.57	11	0.60	10	0.59	6	0.50	15	0.58
Pruritus	156	3.29	81	4.43	49	2.91	26	2.16	48	1.85
Prutitus at Site	122	2.57	75	4.11	34	2.02	13	1.08	51	1.97
Rash	23	0.48	10	0.55	7	0.42	6	0.50	6	0.23
Rash at Site	40	0.84	20	1.09	12	0.71	8	0.67	53	2.05
Sweating	38	0.80	18	0.99	11	0.65	9	0.75	9	0.35
Total Events	2786	58.69	1538	84.18	730	43.30	518	43.06	862	33.27
Source: Number of events taken from Table 2 (Attachment 4) in Sponsor submission of July 26, 2001 Person-years of exposure derived from data submitted in Sponsor submission of July 8, 2001										

Review of the above table indicates that for many adverse events, the risk is highest at the BTDS 5 level, and decreases at the two higher dose levels. This finding is consistent with the Sponsor's analysis that many of the common adverse events occur early in the course of treatment.

7.10 Laboratory Findings

7.10.1 Extent of Laboratory Testing in the Development Program

In the adequate and well-controlled Phase 2 (BP96-0104) and Phase 3 (BP96-0101, BP96-0102, BP96-0604, BP98-1201, and BP99-0203) studies, clinical laboratory tests were conducted at screening and at the end of the study or at early termination.

In the Phase 3 open-label study BP96-0103, clinical laboratory tests were conducted at baseline, every 12 months, and at the end of the study or at the time of early termination. For some sites in the open-label study, laboratory tests were performed by local laboratories, while for other sites laboratory tests were preformed at a central laboratory.

For the clinical pharmacology studies, clinical laboratory tests were conducted at screening and at the end of the study or at early termination. In BP97-0501, laboratory tests were also conducted preapplication for the BTDS groups, and predose for the BIV group.

7.10.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The Sponsor has analyzed laboratory data in the following three ways:

- Analysis of changes from screening to final visit, to assess laboratory values over time. In addition to the mean change, the standard error (SE) and the 95% confidence interval were summarized.
- Shift table analyses that categorized laboratory values as normal, high, or low in order to evaluate individual patient changes from screening to the end of the study.
- Identification of individual clinically significant laboratory abnormalites.

Reference ranges for all laboratory values are contained in the appendices of the individual study reports. The Sponsor-defined alert ranges, which are predefined ranges for clinical laboratory values falling outside of the reference range, are listed in Sponsor Table 8.13.7.2 in the ISS, which is reproduced below:

TABLE 8.13.7.2.
BTDS Integrated Summary of Safety: Phase 3 Adequate and Well-controlled Studies
Sponsor-defined Alert Ranges for Clinical Laboratory Values
(b) (4)

Hematology Panel	>/<[a]	Alert Range	Chemistry Panel	>/<[a]	Alert Range
Red cell count (x 10^6/mm^3)	<	3.4	Glucose (mg/dL)	<	45
Hemoglobin (g/dL)	<	10.0		>	200
Hematocrit (%)	<	32.0	Sodium (mEq/L)	<	125
Platelet count (x 10^3/mm^3)	<	115		>	160
	>	450	Potassium (mEq/L)	<	3.0
White cell count (x 10^3/mm^3)	<	3.0		>	6.0
	>	12.9	Chloride (mEq/L)	<	80
Neutrophils, segmented (%)	<	28.0		>	120
	>	80.0	CO_2 (mEq/L)	<	12
Lymphocytes (%)	<	13.0		>	50
	>	60.0	Uric acid (mg/dL)	>	9.0
Monocytes (%)	>	15.0	Protein (g/dL)	<	5.9
Eosinophils (%)	>	10.0	Albumin (g/dL)	<	3.0
Basophils (%)	>	2.0		>	5.0
			Globulin (g/dL)	<	2.2
				>	4.2
			Calcium (mg/dL)	<	8.0
				>	10.8
			Phosphorus, inorganic (mg/dL)	<	2.0
				>	4.7
			Alkaline phosphatase (U/L)	>	135
			AST (SGOT) (U/L)	>	65
			ALT (SGPT) (U/L)	>	80
			LDH (U/L)	>	300
			Bilirubin, total (mg/dL)	>	1.7
			BUN (mg/dL)	>	30
			Creatinine (mg/dL)	>	1.7
			Triglycerides (mg/dL)	>	700
			Cholesterol, total (mg/dL)	>	350

[a]Direction of concern.
Source: Sponsor Table 8.13.7.2 in the ISS

7.10.3 Clinical Laboratory Values Over Time

Apart from some mean changes from baseline that may be the result of erroneous laboratory data (see correspondence to Sponsor on July 9, 2001), there were no significant mean changes from baseline in any laboratory measures in the clinical pharmacology studies, controlled Phase 3 studies, or open-label Phase 3 study. Mean changes from baseline were not calculated for the Phase 2 study BP96-0104. The Sponsor has been requested to perform this analysis.

7.10.4 Shift Tables of Laboratory Values

Shift tables were used to summarize changes in laboratory values characterized as low, normal, or high from screening to the end of the study.

In the titration-to-effect studies, shifts from normal to low were as frequent or less frequent in the BTDS group compared to the other treatment groups. For selected laboratory measures, the Sponsor summarized the frequencies of shifts form normal to low in Sponsor Table 8.13.7.2.2B.1, which upon review was found to have discrepancies with regard to its source, Table 8.14.2.3.1.2. The table below is a modification of Sponsor Table 8.13.7.2B.1, reflecting the data in the source table.

Shift Tables of Patient Changes[a] by Treatment: Titration-to-Effect Studies
Shifts From Normal to Low
Safety Population (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

	No. (%) of Patients			
	BTDS	Oxycodone/ APAP	Hydrocodone/ APAP	Placebo
Normal to Low	N = 338	N = 43	N = 130	N = 208
HEMATOLOGY				
Hemoglobin	24 (8%)	3 (9%)	16 (13%)	8 (4%)
Hematocrit	25 (8%)	2 (6%)	15 (13%)	7 (4%)
WBC	5 (2%)	0	3 (3%)	3 (2%)
Platelets	2 (<1%)	0	1 (<1%)	1 (<1%)
CLINICAL CHEMISTRY				
Electrolytes				
Sodium	4 (1%)	1 (3%)	2 (2%)	1 (<1%)
Potassium	3 (1%)	0	1 (<1%)	1 (<1%)
Chloride	2 (<1%)	1 (3%)	0	0
CO_2	4 (1%)	0	5 (4%)	9 (5%)
Metabolic Tests				
Glucose	4 (1%)	0	3 (3%)	3 (2%)
Calcium	0	0	0	0
Phosphorus	7 (2%)	0	1 (<1%)	3 (2%)

(Cross-reference: Table 8.14.2.3.1.2.)

[a]Patients with laboratory values at both screening and final visits.

Source: Sponsor Table 8.13.7.2.2B.1 and Table 8.14.2.3.1.2

Review of the above table is notable for the fact that the frequency of shifts in hemoglobin and hematocrit from normal to low is higher for the BTDS group (8% for both tests) than it is for Placebo (4% for both tests). In the Placebo group, the mean change from baseline in the titration-to-effect studies was –0.06 gm/dl for hemoglobin and –0.22% for hematocrit. The corresponding mean changes form baseline in the BTDS group were -0.3 gm/dl for hemoglobin and –0.99% for hematocrit. The frequency of shifts from normal to low for other lab tests is similar for the BTDS group and the Placebo group.

The frequency of shifts from normal to low was also examined in the forced-titration studies. Frequencies of shifts for selected laboratory tests are presented in Sponsor Table 8.13.7.2.2C.1, which is reproduced below:

TABLE 8.13.7.2.2C.1.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Shift Tables of Patient Changes[a] by Treatment: Forced-Titration Studies
Shifts From Normal to Low
Safety Population (N = 519)
BP96-0101 and BP96-0102 Combined

	No. (%) of Patients					
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo
Normal to Low	N = 312	N = 105	N = 103	N = 104	N = 107	N = 100
HEMATOLOGY						
Hemoglobin	19 (7%)	3 (3%)	7 (8%)	9 (10%)	6 (6%)	4 (5%)
Hematocrit	18 (7%)	2 (3%)	5 (6%)	11 (12%)	10 (10%)	8 (9%)
WBC	8 (3%)	4 (5%)	1 (1%)	3 (3%)	0	0
Platelets	4 (2%)	1 (1%)	0	3 (3%)	1 (1%)	0
CLINICAL CHEMISTRY						
Electrolytes						
Sodium	4 (2%)	0	2 (2%)	2 (2%)	4 (4%)	1 (1%)
Potassium	4 (2%)	1 (1%)	3 (3%)	0	3 (3%)	2 (2%)
Chloride	3 (1%)	3 (4%)	0	0	1 (1%)	2 (2%)
CO_2	16 (9%)	3 (5%)	6 (10%)	7 (12%)	3 (4%)	0
Metabolic Tests						
Glucose	1 (<1%)	0	0	1 (1%)	4 (4%)	3 (3%)
Calcium	5 (2%)	0	0	5 (6%)	1 (1%)	3 (3%)
Phosphorus	7 (3%)	3 (4%)	3 (4%)	1 (1%)	1 (1%)	1 (1%)

(Cross-reference: Table 8.14.2.3.1.1.)
[a]Patients with laboratory values at both screening and final visits.
Source: Sponsor Table 8.13.7.2.2c.1 in the ISS

In the above table, the increased frequency of shifts from normal to low in the Total BTDS group, relative to placebo, in hemoglobin noted in the titration-to-effect studies is also noted in the forced-titration studies. However, in the titration-to-effect studies, the frequency of shifts from normal to low in hematocrit were higher in the BTDS group than in the Placebo group, an observation that was not confirmed when comparing the Total BTDS group to the Placebo group in the forced-titration studies. Data in the above table are also notable for the increase in frequencies of shifts from normal to low for hemoglobin and hematocrit with increasing assigned dose (ie, BTDS 5, BTDS 10 and BTDS 20). Because the above table reports frequencies for assigned dose groups (and not actual doses received), the above data can not be interpreted as a dose-dependent reduction in hemoglobin or hematocrit. However, to the extent that patients actually received the dose they were assigned, the data raise the possibility that a dose-dependent relationship may be at work. Review of the mean changes from baseline for hemoglobin and, to a lesser extent hematocrit, reveals the same pattern:

Mean Change from Baseline in hemoglobin and Hematocrit BP96-0101 and BP96-0102 Combined						
	Mean Change from Baseline (SE)					
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo
	N = 312	N = 105	N = 103	N = 104	N = 107	N = 100
Hemoglobin	-0.24 (0.05)	-0.08 (0.11)	-0.18 (0.08)	-0.45 (0.09)	-0.24 (0.07)	-0.06 (0.08)
Hematocrit	0.78 (1.32)^	3.85 (4.02)*	-0.41 (0.24)	-0.99 (0.26)	-0.6 (0.23)	-0.11 (0.25)
Source: Sponsor Table 8.13.A.6B. in the ISS Reviewer Notes: ^Presumably influenced by the presence of clinically implausible data in the BTDS 5 group. *Presumed to be an erroneous value, based on clinically implausible data which Sponsor has been asked to correct.						

The clinical significance of these changes in hemoglobin and hematocrit in the BTDS group, which are generally in the same range as the corresponding changes in the Oxy/APAP and HCD/APAP groups, is not obvious. Further analyses, based on actual doses that patients received, will be necessary to determine if there is a dose-dependent reduction in hemoglobin and hematocrit. Finally, the effect of clinically implausible data that are included in the analyses limits any conclusions.

Of note, the frequency of shifts from normal to low in platelets in the Total BTDS group (n=4, 2%) is accounted for mainly by a relatively high frequency of shifts from normal to low in the BTDS 20 group (n=3, 3%). The mean change from baseline for platelets in the BTDS 20 group was –8.65 x 10^3/mm^3, compared to –2.78 x 10^3/mm^3 , -3.04 x 10^3/mm^3, and +3.32 x 10^3/mm^3 for the BTDS 5, BTDS 10, and Placebo groups, respectively.

The frequencies of shifts from normal to low were similar for the BTDS groups and the Placebo group for all other laboratory tests.

The frequencies of shifts from normal to high for selected laboratory tests in the titration-to-effect studies were summarized in Sponsor Table 8.13.7.2.2B.2 in the ISS, which is summarized below:

TABLE 8.13.7.2.2B.2
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Shift Tables of Patient Changes[a] by Treatment: Titration-to-Effect Studies
Shifts From Normal to High
Safety Population (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

	No. (%) of Patients			
	BTDS	Oxycodone/ APAP	Hydrocodone/ APAP	Placebo
Normal to High	N = 338	N = 43	N = 130	N = 208
HEMATOLOGY				
WBC	7 (2%)	2 (6%)	1 (<1%)	7 (4%)
Platelets	3 (1%)	0	1 (<1%)	2 (1%)
CLINICAL CHEMISTRY				
Renal Function Tests				
BUN	7 (2%)	1 (3%)	6 (5%)	5 (3%)
Creatinine	2 (<1%)	0	1 (<1%)	0
Electrolytes				
Sodium	4 (1%)	0	1 (<1%)	2 (1%)
Potassium	2 (<1%)	0	5 (4%)	3 (2%)
Chloride	15 (5%)	1 (3%)	8 (7%)	7 (4%)
CO_2	0	0	3 (3%)	2 (1%)
Metabolic Tests				
Glucose	34 (11%)	1 (3%)	16 (14%)	22 (12%)
Calcium	3 (1%)	0	3 (3%)	1 (<1%)
Phosphorus	14 (5%)	1 (3%)	2 (2%)	10 (6%)
Uric acid	5 (2%)	1 (3%)	1 (<1%)	5 (3%)
Cholesterol	13 (4%)	0	11 (9%)	8 (4%)
Triglycerides	29 (10%)	2 (6%)	27 (23%)	17 (9%)
Hepatic Function Tests				
AST (SGOT)	9 (3%)	1 (3%)	1 (<1%)	0
ALT (SGPT)	13 (4%)	2 (6%)	3 (3%)	2 (1%)
Alkaline phosphatase	2 (<1%)	0	0	2 (1%)
Total bilirubin	2 (<1%)	0	1 (<1%)	0
LDH	6 (2%)	0	3 (3%)	1 (<1%)

(Cross-reference: Table 8.14.2.3.1.2.)
[a]Patients with laboratory values at both screening and final visits.

For the laboratory tests related to hematology, renal function, electrolytes, and metabolism, the frequency of shifts from normal to high in the BTDS group was similar to the frequency in the Placebo group. For the hepatic function tests, the frequency of shifts in AST and ALT from normal to high was higher for the BTDS group (3% and 4% for AST and ALT, respectively) than for the Placebo group. (0% and 1% for AST and ALT, respectively). The frequencies of shifts from normal to high for total bilirubin and LDH are slightly higher for BTDS than Placebo. The frequency of shifts from normal to high for alkaline phosphatase are similar for the BTDS and Placebo groups.

TABLE 8.13.7.2.2C.2.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Shift Tables of Patient Changes[a] by Treatment: Forced-Titration Studies
Shifts From Normal to High
Safety Population (N = 519)
BP96-0101 and BP96-0102 Combined

	No. (%) of Patients					
	Total BTDS	BTDS 5	BTDS 10	BTDS 20	Oxy/APAP	Placebo
Normal to High	N = 312	N = 105	N = 103	N = 104	N = 107	N = 100
HEMATOLOGY						
WBC	8 (3%)	3 (3%)	0	3 (3%)	3 (3%)	0
Platelets	1 (<1%)	1 (1%)	0	0	2 (2%)	0
CLINICAL CHEMISTRY						
Renal Function Tests						
BUN	13 (5%)	4 (5%)	4 (4%)	5 (5%)	9 (9%)	4 (5%)
Creatinine	5 (2%)	1 (1%)	2 (2%)	2 (2%)	1 (1%)	1 (1%)
Electrolytes						
Sodium	2 (<1%)	1 (1%)	0	1 (1%)	2 (2%)	0
Potassium	6 (2%)	2 (2%)	2 (2%)	2 (2%)	4 (4%)	0
Chloride	7 (3%)	1 (1%)	1 (1%)	5 (6%)	1 (1%)	1 (1%)
CO_2	5 (3%)	2 (3%)	2 (3%)	1 (2%)	1 (2%)	4 (7%)
Metabolic Tests						
Glucose	29 (11%)	11 (13%)	11 (12%)	7 (8%)	14 (14%)	11 (13%)
Calcium	3 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	4 (5%)
Phosphorus	9 (4%)	4 (5%)	4 (5%)	1 (1%)	2 (2%)	4 (5%)
Uric acid	4 (2%)	2 (2%)	2 (2%)	0	4 (4%)	0
Cholesterol	16 (6%)	3 (4%)	8 (9%)	5 (5%)	7 (7%)	4 (5%)
Triglycerides	24 (10%)	7 (9%)	9 (11%)	8 (10%)	6 (7%)	8 (11%)
Hepatic Function Tests						
AST (SGOT)	5 (2%)	3 (4%)	2 (2%)	0	1 (1%)	3 (3%)
ALT (SGPT)	8 (3%)	2 (2%)	5 (6%)	1 (1%)	1 (1%)	1 (1%)
Alkaline phosphatase	6 (2%)	3 (4%)	2 (2%)	1 (1%)	1 (1%)	1 (1%)
Total bilirubin	0	0	0	0	0	1 (1%)
LDH	7 (3%)	2 (2%)	0	5 (5%)	3 (3%)	1 (1%)

(Cross-reference: Table 8.14.2.3.1.1.)
[a]Patients with laboratory values at both screening and final visits.

Source: Sponsor Table 8.13.7.2.2C.2 in the ISS

Review of the above table indicates that 8 patients (3%) in the Total BTDS group had a shift from normal to high in WBC, while none in the Placebo group had such a shift. While the Sponsor's table notes that no patients in the BTDS 10 group had such a shift, the Sponsor's source table (8.14.2.3.1.1) notes that 2 patients in this group had such a shift, a finding that is consistent with 8 patients in the Total BTDS group having had such a shift.

For the electrolyte tests sodium, potassium, and chloride, the frequencies of shifts from normal to high were slightly higher for the Total BTDS group than for the Placebo group. For carbon dioxide, the frequencies of shifts from normal to high were higher for the Placebo group than for the Total BTDS group. Apart from the 6% shift from normal to high in chloride in the group assigned to BTDS 20, there were no significant differences in the frequencies of shifts from normal to high in electrolytes among the three assigned dose groups.

Among the metabolic tests, the frequency of shifts from normal to high was higher in the Total BTDS group, compared to the Placebo group, for uric acid. For the other metabolic tests, the frequencies of shifts from normal to high were similar between the Total BTDS group and the Placebo group.

Among the hepatic function tests, the frequencies of shifts from normal to high were slightly higher in the Total BTDS group, compared to the Placebo group, for ALT, alkaline phosphatase, and LDH. Frequencies of shifts from normal to high were lower in the Total BTDS group, relative to the Placebo group, for AST and total bilirubin. For all hepatic function tests, the differences in these frequencies between the Total BTDS group and the Placebo group were small, and there was no clear trend in frequencies based on assigned BTDS dose.

Shifts from normal to low or from normal to high in the open-label study BP96-0103 are presented in Sponsor Table 8.13.7.2.2D in the ISS, which is reproduced below:

TABLE 8.13.7.2.2D.
BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103)
Incidence of Laboratory Shifts From Normal at Baseline to Worst Case
Intent-to-Treat/Safety Population (N = 384)

Laboratory Test	No./Total No.[a] (%) of Patients			
	Normal to Low		Normal to High	
HEMATOLOGY				
Hemoglobin	11/310	(4%)	0	
Hematocrit	11/310	(4%)	1/310	(<1%)
Platelets	6/310	(2%)	6/310	(2%)
WBC	3/310	(<1%)	15/310	(5%)
CLINICAL CHEMISTRY				
Renal Function Tests				
BUN	1/307	(<1%)	5/307	(2%)
Creatinine	22/307	(7%)	10/307	(3%)
Electrolytes				
Sodium	5/306	(2%)	10/306	(3%)
Potassium	4/305	(1%)	8/305	(3%)
Chloride	3/298	(1%)	10/298	(3%)
CO_2	1/206	(<1%)	16/206	(8%)
Metabolic Tests				
Glucose	10/307	(3%)	23/307	(7%)
Calcium	5/302	(2%)	11/302	(4%)
Phosphate	5/283	(2%)	10/283	(4%)
Uric acid	9/290	(3 %)	0	
Triglycerides	0		34/275	(12%)
Cholesterol	0		19/292	(7%)
Hepatic Function Tests				
Alkaline phosphatase	2/301	(<1%)	1/301	(<1%)
AST (SGOT)	NA[b]		7/303	(2%)
ALT (SGPT)	NA		11/292	(4%)
Total bilirubin	NA		4/302	(1%)

(Cross-reference: Tables 8.14.3.3.3.1 and 8.14.3.3.3.2)
[a]The population used as the denominator for calculating percentages could differ for each laboratory variable and was based on the total number of patients with the particular laboratory value at both baseline and at 12 months and/or final visit. The numerator was the number of patients with a laboratory value that shifted from normal to low or normal to high.
[b]NA = not applicable because the lower reference range is 0.

Source: Sponsor Table 8.13.7.2.2D in the ISS

In general, the frequencies of shifts from normal to low and from normal to high in the open-label study BP96-0103 were in the same range as those observed in the BTDS patients in the controlled Phase 3 studies. Some exceptions include slight higher frequencies of shifts from normal to high in the open-label study for WBC (5%), platelets (2%), creatinine (3%), calcium (4%), ALT (4%), and total bilirubin (1%).

Shifts from normal to low or from normal to high in the Phase 2 study BP96-0104 are presented in Sponsor Table 12.4.2.2 in the BP96-0104 Study Report, which is reproduced below:

TABLE 12.4.2.2.
Study BP96-0104
Laboratory Values That Changed From Normal at Screening to Abnormal at End of Study in
≥ 3 Patients in Any Treatment Group
Intent-to-treat/Safety Population (N = 110)

	Placebo	BTDS 5		BTDS 10	BTDS 20
Laboratory Value	(N = 11)[a]	(N = 33)[a]		(N = 33)	(N = 33)
Normal to Low			n (%)[b]		
Hematology					
RBC ($\times 10^6/mm^3$)	4/11 (36%)	15/32 (47%)		15/33 (46%)	18/33 (55%)
Hemoglobin (gm/dL)	5/11 (46%)	19/32 (59%)		17/33 (52%)	20/33 (61%)
Hematocrit (%)	2/11 (18%)	11/32 (34%)		11/33 (33%)	10/33 (30%)
Lymphocytes (%)	4/11 (36%)	11/32 (34%)		14/33 (43%)	15/33 (46%)
Blood Chemistry					
BUN (mg/dL)	3/11 (27%)	2/32 (6%)		1/33 (3%)	3/33 (9%)
Creatinine (mg/dL)	1/11 (9%)	1/32 (3%)		1/33 (3%)	3/33 (9%)
Sodium (mEq/L)	2/11 (18%)	6/32 (19%)		6/33 (18%)	9/33 (27%)
Potassium (mEq/L)	1/11 (9%)	9/32 (28%)		10/33 (30%)	6/33 (18%)
Chloride (mEq/L)	2/11 (18%)	5/32 (16%)		6/33 (18%)	10/33 (30%)
CO_2 (mEq/L)	0/11 (0%)	2/32 (6%)		3/33 (9%)	0/33 (0%)
Uric acid (mg/dL)	2/11 (18%)	5/32 (16%)		5/32 (16%)	7/33 (21%)
Total protein (g/dL)	6/11 (55%)	20/32 (63%)		26/32 (81%)	21/33 (64%)
Albumin (g/dL)	9/11 (82%)	28/32 (88%)		26/32 (81%)	25/33 (76%)
A/G ratio	7/11 (64%)	20/32 (63%)		19/32 (59%)	20/33 (61%)
Calcium (mg/dL)	6/11 (55%)	12/32 (38%)		21/32 (66%)	17/33 (52%)
Phosphate (mg/dL)	2/11 (18%)	8/32 (25%)		10/32 (31%)	10/33 (30%)
Alkaline phosphatase (U/L)	0/11 (0%)	0/32 (0%)		3/32 (9%)	1/33 (3%)
AST/(SGOT) (U/L)	0/11 (0%)	0/32 (0%)		3/32 (9%)	1/33 (3%)
ALT/(SGPT) (U/L)	3/11 (27%)	6/32 (19%)		2/32 (6%)	2/33 (6%)
Cholesterol (mg/dL)	0/11 (0%)	4/32 (13%)		10/32 (31%)	8/33 (24%)
Urinalysis					
Specific gravity	1/9 (11%)	12/32 (38%)		14/31 (45%)	15/28 (54%)
Normal to High					
Hematology					
WBC ($\times 10^3/mm^3$)	0/11 (0%)	6/32 (19%)		11/33 (33%)	5/33 (15%)
Neutrophils (%)	0/11 (0%)	3/32 (9%)		4/33 (12%)	4/33 (12%)
Bands (%)	1/10 (10%)	0/32 (0%)		3/32 (9%)	1/33 (3%)
Monocytes (%)	4/10 (40%)	8/32 (25%)		8/33 (24%)	12/33 (36%)
Blood Chemistry					
Glucose (mg/dL)	5/11 (46%)	20/32 (63%)		13/33 (39%)	17/33 (52%)
Creatinine (mg/dL)	0/11 (0%)	0/32 (0%)		3/33 (9%)	0/33 (0%)
Alkaline phosphatase (U/L)	2/11 (18%)	2/32 (6%)		3/32 (9%)	0/33 (0%)
AST/SGOT) (U/L)	3/11 (27%)	9/32 (28%)		6/32 (19%)	10/33 (30%)
ALT/(SGPT) (U/L)	2/11 (18%)	1/32 (3%)		2/32 (6%)	3/33 (9%)
LDH (U/L)	3/10 (30%)	4/32 (13%)		8/31 (26%)	10/33 (30%)
Total bilirubin (mg/dL)	2/11 (18%)	0/32 (0%)		3/32 (9%)	2/33 (6%)
Triglycerides	3/10 (30%)	2/30 (7%)		6/31 (19%)	7/33 (21%)
Cholesterol (mg/dL)	6/11 (55%)	12/32 (38%)		7/32 (22%)	10/33 (30%)
Urinalysis					
pH	3/10 (30%)	6/32 (19%)		3/33 (9%)	5/32 (16%)
WBC/HPF	2/10 (20%)	3/31 (10%)		0/30 (0%)	1/32 (3%)
Bacteria/HPF	2/10 (20%)	0/31 (0%)		3/28 (11%)	3/30 (10%)
Bile	2/10 (20%)	1/32 (3%)		7/33 (21%)	1/31 (3%)

(Cross-reference: Table 14.3.4.2C.)
[a]The given N is the total safety population for each treatment group.
[b]The population from which the percentage was based could differ for each laboratory variable and was based on the total number of patients in each treatment group who had the particular laboratory test at both screening and end of study.
Source: Table 12.4.2.2 in the BP96-0104 Study Report

Review of the above table is notable for the fact that for most laboratory tests, the frequencies of shifts, either from normal to high or normal to low, are considerably higher in the Phase 2 study than in the Phase 3 studies. This pattern is true both for the BTDS groups and for the Placebo group. The most likely explanation for this overall difference between the Phase 2 study and the Phase 3 studies is that the clinical setting of the Phase 2 study, the acute post-operative period, is different from the clinical setting of the Phase 3 studies, the outpatient setting. The acute post-operative period can be associated with many more laboratory abnormalities.

Despite the differences in clinical setting, there are some notable differences between the BTDS groups and the Placebo groups in the frequencies of shifts from normal to low. Specifically, notably higher frequencies of shifts from normal to low were observed in BTDS patients, relative to Placebo, for: RBC, hemoglobin, hematocrit, BUN (of questionable clinical relevance), sodium (BTDS 20 group only), potassium, chloride (BTDS 20 only), CO2, total protein, phosphate, and urinary specific gravity. The shifts from normal to low for the hepatic function tests is probably not of any clinical relevance.

Notable differences between the BTDS groups and the Placebo group in the frequency of shifts from normal to high occurred for WBC, neutrophils %, and creatinine (BTDS 10 only).

While some of the shifts in frequency from normal to low or normal to high may be explained by changes in intravascular volume in the post-operative period (eg, BUN, hemoglobin, hematocrit, RBC), this change in intravascular volume would not explain the observed differences between Placebo and BTDS. It is important to note that the percentages in the Placebo group are based on only 11 patients, so a difference of one or two patients in that group can a have a large impact on the observed frequency of a shift.

Shifts from normal to low or from normal to high in the clinical pharmacology studies are presented in Sponsor Table 8.13.7.2.2E in the ISS, which is reproduced below:

TABLE 8.13.7.2.2E.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Shift Tables of Subject Changes
All Subjects (N = 449)
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1204, and BP99-0204 Combined

	Normal to Low		Normal to High	
	N[a]	No. (%) of Subjects	N[a]	No. (%) of Subjects
HEMATOLOGY				
Hemoglobin	445	55 (12%)	445	NA
CLINICAL CHEMISTRY				
Renal Function Tests				
BUN	427	13 (3%)	427	19 (4%)
Creatinine	447	7 (2%)	447	4 (1%)
Hepatic Function Tests				
AST (SGOT)	447	1 (<1%)	447	17 (4%)
ALT (SGPT)	447	3 (1%)	447	18 (4%)
Total bilirubin	447	NA[b]	447	12 (3%)

(Cross-reference: Table 8.14.1.3.1.1.)
[a]Number of subjects with values at both screening and final visits.
[b]NA = shift direction not applicable to laboratory value.

It is not clear if the above table includes only subjects who received BTDS, or if it include subjects who received Placebo treatment as well. The Sponsor has noted in the ISS that the relatively large frequency of shifts from normal to low most likely reflects the frequent blood draws that occur in clinical pharmacology studies. The above table is also notable for the 4% frequency of shifts from normal to high for AST and ALT, as well as the 3% shift from normal to high for total bilirubin. While the frequencies of shifts from normal to high in AST and ALT are similar to those seen in the Phase 3 studies, the 3% shift from normal to high in total bilirubin is higher than the frequency observed in the Phase 3 studies. These results will be discussed in more detail below in the section on hepatic test results.

7.10.5 Individual Clinically Significant Abnormal Laboratory Values

In evaluating clinically significant abnormal laboratory values, the Sponsor has analyzed the frequencies of treatment-emergent clinically significant abnormal laboratory values, defined as 1) those values that were considered clinically significant by the investigator at the end of the study and changed in the direction of concern, and/or 2) those that were outside the sponsor-defined alert ranges and changed in the direction of concern.

For the titration-to-effect and forced-titration studies, the Sponsor has computed the frequencies of clinically significant abnormal laboratory values. The frequency of clinically signficant abnormal values is generally less than 6% for most lab tests. In both of these sets of studies, the frequency of clinically significant abnormal laboratory values is similar for BTDS and non-BTDS groups (ie, active comparators and placebo). A notable exception to this patter is the higher proportion of Bun and creatinine increases in the BTDS groups, compared to the Placebo group, in the forced-titration studies. The frequency of clinically significant increases in BUN was 4.6% for the BTDS 5 group, 2.2% for the BTDS 10 group, 5.4% for the BTDS 20 group, 4.1% for the Oxy/APAP group, and 2.3% for the Placebo group. For creatinine, the frequencies were 2.3% for

the BTDS 5 group, 1.1% for the BTDS 10 group, 3.3% for the BTDS 20 group, 1.0% for the Oxy/APAP group, and 0% for the Placebo group. In the forced-titration studies, the frequency of platelet counts below 115,000/mm3 ranged between 1.1 and 2.2% for the three BTDS group, and was 0% for the Oxy/APAP groups.

The Sponsor did not supply an integrated line listing of all clinically significant abnormal laboratory values. The Agency requested one in a letter dated July 10,2001.

Because frequency tables of clinically significant abnormal laboratory values do not provide any insight into the nature of the individual abnormalities, the line listings of clinically significant abnormal laboratory data from each of the Phase 2/3 studies were reviewed. Review of these listings is notable for the following:

- Many of the clinically significant abnormal laboratory values were at screening, and not while on study drug or at the end of the study.
- In some cases, there was no obvious reason for a lab value to be considered clinically significantly abnormal, since it was neither abnormal not markedly different from a previous value.
- Many of the clinically significantly abnormal laboratory values were for cholesterol and triglycerides.

Given the problems with laboratory values noted above in the section on data integrity, further review of the clinically significant abnormal laboratory values will not be performed. One example of the type of data errors that preclude meaningful analysis of the lab data follows. The line listing for Subject 29004 (Investigator 1741) in Study BP96-0101 reads as follows (see BP96-0101 Study Report, Table 14.3.4.1.C1):

Treatment: BTDS 25 ug/hr								
Investigator Number	Patient Number	Lab Test	Lab Result	Lab Date	Visit	Abnormal?	Investigator Assessment	Sponsor Alert Range
1741	29004	BUN mg/dL	20.00	(b) (6)	Screening	Normal		
			20.00	(b) (6)	End of Study	Normal	Clinically Significant	
		Creatinine mg/dL	1 50	(b) (6)	Screening	Normal		
			16.00	(b) (6)	End of Study	High	Clinically Significant	High
Source: Study Report BP96-0101, Table 14.3.4.1C1								

Review of the above data does not indicate why the BUN at the end of the study is considered clinically significant, since it is unchanged from screening and it is not outside the normal range. Review of this patient's CRFs indicates that the screening values and the end-of-study values are numerically correct, but the units on the CRF at both time points are mmol/L for BUN and umol/L for creatinine. Thus, the CRFs and the data listing are discrepant with regard to the units of the BUN and creatinine measures. This discrepancy precludes any further meaningful analysis of these data.

7.10.6 Hepatic Test Results

To assess hepatic test results, the Sponsor calculated the frequencies and rates (event/patient-year) of elevated AST, ALT, or total bilirubin. Two cut-off criteria were used for AST and ALT: 3 X upper limit of normal and 5 X upper limit of normal. For total bilirubin, the two cut-off values were >1.3 mg/dl and >2.0 mg/dl. The results of this analysis are presented in Sponsor Table 8.13.7.2.3.1A in the ISS, which is reproduced below:

TABLE 8.13.7.2.3.1A.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Incidence and Rate per Patient-Year of Elevated AST, ALT, or Total Bilirubin Values After Baseline: Titration-to-Effect and Forced-Titration Studies
Safety Population (N = 1238)
BP96-0101, BP96-0102, BP96-0604, BP98-1201, and BP99-0203 Combined

		BTDS			Placebo		
Parameter	Elevation	N	No. (%) Patients With Event	Events/ Patient-Year	N	No. (%) Patients With Event	Events/ Patient-Year
AST (SGOT)	> 5 x ULN[a]	705	1 (<1%)	0.012	294	1 (<1%)	0.041
	> 3 x ULN	705	3 (<1%)	0.035	294	1 (<1%)	0.041
ALT (SGPT)	> 5 x ULN	705	1 (<1%)	0.012	294	0	0
	> 3 x ULN	705	4 (<1%)	0.047	294	4 (1.4%)	0.163
Total bilirubin	> 2.0 mg/dL	704	0	0	294	1 (<1%)	0.041
	> 1.3 mg/dL	704	7 (1%)	0.082	294	6 (2%)	0.245

(Cross-reference: Table 8.14.2.3.4.1.)
[a]ULN = upper limit of normal. For the forced-titration studies, ULN was study and center specific. For the titration-to-effect studies, the ULN of [redacted] (b) (4) was used for all studies (Table 8.13.7.2).

Source: Sponsor Table 8.13.7.2.3.1A in the ISS.

The individual patients in the BTDS or Placebo groups who had at least one post-baseline abnormal hepatic function test meeting the above criteria are listed in Sponsor's Table Table 8.14.2.3.5.1 in the ISS, which is reproduced below:

Lsiting of Patients in Phase 2/3 Controlled Studies With AST or ALT > #x Upper Limit of Normal and/or Total Bilirubin > 1.3 mg/dl							
Protocol	Inv. No.	Pat. No.	Visit	Treatment	AST	ALT	Total Bili.
BP960102	1627	20216	End of Study	Placebo	17	14	7.600**
BP960102	1723	27201	End of Study	Placebo	52	184.000 *	0.4
BP960104	1215	9	End of Study	Placebo	246.000**	271.000 *	0.7
BP960104	1215	66	End of Study	Placebo	109	96	1.400 *
BP960104	1215	76	End of Study	Placebo	11	27	1.500 *
BP960604	1723	3612	Post-Trt / Pre-Complt	Placebo	18	14	1.700 *
BP990203	639	2105	End of Study	Placebo	13	12	1.900 *
BP990203	1820	1026	End of Study	Placebo	112	155.000 *	0.4
BP990203	2063	1165	End of Study	Placebo	64	150.000 *	0.6
BP990203	2094	1113	End of Study	Placebo	24	20	1.600 *
BP960604	100	2603	End of Study	BTDS	215.000 *	148.000 *	0.7
BP981201	1215	5034	End of Study	BTDS	146.000 *	81	0.6
BP981201	1807	12074	End of Study	BTDS	116	266.000**	0.9
BP981201	1878	2254	End of Study	BTDS	63	161.000 *	0.7
BP981201	1944	16142	End of Study	BTDS	36	55	1.900 *
BP990203	1995	2012	End of Study	BTDS	15	9	1.500 *
BP990203	1995	2173	End of Study	BTDS	24	24	1.400 *
BP960102	131	8208	Post-Trt / Pre-Complt	BTDS	14	19	1.600 *
BP960104	1215	5	End of Study	BTDS	58	50	1.400 *
BP960104	1215	10	End of Study	BTDS	24	30	1.500 *
BP960102	1721	26215	Post-Trt / Pre-Complt	BTDS	14	13	1.400 *
BP960104	1215	108	End of Study	BTDS	221.000**	228.000 *	0.6
Source: Sponsor Table 8.14.2.3.5.1 in the ISS *= 3 X Upper Limit of Normal **=5 X Upper Limit of Normal							

Review of the above tables reveals that the frequency of abnormal hepatic function tests was similar between the Placebo and BTDS groups. Furthermore, apart from the total bilirubin value of 7.6 mg/dl in Patient 20216 in the Placebo group, total bilirubin values were not markedly elevated – there were no values above 2.0. No patient who had a transaminase elevation greater than three times the upper limit of normal had an associated abnormal total bilirubin. The Sponsor notes hat the one patient who received BTDS in the controlled Phase 2/3 studies who had an ALT or AST value more than 5 X ULN at the end of the study (Patient 12074 in BP98-1201) had an elevated ALT at screening attributed to a prior history of "hepatic infection."

Further review of the Sponsor's data indicates that one BTDS-treated patient (2603 in BP96-0604) had both an elevated AST (215 U/L) and ALT (148 U/L) at the end of the study, with a total bilirubin of 0.7 mg/dl. These LFTs were measured again about seven days later, and the repeat values were notable for normalization of AST (25 U/L) and ALT (26 U/L), but there was a rise in total bilirubin (1.8 mg/dl).

The other BTDS-treated patients who had an elevation of both AST and ALT at least 3 X ULN was patient 108 (Study BP960104). No follow-up lab data were available for this patient.

In addition to the values noted in the above table, Patient 2119 in Study BP99-0203 had mildly elevated AST and ALT at screening (72 and 77 U/L, respectively), which increased to 120 and 122 U/L, respectively, at the end of the study. Neither of these values is more than 3 X ULN (ULN = 48). However, repeat values measured about one week later were above 3 X ULN (154 and 152 U/L, respectively). No additional measurements were reported. Total bilirubin values were 0.3-0.4 mg/dl at each visit.

To assess hepatic function in the open-label study BP96-0103, the Sponsor calculated the incidence and rate per patient-year of elevated AST, ALT and total bilirubin. These results are presented in Sponsor Table 8.13.7.2.3.1B in the ISS, which is reproduced below:

TABLE 8.13.7.2.3.1B.
BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103)
Incidence and Rate per Patient-Year of Elevated AST, ALT, or Total Bilirubin Values After Baseline
Intent-to-Treat/Safety Population (N = 384)

Parameter	Elevation	N	No. (%) Patients With Event	Events/Patient-Year
AST (SGOT)	> 5 x ULN[a]	331	0	0
	> 3 x ULN	331	2 (<1%)	0.009
ALT (SGPT)	> 5 x ULN	316	0	0
	> 3 x ULN	316	3 (<1%)	0.014
Total bilirubin	> 2.0 mg/dL	330	2 (<1%)	0.009
	> 1.3 mg/dL	330	6 (2%)	0.027

(Cross-reference: Table 8.14.3.3.6.)
[a]ULN = upper limit of normal.
Source: Sponsor Table 8.13.7.2.3.1B

Individual LFT abnormalities meeting the above criteria are presented in Sponsor Table 8.14.3.3.8 in the ISS, which is reproduced below:

TABLE 8.14.3.3.8
LISTING OF PATIENTS WITH AST, ALT, OR TOTAL BILIRUBIN ELEVATIONS*
POPULATION: Patients Valid for Safety in BP96-0103

PROTOCOL NUMBER	INVESTIGATOR NUMBER	PATIENT NUMBER	VISIT	Treatment	AST	ALT	Bilirubin
BP960103	100	4322	Dosing Period	BTDS	23.000	16.000	1.500 *
BP960103	100	4334	Dosing Period	BTDS	215.000 *	148.000 *	1.800 *
BP960103	1139	6330	End Of Study	BTDS	217.000 *	204.000 *	0.700
BP960103	1215	21311	End Of Study	BTDS	60.000	157.000 *	0.300
BP960103	1215	21330	Dosing Period	BTDS	22.000	29.000	1.600 *
BP960103	1215	21361	End Of Study	BTDS	29.000	45.000	6.900**
BP960103	1693	2306	End Of Study	BTDS	28.000	59.000	1.400 *
BP960103	1693	2307	Dosing Period	BTDS	19.000	32.000	7.300**

Source: Sponsor Table 8.14.3.3.8 in the ISS

The Sponsor notes that no patient had an elevated AST or ALT more than 5 X ULN. The Sponsor also notes that no patient had an AST or ALT elevation above 3 X ULN and a total bilirubin above 1.3 mg/dl at the end of the study. Review of the above table of individual patient data indicates that Patient 4334 had an elevated AST and ALT (both greater than 3X ULN) and a total bilirubin greater than 1.3 mg/dl during the dosing period. Further review of this patient's data indicates that this person had participated in BP96-0604 (with Patient No. 2603). At the final visit for that study, AST and ALT were elevated (215 and 148 U/L, the same values reported for the dosing period above). In fact, these are the same results, as they were taken on the same day (b) (6) was the end-of-study visit date in BP96-0604 and the "baseline" day in BP96-0103). A second set of LFTs was drawn about a week later (b) (6) which showed normalization of AST and ALT (25 and 26 U/L, respectively) but a rise in total bilirubin (1.8 mg/dl). The patient discontinued the study on (b) (6) because of angina, and at that time AST, ALT, and total bilirubin were all normal (AST = 32 U/L, ALT = 54 U/L, total bilirubin = 0.7 mg/dl).

Patient 6330 in BP96-0103 had previously participated in Study BP96-0102 (Patient No. 6215 at the site of Investigator 1139), and was randomized to BTDS 10 during that study. Screening LFTs in Study BP96-0102 were normal (AST 21 U/L, ALT 22 U/L, total bilirubin 0.4 mg/dl). At the time of the patient's completion in BP96-0102, no end-of-study laboratory tests were performed, and no screening laboratory tests were performed upon entry into BP96-0103. AST and ALT were elevated (217 and 204 U/L, respectively), at the end of BP96-0103, but follow-up AST and ALT were normal 20 days later (20 and 24 U/L).

Patient 2307 had an isolated marked elevation of total bilirubin (7.3 mg/dl) at the 12-month visit, which reverted to normal (0.5 mg/dl) at the final visit. Of note, this investigator did not comment on this abnormal value. Patient 21361 had an isolated marked elevation of total bilirubin (6.9 mg/dl) at the end-of-study visit. The investigator did not comment on this value, and there is no follow-up value.

The frequency of elevated hepatic function tests in the clinical pharmacology studies is presented in Sponsor table 8.13.A.6C in the ISS. A listing of individual abnormal hepatic function tests from those studies is presented in Sponsor Table 8.14.1.3.5.1 in the ISS. Each of these tables is reproduced below:

TABLE 8.13.A.6C.
BTDS Integrated Summary of Safety: Clinical Pharmacology Studies
Incidence and Rate per Patient-Year of Elevated AST, ALT, or Total Bilirubin Values After Baseline
Safety Population (N = 449)
BP95-0901, BP96-0304, BP96-0501, BP96-0702, BP96-0803, BP96-1102, BP97-0112, BP97-0303, BP97-0501, BP97-1001, BP98-0201, BP98-0202, BP98-1204, and BP99-0204 Combined

Parameter	Elevation	N	BTDS No. (%) Patients With Event	Events/Patient-Year
AST (SGOT)	> 5 x ULN[a]	447	1 (<1%)	0.091
	> 3 x ULN	447	3 (1%)	0.273
ALT (SGPT)	> 5 x ULN	447	1 (<1%)	0.091
	> 3 x ULN	447	2 (<1%)	0.182
Total bilirubin	> 2.0 mg/dL	447	4 (1%)	0.364
	> 1.3 mg/dL	447	20 (4%)	1.819
(Cross-reference: Table 8.14.1.3.4.1.)				
Source: Sponsor Table 8.13.A.6C in the ISS				

TABLE 8.14.1.3.5.1
LISTING OF SUBJECTS WITH AST, ALT, OR TOTAL BILIRUBIN ELEVATIONS*
POPULATION: Patients Valid for Safety

PROTOCOL	INVESTIGATOR NUMBER	PATIENT NUMBER	VISIT	AST	ALT	Bilirubin
BP950901	1544	9	End of Study	20.000	15.000	1.988 *
BP950901	1544	22	End of Study	19.000	9.000	1.579 *
BP950901	1544	26	End of Study	19.000	13.000	1.579 *
BP960501	1672	22	End of Study	17.000	29.000	1.620 *
BP960803	1663	2	End of Study	24.000	24.000	1.400 *
BP960803	1663	9	End of Study	21.000	29.000	1.900 *
BP961102	1747	8	End of Study	94.000	161.000 *	0.400
BP970112	328	1	End of Study	34.000	13.000	1.600 *
BP970112	328	2	End of Study	55.000	17.000	1.400 *
BP970112	328	4	End of Study	74.000	41.000	2.100**
BP970112	328	5	End of Study	150.000 *	98.000	3.200**
BP970112	328	11	End of Study	42.000	22.000	3.400**
BP970303	1695	111	End of Study	199.000 *	492.000**	4.800**
BP971001	1929	16	End of Study	20.000	25.000	1.500 *
BP980201	1925	31	End of Study	18.000	14.000	1.600 *
BP980201	1925	39	End of Study	17.000	19.000	1.400 *
BP980201	1925	41	End of Study	16.000	8.000	1.500 *
BP980201	1925	65	End of Study	14.000	7.000	1.400 *
BP980201	1925	76	End of Study	278.000**	100.000	0.700
BP980201	1925	78	End of Study	17.000	11.000	1.600 *
BP980201	1925	80	End of Study	15.000	18.000	1.400 *
BP980201	1925	82	End of Study	17.000	14.000	1.400 *

Review of the above tables indicates that post-baseline abnormalities of total bilirubin were relatively common, occurring in about 4% of subjects. Not all of these end-of-study values,

however, represented treatment-emergent increases in total bilirubin. Subjects whose final total bilirubin value was above 1.3 mg/dl and higher than baseline include: Subjects 1544/9, 1544/22, 1663/2,1663/9, 328/2, 328/5, 1695/111, 1929/16, 1925/31, 1925/39, 1925/41, 1925/80. Subject 1544/26 had a screening bilirubin value of 1.579 mg/dl, which upon repeat tests was 0.994 mg/dl. At the final visit, the first end-of-study value was 1.579 mg/dl, and upon repeat tests it was 0.994. Subject 1663/9 had a baseline value of 1.0 mg/dl. At the end of the study it was 1.9 mg/dl, and upon repeat testing it was 1.4 mg/dl.

Subjects 328/1, 328/2, 328/4, 328/5, and 328/11 were participating in Study BP97-0112, a study of BTDS pharmacokinetics in hepatic impairment. For Subjects1, 4, and 11, the final total bilirubin value was lower than the screening value. For subjects 2 and 5, the final value was only slightly higher than the screening value (Subject 2: 1.0 at screening and 1.4 at the end of the study; Subject 5: 3.1 at screening and 3.2 at the end of the study).

Subject 111 in Study BP97-0303 had cholecystitis and a cholecystectomy after completing the study.

7.10.7 Analysis of Neutropenia

In March 200, the Sponsor submitted an initial IND Safety Report of a case of neutropenia in a healthy volunteer in an ongoing clinical pharmacology study. Follow-up information was sent in April 2001. A 23-year-old apparently healthy male volunteer (Subject 038) was enrolled in an open-label study of BTDS 10 mg to assess the effects of varying durations of application site rest periods, with naltrexone blockade. The chronology of laboratory studies and medication administration is as follows:

Date	Medication/Other Event	Lab Value (10^{-3}/uL)*		
		WBC	ANC	ALC
(b) (6)	None	4.1	2.2	1.5
	Start Naltrexone 25 mg po bid	---	---	---
	BTDS 10 mg patch applied	---	---	---
	BTDS 10 mg patch removed	---	---	---
	None – 3 days post-removal of BTDS	3.1	1.2	1.6
	None – 6 days post-removal of BTDS	3.7	1.5	1.9
	BTDS 10 mg patch applied	---	---	---
	BTDS 10 mg patch removed	---	---	---
	Stop Naltrexone	---	---	---
	None	2.9	1.0	1.6
	None	3.1	1.1	1.8
	None	3.4	1.3	1.8
	None	2.6	0.8	1.6
	None	2.8	0.8	1.7
	None	2.9	1.0	1.6
	None	2.5	1.1	1.2
	None	2.8	1.2	1.4
	None	2.4	0.8	1.3
	None	3.1	1.4	1.5
	None	3.3	1.4	1.7
	None	3.0	1.2	1.5
	None	2.5	0.9	1.4
	Subject started taking Tylenol and Dimetapp Cold & Flu	---	---	---
	Subject started taking Tylenol and Dimetapp Cold & Flu	---	---	---
	Subject seen by a hematologist and admitted with a three-day history of fever (100.4 degrees F). Bone marrow aspirate performed ("no arrest in white cell precursors"). G-CSF administered after bone marrow aspirate performed.		.240	
	Discharge from hospital		2.86	
			2.10	
*WBC = White blood cell count, ANC = Absolute neutrophil count, ALC = Absolute lymphocyte count				

The hematologist's initial report notes that the subject was on no medications other than the study medications, and that there were no prior symptoms suggestive of collagen vascular disease, fever, night sweats, or weight loss. When the subject saw the hematologist on March 1, 2001, his complaints were suggestive to the hematologist of a viral syndrome (muscle aches and discomfort). The hematologist's review of the peripheral blood smear was notable only for profound neutropenia. Initial review of the bone marrow revealed that it "looked fine," though results of further studies, such as cytogenetics and immunophenotyping, were not available at the time of the submission of the initial IND safety report (SN172). Anti-neutrophil antibodies were also pending. In the follow-up IND safety report (SN176), the immunophenotypic analysis revealed "no evidence of an abnormal population of cells", and the cytogenetic analysis revealed no metaphases for chromosome analysis. The report also noted that "the number of granulocytes with progressive maturation in the bone marrow in the face of marked leukopenia is suggestive of a peripheral granulocytic consumption/sequestration."

The investigator judged the event to be possibly related to study medication.

In view of the above case, the Agency asked the Sponsor to analyze the occurrence of neutropenia in the NDA clinical pharmacology studies as well as in the Phase 2/3 studies. The Agency requested that the Sponsor categorize absolute neutrophil count (ANC) into five categories: ≥ 2,000/mm^3, 1,500-<2,000, 1,000-<1500, 500-<1,000, and <500. The Agency required a line listing of all patients/subjects with ANC<2,000, as well as a shift table, based on these five categories, comparing screening ANC value to most abnormal post-baseline ANC value.

In the Phase 1 studies, no subject had a post-baseline absolute neutrophil count (ANC) less than 1,000/mm^3. Nine of 377 BTDS subjects (2.4%) and 2 of 24 Placebo subjects (8.3%) had post-baseline ANC values between 1,000 and 1,500 mm^3. Of these nine BTDS subjects, three had screening ANC values above 2,000, four had screening ANC values between 1,500 and 2,000,and two had screening values below 1,500. Of the two Placebo subjects, both had screening ANC values above 1,500.

Using the above Agency-defined ANC categories, the Sponsor noted that a decrease by one or more categories was observed for 36/399 (9.0%) BTDS subjects and for 3/24 (12.5%) Placebo subjects. A decrease by two or more categories was noted for 3/399 (0.8%) BTDS subjects and for 1/24 (4.2%) Placebo subjects.

The Sponsor notes that no subject in Phase 1 studies was discontinued because of neutropenia and no subject in Phase 1 studies required treatment for neutropenia.

In the Phase 2/3 studies, one BTDS-treated patient had a post-baseline ANC < 500. This case will be discussed in more detail below. No other BTDS patient had a post-baseline ANC value less than 1,000. No Placebo-treated patient had a post-baseline ANC less than 1,000. Six of 813 (0.7%) BTDS-treated patients who had a screening ANC value above 2,000 had a lowest post-baseline ANC value between 1,000 and 1,500. By contrast one of 290 (0.3%) Placebo-treated patients who had a screening ANC value above 2,000 had a lowest post-baseline ANC value between 1,000 and 1,500. In the randomized, controlled, Phase 2/3 studies, the frequency of an ANC decrease by one or more categories was 14/703 (2.0%) in the BTDS group and 5/301 (1.7%) in the Placebo group. Across all studies (Phases 1-3), the frequency of an ANC decrease by one or more categories was 59/1249 (4.7%) in the BTDS group and 8/325 (2.5%) in the Placebo group. In the randomized, controlled, Phase 2/3 studies, the frequency of an ANC decrease by two or more categories was 2/703 (0.3%) in the BTDS group and 1/301 (0.3%) in the Placebo group. Across all studies (Phases 1-3), the frequency of an ANC decrease by one or more categories was 10/1249 (0.8%) in the BTDS group and 2/325 (0.6%) in the Placebo group.

The one patient in the Phase 2/3 studies who had a post-baseline ANC < 500 was Patient #4007 in Study BP96-0101, who continued into open-label study Study BP96-0103 as Patient # 4309. To avoid confusion between the two study numbers, she will be referred to by her initials, (b) (6)

(b) (6) was 74-year-old black female with osteoarthritis of the left knee who enrolled in Study BP96-0101. Her medical history was notable for bronchitis (October 1996), umbilical hernia repair (1995), gout, urinary tract infection (1993), hypertension (1976), hysterectomy (1975), appendectomy (1972), heart murmur (1968), questionable myocardial infarction (1968), and hemorrhoids (1940). Medications included amlodipine 5 mg qd (from 1990 through the study for

hypertension), diclofenac sodium 75 mg bid (1994 through the study for osteoarthritis), and allopurinol (1993 through the study for gout).

(b) (6) was assigned to the BTDS 10 mg group in Study BP96-0101. She began study medication on (b) (6), and stopped study medication on (b) (6), at which time she completed the protocol. She enrolled in open-label study BP96-0103, and began BTDS on (b) (6). During the double-blind study BP96-0101, adverse events included constipation, nausea, vomiting, dizziness, somnolence, and pruritus. None of these adverse events was judged to be either serious or severe, though each was judged to be definitely or probably related to study medication. No action regarding study medication or any other action was taken for these adverse events. At the time of completion of Study BP96-0103, no end-of-study laboratory samples were taken. [Note: the patient data listings for this patient from Study BP96-0101 and BP96-0103 are discrepant and confusing, and do not match either the database or the Sponsor's narrative of this patient's clinical course. No CRFs were provided for this patient.] She enrolled in study BP96-0103, and was started on BTDS on (b) (6). Adverse events during this open-label trial included constipation, nausea, drowsiness, and itchiness. All were judged to be definitely related to study drug. No specific action was taken for these adverse events. She prematurely discontinued study medication on (b) (6) at her own request because of "stiffness". Her end-of-study laboratory evaluation (either on (b) (6) or on (b) (6) – the data are too confusing to ascertain the correct date) was notable for WBC = 3.9, neutrophils = 12.3%, ANC = 480/mm^3, bands = 0%, lymphocytes = 40.7% (absolute lymphocyte count = 1590/ mm^3, monocytes = 43%, eosinophils = 4%, basophils = 0%, platelets = 42,000/mm^3, and hemoglobin = 10.9 gm/dl. Of note, baseline values were WBC = 7.1, neutrophils = 60.2%, ANC = 4274/ mm^3, lymphocytes = 25.1%, monocytes = 12.9%, eosinophils = 0.9%, basophils = 0.9%, platelets = 97,000/mm^3, hemoglobin = 11.4 gm/dl). The final platelet count (42,000) report noted that there was platelet clumping, so the actual platelet count may have been higher than the recorded platelet count. None of the abnormal lab tests was reported as clinically significant by the investigator. No follow-up tests were performed. Of note, leukopenia occurs in less than 1% of allopurinol-treated patients, in less than 1% of amlodipine-treated patients, and and in less than 1% of diclofenac-treated patients.

(b) (6) died in (b) (6) two years after completing participation in Study BP96-0103, of causes unknown to the investigator and to the Sponsor.

While the first case of neutropenia in the healthy volunteer may be due to peripheral sequestration, the cause of the neutropenia in the second patient ((b) (6)) is not clear. In fact, the second case of neutropenia was determined only after a retrospective review of the database, and there was no documented clinical correlate of this laboratory finding. The neutropenia in the second cases is also accompanied by thrombocytopenia, though the interpretation of the significance of this finding is limited by the relatively low baseline platelet count and the presence of platelet clumping. While in both cases, a causal role of BTDS can not be definitively excluded, the time course of the neutropenia in the healthy volunteer relative to BTDS exposure and the potential causal role of concomitant medications in the second case ((b) (6)) argue against BTDS as the sole causative agent.

7.10.8 Discontinuations for Laboratory Abnormalities

The Sponsor notes in Section 8.13.7.1 of the ISS that no laboratory value was considered a serious or significant adverse event.

7.11 Vital Signs

7.11.1 Extent of Vital Sign Screening in the Development Program

Vital signs evaluation included measurements of body temperature, pulse, respiratory rate, systolic blood pressure, and diastolic blood pressure. In some clinical pharmacology studies, vital signs were collected in several positions: supine, sitting, and/or standing.

In the Phase 2/3 studies, vitals signs were measured and recorded at the following time points:

Time Points for Measuring and Recording Vital Signs in the Phase 2/3 Program	
Study	Time Point for Measuring and Recording Vital Signs
BP96-0101	Baseline and end of study
BP96-0102	Baseline and end of study
BP96-0104	Baseline and end of study
BP96-0604	Baseline and end of study
BP98-1201	Baseline, Days 7, 14, 21, 28, 35, 42, and 56
BP99-0203	Baseline, Days 7, 14, 21, and 28
BP96-0103	Baseline and end of study
Source: ISS Table 8.13.A.1.3A	

In the clinical pharmacology studies, vital signs were usually recorded at the time of blood draw.

The Sponsor's analysis of vital signs consisted of:

- Between-group analyses of mean changes (baseline to end of study) in vital signs
- Incidence of hypotension, defined as low as decrease systolic blood pressure (<100 mm Hg during treatment and a decrease from baseline of ≥ 30 mm Hg) and/or diastolic blood pressure (<60 mm Hg during treatment and a decrease from baseline ≥ 15 mm Hg).

The Sponsor's reference ranges for vital signs, presented in Table 8.13.8.2A, were clinically appropriate.

7.11.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Analyses of mean changes from baseline for vital signs in the titration-to-effect and forced-titration studies are presented in Sponsor Tables 8.13.8.2B and 8.13.8.2C in the ISS, which are reproduced below:

TABLE 8.13.8.2B.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Vital Signs With Changes From Baseline to Final Visit by Treatment: Titration-To-Effect Studies
Safety Population (N = 719)
BP96-0604, BP98-1201, and BP99-0203 Combined

Vital Signs	N[a]	Baseline	Final	Change From Baseline to Final	
		Mean (SE)		Mean (SE)	95% CI[b]
Systolic blood pressure (mm Hg)					
BTDS	337	132.4 (0.87)	131.1 (0.93)	-1.42 (0.84)	(-3.06. 0.23)
Hydrocodone	130	129.1 (1.35)	129.2 (1.37)	0.20 (1.35)	(-2.46, 2.85)
Oxy/APAP	42	133.1 (2.66)	134.5 (3.15)	1.51 (2.17)	(-2.73, 5.76)
Placebo	207	133.3 (1.10)	132.9 (1.18)	-0.34 (1.12)	(-2.53, 1.85)
Diastolic blood pressure (mm Hg)					
BTDS	337	79.3 (0.52)	77.8 (0.50)	-1.49 (0.49)	(-2.44, -0.54)
Hydrocodone	130	77.8 (0.85)	79.2 (0.83)	1.55 (0.86)	(-0.13, 3.24)
Oxy/APAP	42	80.8 (1.22)	80.6 (1.51)	0.20 (1.36)	(-2.46, 2.86)
Placebo	207	78.9 (0.64)	79.0 (0.61)	0.18 (0.67)	(-1.12, 1.49)
Pulse rate (beats/min)					
BTDS	336	76.4 (0.55)	75.0 (0.54)	-1.35 (0.55)	(-2.42, -0.28)
Hydrocodone	130	77.1 (0.95)	75.0 (0.89)	-2.10 (0.96)	(-3.98, -0.22)
Oxy/APAP	41	74.9 (1.75)	74.9 (1.78)	0.97 (2.30)	(-3.54, 5.49)
Placebo	208	74.0 (0.65)	73.9 (0.66)	-0.02 (0.74)	(-1.47, 1.43)
Respiration rate (breaths/min)					
BTDS	336	18.1 (0.16)	17.8 (0.16)	-0.31 (0.16)	(-0.64, 0.01)
Hydrocodone	130	17.9 (0.27)	17.6 (0.24)	-0.30 (0.23)	(-0.76, 0.15)
Oxy/APAP	41	17.7 (0.35)	17.7 (0.33)	-0.09 (0.26)	(-0.61, 0.43)
Placebo	208	17.9 (0.19)	17.7 (0.20)	-0.14 (0.18)	(-0.50, 0.22)

(Cross-reference: Table 8.14.2.4.1.2.)
[a]Number of patients with data at baseline. The number of patients with data at final visit was less than the number with data at baseline.
[b]95% confidence interval around the mean change from baseline.

Source: Sponsor Table 8.13.8.2B in the ISS

TABLE 8.13.8.2C.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies
Vital Signs With Changes From Baseline to Final Visit by Treatment: Forced-Titration Studies
Safety Population (N = 519)
BP96-0101 and BP96-0102 Combined

Vital Signs	N[a]	Baseline Mean (SE)	Final Mean (SE)	Change From Baseline to Final Mean (SE)	Change From Baseline to Final 95% CI[b]
Systolic blood pressure (mm Hg)					
Total BTDS	310	132.9 (0.93)	132.3 (1.01)	-0.63 (0.97)	(-2.53, 1.27)
BTDS 5	105	132.9 (1.48)	132.4 (1.59)	-0.88 (1.62)	(-4.05, 2.28)
BTDS 10	102	132.7 (1.77)	134.8 (2.02)	2.48 (1.71)	(-0.87. 5.83)
BTDS 20	103	132.9 (1.58)	129.7 (1.60)	-3.44 (1.68)	(-6.73, -0.16)
Oxy/APAP	105	135.9 (1.75)	133.9 (1.75)	-2.83 (1.79)	(-6.35, 0.69)
Placebo	99	135.5 (1.49)	134.6 (1.50)	-1.06 (1.37)	(-3.74, 1.62)
Diastolic blood pressure (mm Hg)					
Total BTDS	310	80.1 (0.52)	79.7 (0.52)	-0.36 (0.52)	(-1.38, 0.66)
BTDS 5	105	80.3 (0.91)	80.2 (0.85)	0.01 (0.81)	(-1.57, 1.59)
BTDS 10	102	79.6 (0.92)	79.9 (0.92)	0.51 (0.96)	(-1.38, 2.40)
BTDS 20	103	80.5 (0.87)	79.0 (0.91)	-1.59 (0.92)	(-3.40, 0.23)
Oxy/APAP	105	80.9 (0.93)	80.0 (1.06)	-1.26 (0.94)	(-3.10, 0.58)
Placebo	99	80.1 (0.96)	79.7 (0.95)	-0.25 (0.97)	(-2.16, 1.66)
Pulse rate (beats/min)					
Total BTDS	310	74.9 (0.56)	74.4 (0.57)	-0.77 (0.66)	(-2.06, 0.52)
BTDS 5	105	75.7 (0.93)	77.1 (1.12)	1.42 (1.17)	(-0.88, 3.72)
BTDS 10	102	74.3 (1.05)	72.5 (0.85)	-2.26 (1.07)	(-4.36, -0.16)
BTDS 20	103	74.5 (0.96)	73.6 (0.91)	-1.43 (1.15)	(-3.67, 0.82)
Oxy/APAP	107	74.1 (0.89)	74.4 (0.95)	0.11 (0.96)	(-1.76, 1.99)
Placebo	99	72.9 (1.11)	76.0 (1.17)	3.12 (1.11)	(0.94, 5.30)
Respiration rate (breaths/min)					
Total BTDS	310	16.9 (0.15)	16.8 (0.16)	-0.07 (0.18)	(-0.43, 0.28)
BTDS 5	105	16.7 (0.27)	16.6 (0.26)	0.15 (0.28)	(-0.40, 0.69)
BTDS 10	102	16.9 (0.28)	16.6 (0.27)	-0.30 (0.34)	(-0.97, 0.36)
BTDS 20	103	17.0 (0.24)	17.1 (0.27)	-0.06 (0.32)	(-0.69, 0.57)
Oxy/APAP	107	16.9 (0.24)	16.7 (0.25)	-0.14 (0.27)	(-0.67, 0.40)
Placebo	99	16.6 (0.25)	17.0 (0.27)	0.36 (0.28)	(-0.19, 0.90)
Body Temperature					
Total BTDS	310	36.7 (0.03)	36.7 (0.02)	-0.01 (0.03)	-0.06, 0.05
BTDS 5	105	36.7 (0.04)	36.7 (0.05)	0.01 (0.05)	-0.10, 0.11
BTDS 10	102	36.8 (0.04)	36.7 (0.04)	-0.04 (0.05)	-0.14, 0.06
BTDS 20	103	36.7 (0.05)	36.8 (0.04)	0.02 (0.05)	-0.08, 0.12
Oxy/APAP	107	36.8 (0.04)	36.7 (0.04)	-0.04 (0.05)	-0.13, 0.05
Placebo	99	36.6 (0.06)	36.7 (0.06)	0.08 (0.07)	-0.06, 0.21

(Cross-reference: Table 8.14.2.4.1.1.)
[a]Number of patients with data at baseline.
The number of patients with data at final visit was less than the number with data at baseline.
[b]95% confidence interval around the mean change from baseline.

Source: Sponsor Table 8.13.8.2C in the ISS

Review of the above tables indicates that all mean values of vital signs for the BTDS and placebo groups were within the normal range at baseline and at the end of the study. Mean changes from

baseline were small, and are probably of no clinical significance. Of note, there is a progressively larger decrease in diastolic blood pressure in the forced-titration studies from the BTDS 5 to BTDS 20 groups. Since these groups are defined based on assigned dose, and not on dose received, these data can not be interpreted as a dose-response relationship.

A summary of the mean changes from baseline for vital signs in the open-label study BP96-0103 is presented in Sponsor Tables 8.13.8.2C in the ISS, which is reproduced below:

TABLE 8.13.8.2D.
BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103)
Vital Signs With Changes From Baseline at End of Study
Intent-to-Treat/Safety Population (N = 384)

Vital Sign	N[a]	Baseline	End of Study	Change From Baseline to End of Study	
		Mean (SE)		Mean (SE)	Range
Systolic blood pressure (mm Hg)	383	130.9 (0.8)	131.1 (0.9)	0.3 (0.9)	-53- 50
Diastolic blood pressure (mm Hg)	383	79.3 (0.5)	78.2 (0.5)	-1.0 (0.6)	-52- 35
Pulse rate (beats/min)	383	74.8 (0.5)	75.1 (0.6)	0.4 (0.6)	-40 -35
Respiratory rate (breaths/min)	383	17.1 (0.1)	17.0 (0.2)	-0.1 (0.2)	-8 -14
Oral body temperature (°C)	381	36.8 (0.02)	36.7 (0.02)	-0.05 (0.02)	-2.12- 1.17

(Cross-reference: Table 8.14.3.4.1.)

[a]Number of patients with data at baseline.
The number of patients with data at the end of study was less than the number with data at baseline.

Source: Sponsor Table 8.13.8.2D in the ISS.

Review of the above table reveals that the baseline and end-of-study values are in the normal range for all vital signs, and that the changes from baseline are small.

In the Phase 2 Study BP96-0104, mean systolic blood pressure, diastolic blood pressure, and respiratory rate were notably lower at the end of the study, compared to screening for all treatment groups. The effect of systolic blood pressure was notably greater for the BTDS 10 and BTDS 20 groups than for the BTDS 5 or Placebo groups. The effect on diastolic blood pressure was lower than the effect on systolic blood pressure, and was least pronounced in the Placebo group, compared to the three BTDS groups. Heart rate was increased in all four treatment groups. The mean changes from baseline are summarized in the table below.

Summary of Mean Changes from Baseline for Vital Signs – Phase 2 Study BP96-0104

	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse (beats/min)	Respiratory Rate (breaths/min)	Temperature (°C)
Placebo	-10.27	-1.55	14.09	-2.00	1.04
BTDS 5	-12.61	-3.52	9.61	-1.24	0.58
BTDS 10	-21.15	-11.55	11.24	-1.09	0.63
BTDS 20	-21.64	-4.24	8.52	-0.88	0.72

Source: Table 14.3.5.1.C in the BP96-0104 Study Report

In the clinical pharmacology studies, mean post-baseline vital signs were generally in the normal range for both BTDS-treated and Placebo-treated subjects. Means changes from baseline were similar for BTDS-treated and Placebo-treated subjects (see Sponsor Table 8.14.1.4.1.1 in the ISS).

7.11.3 Respiratory Rate

In the Phase 2/3 studies, mean baseline and post-baseline respiratory rates were in the normal range in all treatment groups, and mean changes form baseline were not significantly different between BTDS-treated and Placebo-treated patients.

Review of the Sponsor's database for the Phase 3 controlled studies reveals 12 patients with respiratory rates below 10. All were from a single investigator (Investigator 2302) in Study BP98-1201. Seven of these patients were in the hydrocodone/APAP group, and five were in the BTDS group. All had at least one post-baseline respiratory rate of 8, but none had any respiratory rate below 8. Ten of the 12 had a baseline respiratory rate of 8. In two others (one in the HCD/APAP group and one in the BTDS group), the post-baseline respiraotry rate of 8 represented a decrese from baseline (from 12 to 8 in HCD/APAP Patient 6175 and from 16 to 12 to 8 in BTDS Patient 6233).

Adverse event COSTART terms relating to respiratory rate in the Phase 2/3 placebo-controlled studies include the following: Apnea, Dyspnea, Hyperventilation, and Hypoventilation. Each of these is discussed below:

Apnea in the post-operative Phase 2 Study BP96-0104 was reported in two cases, which have been previously reviewed (Sponsor Table 8.14.2.2.1.5 in the 4-month safety update). No cases of apnea were reported in the other Phase 2/3 trials.

Dyspnea was reported in 18/609 (3.0%) of BTDS patients, in 3/150 (2.0%) of Oxy/APAP patients and in 3/319 (0.9%) Placebo patients (Sponsor Table 8.14.2.2.1.5 in the 4-month safety update). Of the 18 BTDS patients, 14 had a maximum severity of mild, 3 had a maximum severity of moderate, and 1 had a maximum severity of severe. For one patient, the episode of dyspnea was a serious adverse event (Patient 88 in Study BP96-0104).

Hyperventilation was reported in 1/609 (0.2%) of BTDS patients, and in no Oxy/APAP or Placebo patients, in the placebo-controlled Phase 2/3 studies. This patient (1026 in Study BP96-0101) had two episodes, each of which was judged to be not serious. The first episode, on Day 23, lasted 0.1 days and was judged to be mild. The second episode, on the first day after study drug was discontinued, last 0.5 days and was judged to be mild in severity.

Hypoventilation was reported in 2/609 (0.3%) of BTDS patients, in no Oxy/APAP patients, and in 1/319 (0.3%) Placebo patients. None of the cases was serious or severe, though each was judged possibly related to study medication. In addition, two patients in the active-controlled Phase 3 study BP98-1201 each had a single episode of a mild, non-serious episode of hypoventilation. The investigator verbatim terms for these events were "involuntary shallow respirations" and "slowed breathing".

In the open-label study BP96-0103, mean baseline and post-baseline vital respiratory rates were in the normal range in all treatment groups, and mean changes form baseline were not significantly different from those observed in the controlled clinical trials.

Adverse event COSTART terms relating to respiratory rate in the open-label study include the following: Apnea, Dyspnea, Hyperventilation, and Hypoventilation. Each of these is discussed below:

Apnea in the open-label Study BP96-0103 was reported in two patients – 24303 and 20304. Each of these cases occurred after study drug had been stopped. The case of Patient 20304, who died during a hospitalization for a fall, was reviewed in Section 7.6 (Deaths) above. Patient 24203 suffered a respiratory arrest 14 days after discontinuing study medication. The respiratory arrest was attributed to an overdose of benzodiazepines.

Dyspnea was reported in 9/384 (2.3%) of BTDS patients in Study BP96-0103 (Sponsor Table 14.3.1.1 in the BP96-0103 Study Report). Of the 9 BTDS patients, 8 had one report of dyspnea and 1 had two reports. Six of the ten reports occurred at the BTDS 20 dose, 2 occurred at the BTDS 10 dose, and 2 occurred at the BTDS 5 dose. One patient (4306) required hospitalization; in the other 8 patients the event was non-serious. Study medication was discontinued for four patients. Causality was judged as possible in 3 patients, and as probable in one. In Pateintt 4306, the causality was judged as none.

Hyperventilation and hypoventilation were not reported in any patient in Study BP96-0103.

In the clinical pharmacology studies, mean baseline and post-baseline vital respiratory rates were in the normal range, and mean changes form baseline were not significantly different from those observed in the controlled clinical trials. In ISS Table 8.14.1.4.5, the Sponsor has listed all subjects in the clinical pharmacology studies with a respiratory rate below 12. A total of 40 BTDS-treated subjects had one or more recording of respiratory rate between 8 and 11, inclusive. No BTDS-treated subject had a respiratory rate below 8. One BIV-treated healthy young volunteer had a respiratory rate of 7, and one had a respiratory rate of 6. No other respiratory rates below 8 were recorded. The distribution by treatment, dose and subject group was as follows:

Summary of BTDS-treated Subjects in Clinical Pharmacology Studies With Respiratory Rate Below 12		
Treament/Dose	Subject Group	Number of Subjects
BTDS 5	Healthy Young	1
BTDS 10	Healthy Young	2
BTDS 10	Healthy Elderly	3
BTDS 10	Treated with midazolam or prochloperazine	1
BTDS 20	Healthy Young	15
BTDS 20	Healthy Elderly	10
BTDS 20	Elderly Hypertensive	8
Placebo	Treated with midazolam or prochloperazine	3
Duragesic	Treated with midazolam or prochloperazine	4
BIV	Healthy Young	21
BIV	Adult with Hepatic Impairment	3
Source: Data in Sponsor Table 8.14.1.4.5 in the ISS		

Adverse event COSTART terms relating to respiratory rate in the clinical pharmacology studies include the following: Apnea, Dyspnea, Hyperventilation, and Hypoventilation. Each of these is discussed below:

Apnea and hyperventilation were not reported for any subjects in the clinical pharmacology studies.

Dyspnea was reported in 8/377 (2.1%) of BTDS subjects and in no Placebo subjects in the clinical pharmacology studies (Sponsor Table 8.14.1.2.1.1 in the ISS). Ten events were reported

in 8 subjects. For 8 episodes that were judged to be mild in severity, the judged relationship to study drug was possible in 4 cases, probable in 2 cases, and none in 2 cases. No action was required for study drug for these 8 cases. Of the two cases that were judged to be moderate in severity, one was judged to be probably related to study drug (and required discontinuation of study medication) and one was judged not related to study medication. None of these ten events was judged to be serious.

Hypoventilation was reported in 2/377 (0.5%) BTDS subjects, 1/83 (1.2%) BIV subjects, and 1/24 (4.2%) Duragesic subjects in the clinical pharmacology studies. In the two BTDS-treated subjects, five episodes were reported – one in Subject 36 (Inv 195) and four in Subject 1 (Inv 1277). None of the episodes was judged to be serious. Subject 36 was reported to have "subjective decreased respiratory drive" (investigator verbatim term), but never had a respiratory rate below 12 (see Data Listing 16.9.2.1 in the BP98-0201 Study Report). Subject 1, whose case is reviewed in detail above in the section on adverse events that led to study drug discontinuation, had several episodes of apnea and at least one episode of oxygen desaturation.

7.11.4 Pulmonary Function Tests and Hypoxia

Pulmonary function tests were performed in the Phase 2 Study BP96-0104. These tests included respiratory rate, peak flow rate, forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and oxygen saturation. The Sponsor reports in Section 8.13.8.7 of the ISS that "no clinically important changes were observed in peak flow rate, FEV1, or FVC within or between treatment groups. Greater percentages of patients had low O2 saturation values in the BTDS 20 and placebo groups compared with those in the BTDS 5 and 10 groups. The percentage of patients with low O2 saturation values appeared to increase with increasing dosages of BTDS, indicating a possible dose-response relationship." The Sponsor further notes that, after adjustment for covariates, the adjusted least-squares mean respiratory rates were similar between the three BTDS dose groups and the placebo group. Four BTDS-treated patients developed hypoxia, two of whom experienced serious respiratory adverse events (Patients 88 and 79, who are discussed in the serious adverse event section of this review). Because these data are applicable primarily to the post-operative setting, a setting for which BTDS use is not intended by the Sponsor, these data from the Phase 2 study will not be reviewed any further.

Oxygen saturation was measured by pulse oximetry in clinical pharmacology Studies BP95-0901, BP97-1001, BP97-0303, and BP98-0202. The frequency of O2 saturation less than 94% is summarized in the tables below. Most of the low values were in the 90-93% range. The high frequency of low oxygen saturation in the Placebo groups is confounded to some degree by the co-administration of either midazolam or prochlorperazine. It is not clear if any of these measure occurred while subjects were asleep.

Frequency of O2 saturation < 94% in Clinical Pharmacology Studies – BP97-1001, BP98-0202, BP95-0901, BP97-0303			
BP971001 (co-administration with midazolam)			
	BTDS 10	Fentanyl	Placebo
	11/12	9/12	8/12
BP980202 (co-adminstration with prochlorperazine)			
	BTDS 10	Fenatanyl	Placebo
	11/12	8/12	10/12
BP950901			
	BTDS 20	BTDS 20X3	BIV
	14/25	?/27	17/25
BP970303			
	Young Healthy	Elderly Health	Elderly Hypertensive
	10/12	13/13	11/11
? = not available from data BIV = IV buprenorphine Source: Numerators from Table 8.14.1.4.4 in the ISS, denominators from individual study reports			

7.11.5 Blood Pressure

Blood pressure was analyzed by examining mean changes from baseline in systolic and diastolic blood pressure. In addition, the Sponsor analyzed the frequency of low and decreased blood pressure, which is defined for the adequate and well-controlled studies and the open-label Study BP96-0103 in Table 8.13.8.6.1A of the ISS, which is reproduced below. A patient meeting either or both of the criteria was defined as hypotensive.

TABLE 8.13.8.6.1A.
BTDS Integrated Summary of Safety: Adequate and Well-controlled Studies and Open-Label Study (BP96-0103)
Criteria for Low and Decreased Blood Pressure

Blood Pressure	During Treatment	Decrease From Baseline
Systolic	< 100 mm Hg	≥ 30 mm Hg
Diastolic	< 60 mm Hg	≥ 15 mm Hg
Source: Sponsor Table 8.13.8.6.1A in the ISS		

In the Phase 3 controlled studies, mean systolic and diastolic blood pressures were within the normal range at screening and at the end of the study. The mean change from baseline was small and not clinically significant for both of these measures. In the titration-to-effect studies, one subject in the Oxy/APAP group had a systolic blood pressure of 150 mm Hg at Day 30. In titration-to-effect studies, low and decreased systolic blood pressure was noted in 2/338 (<1%) BTDS patients and in no Placebo patients. Low and decreased diastolic blood pressure was noted in 6/338 (2%) BTDS patients and in 1/208 (<1%) Placebo patients. Low and decreased systolic and diastolic blood pressure (ie, patient met both criteria) was observed in 1/338 (<1%) BTDS patients and no Placebo patients. The Sponsor reports that this patient had a history of hypertension and hyperthyroidism, and was on several antihypertensive medications. Hypotension (ie, patient met either or both criteria) was observed 7/338 (2%) BTDS patients and 1/208 (<1%) placebo patients. In the forced-titration studies, no patients in the BTDS groups or in

the Placebo group had low and decreased systolic blood pressure. Five of 312 (2%) BTDS patients and 1/100 (1%) Placebo patients had low and decreased systolic blood pressure, and these same patients were the only ones in the forced-titration studies who met criteria for hypotension.

In the Phase 2 study BP96-0104, mean systolic and diastolic blood pressures were lower at the end of the study compared to screening (see table below). The Sponsor suggests that these changes in blood pressure between the pre-operative period and the post-operative period may be due to factors other than BTDS. The frequency of decreased blood pressure in this study, as well as the definitional criteria for low and decreased blood pressure, is presented in Sponsor's Table 12.5.1B in the BP96-0104 Study Report, which is reproduced below:

TABLE 12.5.1B.
Study BP96-0104
Number of Patients With Abnormal Blood Pressure at End of Study and/or Decreases From Screening to End of Study: Intent-to-treat/Safety Population (N = 110)

	Placebo	BTDS 5	BTDS 10	BTDS 20
	(N = 11)	(N = 33)	(N = 33)	(N = 33)
Blood Pressure Criteria[a]	n (%)	n (%)	n (%)	n (%)
Systolic				
Low (<100 mmHg)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Decrease (≥ 30 mmHg)	2 (18%)	6 (18%)	12 (36%)	13 (39%)
Both low and decrease[b]	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Diastolic				
Low (<60 mmHg)	3 (27%)	11 (33%)	9 (27%)	12 (36%)
Decrease (≥ 15 mmHg)	2 (18%)	11 (33%)	13 (39%)	9 (27%)
Both low and decrease[b]	1 (9%)	7 (21%)	7 (21%)	5 (15%)
Both Systolic and Diastolic				
Low (<100 and <60 mmHg)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Decrease (≥30 and ≥ 15 mmHg)	1 (9%)	5 (15%)	9 (27%)	6 (18%)
Both low and decrease[b]	0 (0%)	0 (0%)	0 (0%)	0 (0%)

(Cross-reference: Appendix 16.2.9.1.)
[a]Patients could be counted in more than 1 category.
[b]Patients meeting these criteria are presented in Table 12.5.1D.
Blood pressure was evaluated at screening and end of study (78 hours, or 6 hours after system removal if patient discontinued early).

Source: Sponsor Table 12.5.1B in the BO96-0104 Study Report

Review of the above table is notable for the relatively high frequencies of decreased systolic blood pressure in the BTDS 10 and BTDS 20 groups, compared to the BTDS 5 and Placebo groups. Decreases in diastolic blood pressure were more frequent in the all BTDS groups, compared to the Placebo group. Decreases in both systolic and diastolic blood pressure were also more frequent in the BTDS group, compared to the Placebo groups. Of the 20 patients with both low and decreased diastolic blood pressure, 10 had a history of hypertension (see Sponsor Table 12.5.1D in the ISS). Sixteen of these 200 patients had a screening systolic blood pressure above 140 mm Hg. In most cases, the Sponsor attributed the change in blood pressure to the combined effects of concomitant illness, advanced age, and the post-operative use of IV morphine. Given the higher frequencies of decreases in blood pressure in the BTDS-treated patients, relative to the Placebo patients, a contributory role for BTDS can not be excluded. Alternatively, Placebo-treated patients may have had higher blood pressure because of less adequately treated pain. Because BTDS is not indicated in the post-operative setting, this hypothesis will not be explored further.

Adverse events in the placebo-controlled Phase 2/3 trials related to blood pressure include hypertension, hypotension, and postural hypotension. Each of these is discussed below.

Hypertension as an adverse event occurred in 6/609 (1.0%) of BTDS patients and 1/319 (0.3%) Placebo patients. One case in a BTDS patient (22209 in Study BP96-0102) who developed a blood pressure of 168/72 required intervention (initiation of anti-hypertensives and referral to his general physician), and the rest were non-serious. One severe case (Patient 29004 in Study BP96-0101) developed a blood pressure of 168/92 while on BTDS 10, and the study medication was stopped.

Hypotension was not reported as an adverse event in the Phase 2/3 placebo-controlled studies.

Postural hypotension was reported in 1/609 (0.2%) BTDS patients and 2/319 (0.6%) Placebo patients. In all cases, it was judged to be mild and no specific action was taken. In all cases, it was also judged to be possibly or probably related to study drug.

In the open-label study BP96-0103, mean systolic and diastolic blood pressures were within the normal range at screening and at the end of the study. The mean change from baseline was small and not clinically significant for both of these measures. The frequency of decreased and low blood pressure in this open-label study is presented in Sponsor's Table 8.13.8.6.1D in the ISS, which is reproduced below:

TABLE 8.13.8.6.1D.
BTDS Integrated Summary of Safety: Open-Label Study (BP96-0103)
Incidence of Low and Decreased Blood Pressure
Intent-to-Treat/Safety Population (N = 384)

Blood Pressure Criteria[a]	No. (%) of Patients
Systolic	
Low[b] (< 100 mm Hg)	3 (<1%)
Decrease (≥ 30 mm Hg)	12 (3%)
Both low and decreased[c]	0
Diastolic	
Low (< 60 mm Hg)	5 (1%)
Decrease (≥ 15 mm Hg)	36 (9%)
Both low and decreased[c]	3 (<1%)
Both Systolic and Diastolic	
Low (< 100 and < 60 mm Hg)[c]	0
Decrease (≥ 30 and ≥ 15 mm Hg)[c]	5 (1%)
Both low and decreased[c]	0

(Cross-references: Tables 8.14.3.4.3 and 8.14.3.4.4.)
[a]Patients can be counted in more than 1 category.
[b]Patients were not counted in the low category if the value also met the criteria at baseline.
[c]Patients in these categories are further evaluated in Table 12.5.1D of Clinical Study Report BP96-0103.

Source: Sponsor Table 8.13.8.6.1D in the ISS

For diastolic blood pressure, the rates of decreased and/or low blood pressure are higher for the open-label study than for the controlled clinical studies. Of the five patients who had a decrease in both systolic and diastolic blood pressure, four had a history of hypertension, and all five had a

baseline systolic blood pressure above 150 (see Sponsor Table 12.5.1D in the BP96-013 Study Report).

In the open-label study BP96-0103, hypertension was reported as an adverse event in 5/385 (1.3%) patients. Hypotension was reported as an adverse event in 1/384 (0.3%) patients, and postural hypotension was reported as an adverse event in 1/384 (0.3%) patients. None of these cases was a serious adverse event.

In the clinical pharmacology studies, mean systolic and diastolic blood pressures were within the normal range at screening and at the end of the study. The mean changes from baseline were variable over time, and tended to be more variable for the BTDS 20 group than for the other BTDS groups or for the Placebo group. In general, however, the mean changes were small and not clinically significant.

In the clinical pharmacology studies, hypotension was defined as a simultaneous decrease from baseline of ≥ 20 mm Hg in systolic blood pressure and ≥ 10 mm Hg in diastolic blood pressure. Among all BTDS-treated subjects, a decrease in systolic blood pressure of at least 20 mm Hg was observed in 152/564 (27%) of subjects. Such decreases in systolic blood pressure appeared dose-related, occurring in 13% of BTDS 5 subjects, 25% of BTDS 10 subjects, and 33% of BTDS 20 subjects. The frequency of a reduction of 10 mm Hg or more is diastolic blood pressure was even more common, occurring in 322/564 (57%) of all BTDS subjects, without any clear relationship to dose. Hypotension, as defined above, appeared dose-related, occurring in 3/40 (8%) BTDS 5 subjects, 53/350 (15%) BTDS 10 subjects, and 35/127 (28%) BTDS 20 subjects. At any BTDS dose, hypotension occurred in 16/25 (64%) healthy elderly subjects compared to 66/483 (14%) healthy young subjects (see Sponsor Table 8.13.8.6.1E in the ISS). The timing of hypotension and other changes in blood pressure was examined over the first 96 hours of patch placement, and no temporal pattern could be discerned (see Table 8.13.A.7B in the ISS).

Hypertension was not reported as an adverse event in any of the clinical pharmacology studies. Hypotension was reported as an adverse event in 2/377 (0.5%) BTDS subjects and in no Placebo subjects. In both cases it was judged to be mild, and in both cases it was judged to be related to study medication (definite in one case and probable in another). Postural hypotension was reported as an adverse event in 1/377 (0.3%) BTDS subjects and in no Placebo subjects. The event was not serious, but was judged to be possibly related to study medication.

In the adequate and well-controlled studies, orthostatic hypotension was defined as a decrease of ≥ 30 mm Hg in systolic blood pressure and of ≥ 15 mm Hg in diastolic blood pressure from recumbent to standing positions. Orthostatic hypotension was not evaluated in the titration-to-effect studies. In the forced titration studies, the mean changes in systolic and diastolic blood pressure from recumbent to standing were small and at no point did they meet the criteria for orthostatic hypotension. In each forced-titration study, orthostatic hypotension was reported for only one patient at one study visit. In Study BP96-0101, Patient 4002, who was receiving Placebo, had on Day 60 a change in blood pressure from 132/70 (recumbent) to 98/52 (standing). In Study BP96-0102, Patient 20201, who was receiving BTDS 10, on Day 9 had a drop in blood pressure from 144/78 (recumbent) to 104/62 (standing). Orthostatic hypotension was not evaluated in the open-label study BP96-0103.

In the clinical pharmacology studies, orthostatic hypoetnsion was assessed in Study BP97-0303, which was designed to assess the effects of BTDS in young healthy subjects, elderly healthy subjects, and elderly hypertensive subjects who were receiving thiazide diuretics, a group that was considered particularly vulnerable to any potential orthostatic hypotensive effects of BTDS.

Subjects received BTDS 5 for 3 days, BTDS 10 for 3 days, and BTDS 20 for 7 days. Orthostatic blood pressure data, including mean changes at various time points, are summarized in Sponsor Table 11.2.2A through 11.2.2C in the BP97-0303 study report. Mean changes in blood pressure from standing to supine were small in all groups.

7.11.6 Pulse Rate

In the Phase 3 forced-titration and titration-to-effect studies, mean baseline and end-of-study pulse rates were in the normal ranges. In both sets of Phase 3 studies, mean changes from baseline were small and not clinically significant (see Sponsor Tables 8.13.8.2C and 8.14.2.4.1.2 in the ISS, both of which are reproduced above).

In Phase 2 Study BP96-0104, mean pulse rates at baseline and at the end of the study were in the reference range for all treatment groups. Mean changes from baseline ranged from +8 to +14 beats per minute, with no clear relationship to treatment group (14 bpm, 10 bpm, 11 bpm, and 9 bpm, for the Placebo, BTDS 5, BTDS 10, and BTDS 20 groups, respectively). Three patients had a pulse rate below 60 bpm at the end of study: 1 patient who received placebo (patient 76, whose pulse was 50 at baseline and 58 at the end of the study), 1 patient who received BTDS 10 (patient 70, whose pulse was 48 at baseline and 59 at the end of the study), and 1 patient who received BTDS 20 (patient 15, whose pulse was 66 at baseline and 55 at the end of the study). Two patients in the BTDS 5 group (patients 39 and 109, whose baseline pulse rates were 102 and 108, respectively, and whose end-of-study pulse rates were 86 and 83, respectively) and 1 patient in the BTDS 20 group (patient 4, whose pulse was 84 at baseline and 68 at the end of the study) had a decrease in pulse ≥15 bpm from screening to the end of study. No patient had a pulse rate below 60 bpm at the end of study and a decrease in pulse of ≥15 bpm from baseline.

In the open-label study BP96-0103, mean pulse rates at baseline and at the end of the study were within the normal range. The mean change from baseline was small (0.4 bpm), and not clinically meaningful (see Sponsor Table 8.13.8.2C in the ISS, reproduced above). Two patients in Study BP96-0103 had an end-of-study pulse rate that was both more than 15 bpm lower than the baseline pulse rate and was also below 60 bpm. Patient 6330, who had no cardiac history, had a baseline pulse of 72 bpm, which decreased to 48 at the end of the study. This patient developed muscle weakness on Day 86, 4 days after drug discontinuation. Vital signs were measured on Day 91, 5 days after the muscle weakness occurred. Patient 1318, who had a history of congestive heart failure, hypertension, and irregular heart beat, had had a baseline pulse of 70 and an end-of-study pulse of 50. Concomitant medications included nifedipine, furosemide, coumadin, lanoxin, metoprolol, and ferrous sulfate.

In the clinical pharmacology studies, mean pulse rates were within the reference range. Occasional pulse rates below 50 bpm were recorded in some subjects. One subject (Subject 10 in BP97-1001) had a screening pulse of 47, and 25 post-screening pulse measurements of 50 or less. Bradycardia was reported for this subject, though the changes in pulse rate were not considered clinically significant.

7.11.7 Body Temperature

In the Phase 3 forced-titration studies, the Phase 2 study BP96-0104, the open-label study BP96-0103, and in the clinical pharmacology studies, the mean baseline and final oral body temperatures were at or slightly below the references ranges. Subjects challenged with oral

endotoxin in Study BP96-1102 had a mean change in oral body temperature of 0.56°C. However, mean body temperatures for these subjects were still within the upper limit of the reference range. For all other study groups, the difference in mean change from baseline were small and not significantly different between treatment groups.

7.12 Physical Examination Findings

In the Phase 2/3 trials, physical examination findings were recorded at baseline and at the end of the study. Review of the data listings reveals that many of the abnormalities were related to underlying muscoloskeletal diseases, such as osteoarthritis and low back pain. There was no pattern of treatment-emergent abnormalities in physical examination findings. Abnormalities of the skin, such as rash, are reviewed in the adverse event section of this review. The Sponsor also notes in Section 8.13.9.2 of the ISS that no clinically significant abnormalities on the physical examination were noted in the clinical pharmacology studies.

7.13 Electrocardiograms

There were no electrocardiograms performed during any of the Phase 3 controlled studies or during the open-label study BP96-0103.

In the Phase 2 study, electrocardiograms were recorded at screening and at the end of the study. A shift table of the frequency of changes from normal to abnormal is provided in Sponsor's Table 12.5.6 in the BP96-0104 study report, which is reproduced below:

TABLE 12.5.6.
Study BP96-0104
ECG Results From Screening to End of Study: Intent-to-treat/Safety Population (N = 110)

	Placebo (N = 11)		BTDS 5 (N = 33)		BTDS 10 (N = 33)		BTDS 20 (N = 33)	
End of study	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Normal at screening	1 (9%)	2 (18%)	3 (9%)	6 (18%)	4 (12%)	4 (12%)	0	5 (15%)
Abnormal at screening	1 (9%)	7 (64%)	3 (9%)	21 (64%)	2 (6%)	23 (70%)	4 (12%)	24 (73%)
(Cross-reference: Appendix 16.2.9.4.)								
Source: Sponsor Table in BP96-0104 Study Report								

Overall, the frequency of shifts from either Normal to Abnormal or from Abnormal to Normal is similar for the four treatment groups. Such an analysis, however, is limited by the fact that the nature of these abnormalities is not clear. Data Listing 16.2.9.4 in the BP96-0104 study report lists the ECG status (ie, Normal or Abnormal) at screening at baseline, and provides the investigator's summary of and comments on the ECG abnormalities. Review of this listing is limited by the fact that when compared to the case report forms, many of the comments are truncated, that is, the final words or phrases are missing. Thus, a full review of these ECG changes is not possible.

7.14 Drug-Demographic Interactions

To assess drug-demographic interactions, the Sponsor assessed the influence of four factors on the adverse event profile of BTDS: gender, body weight, age group (18-64 years versus ≥ 65 years), race (white versus nonwhite), and previous opioid use (opioid-naïve versus opioid experienced).

7.14.1 Gender Differences

In the titration-to-effect studies, nausea, headache, dizziness and vomiting were each notably more common in females treated with BTDS than in males treated with BTDS. For each of these adverse events, the difference in frequency between genders was notably higher than the gender difference in placebo-treated patients (see Sponsor Table 8.13.10.2A in the ISS).

In the forced-titration studies, constipation, nausea, dry mouth, headache, and vomiting were each notably more common in females treated with BTDS than in males treated with BTDS. However, a notable gender difference was also noted in the placebo group for dizziness and pruritus. For constipation, nausea, dry mouth and headache, the difference in frequency between genders was notably higher than the gender difference in placebo-treated patients (see Sponsor Table 8.13.10.2B in the ISS).

In the open-label study BP96-0103, between-gender differences of 7% in the frequency of adverse events were noted for pruritis, nausea, constipation, rash, headache, and vomiting. Each of these adverse events was more common in female BTDS-treated patients than in male BTDS-treated patients (see Sponsor Table 8.13.10.2C).

In the clinical pharmacology studies, between-gender differences of 7% in the frequency of adverse events were noted for headache, nausea, vomiting, constipation, somnolence, asthenia, and pruritis at site. Each of these adverse events was more common in female BTDS-treated subjects than in male BTDS-treated subjects (see Sponsor Table 8.13.10.2C).

7.14.2 Body Weight Differences

Body weight was recorded only in the clinical pharmacology studies. The Sponsor has analyzed the frequencies of adverse events in each of three body weight categories: < 65 kg, 65 kg - < 80 kg, and ≥ 80 kg. There appeared to be an inverse relationship of the frequency of nausea and vomiting with respect to weight: the highest incidences of both nausea and vomiting were reported in the lowest body weight group, and the lowest incidences were reported in the highest body weight group. Asthenia was less common in the highest body weight group compared to the two other weight groups (see Sponsor Table 8.13.10.3 in the ISS).

7.14.3 Age Group Differences

In the titration-to-effect and forced-titration studies, the Sponsor analyzed the frequency of adverse events for three ages groups: 18-64 years (young), ≥ 65 years (elderly), and ≥ 75 years (older elderly, which is a subgroup of the ≥ 65 years group).

In the titration-to-effect studies, differences in frequencies between the young (18-64 years) and elderly (≥ 65 years) group of 7% or more in BTDS-treated patients that were not also noted in Placebo patients occurred for constipation (more common in the elderly) and somnolence (more common in the young) (see Sponsor Table 8.13.10.4A.1). In the titration-to-effect studies,

differences in frequencies between the young (18-64 years) and older elderly (≥ 75 years) group of 7% or more in BTDS-treated patients that were not also noted in Placebo patients occurred for constipation (more common in the older elderly) and for headache, somnolence, vomiting, dry mouth, and erythema at site (all more common in the young) (see Sponsor Table 8.13.10.4A.2).

In the forced-titration studies, differences in frequencies between the young (18-64 years) and elderly (≥ 65 years) group of 7% or more in BTDS-treated patients that were not also noted in Placebo patients occurred for pruritus, dry mouth, and asthenia (more common in the elderly) and headache and pruritus at site (more common in the young). Nausea was notably more frequent in younger BTDS-treated patients compared to older BTDS-treated patients, but it was also notably more common in elderly placebo-treated patients compared to younger placebo-treated patients (see Sponsor Table 8.13.10.4B.1). In the forced-titration studies, differences in frequencies between the young (18-64 years) and older elderly (≥ 75 years) group of 7% or more in BTDS-treated patients that were not also noted in Placebo patients occurred for dry mouth and asthenia (more common in the older elderly) and for headache and pruritus at site (all more common in the young). Dizziness was notably more frequent in younger BTDS-treated patients compared to older elderly BTDS-treated patients, but it was also more common in older elderly Placebo-treated patients compared to younger Placebo-treated patients (see Sponsor Table 8.13.10.4B.2).

In the open-label study BP96-0103, patient age was divided into four groups for analysis of frequency of common adverse events: 18-49, 50-64, 65-74, and ≥ 75 years. The frequency of constipation and somnolence increased with increasing age, while the frequency of headache decreased with increasing age (see Sponsor Table 8.13.A.8F).

In the clinical pharmacology studies, age was divided into two groups for analysis of frequent adverse events: < 65 years and ≥ 65 years (see Sponsor Table 8.13.A.8G). Headache, nausea, vomiting, pruritus, and rash at site were notably more common in younger subjects compared to older subjects. Dizziness, constipation, and abdominal pain were more common in the older subjects compared to younger subjects. Of note, there were only 25 older subjects, compared to 317 younger subjects.

7.14.4 Racial Differences

The majority of patients and subjects in the clinical development program were white, accounting for over 85% of patients in the Phase 2/3 program and over 60% of patients in the clinical pharmacology studies. Because of the relatively small numbers of non-whites in the Phase 2/3 program (and thus the even smaller numbers in any specific treatment group), and because non-whites are not further subdivided in the analyses of adverse events into the reported racial categories (non-white itself is not a specific racial category), it is difficult to interpret the frequency of adverse events by racial groups. Review of Sponsor Tables 8.13.10.5A, 8.13.10.5B, 8.13.A.8H, and 8.13.A.8I indicate that there are no major differences in the occurrence of adverse events between whites and non-whites.

7.14.5 Previous Opioid Use

To determine the impact of previous opioid use on adverse events, the frequencies of adverse events were calculated for opioid-naïve patients and opioid-experienced patients in the titration-to-effect and forced-titration studies (see Sponsor Tables 8.13.10.6A and 8.13.10.6B in the ISS). Among BTDS-treated patients nausea, dizziness, somnolence, constipation, dry mouth and

pruritus were notably more common in opioid-naïve patients compared to opioid-experienced patients. This difference was most striking in the forced-titration studies.

7.15 Drug-Drug Interactions

In the Phase 3 controlled studies, analysis of drug-drug interaction was limited to concomitant benzodiazepine use. In both the forced-titration studies and the titration-to-effect studies, the frequency of adverse events was not substantially different between benzodiazepine-treated subjects and those who did not use benzodiazepines (see Sponsor Tables 8.13.11.2A and 8.13.112.B in the ISS). In a multivariate logistic regression model using data from the titration-to-effect studies, headache was more common in benzodiazepine-treated patients than in those without such treatment (adjusted odds ratio = 2.82, 95% CI: 1.226-6.244, p =0.0117, see Sponsor Table 8.13.A.8C.7 in the ISS). Benzodiazepine use was not statistically significant in any other covariate model.

Durg-drug interactions assessed in the clinical pharmacology program included midazolam (BP97-1001), prochlorperazine (BP98-0202), and thiazide diuretics (BP97-0303).

In Study BP97-1001, BTDS 10 and fentanyl transdermal system were not associated with a difference in respiratory depression in healthy subjects when coadministered midazolam 1 mg IV.

In Study BP98-0202, coadministration of the BTDS 10 and a 25-mg prochlorperazine suppository was not associated with clinically important changes in vital signs or oxygen saturation. Results for the BTDS 10 and the fentanyl transdermal systems were similar.

In Study BP97-0303, the application of the BTDS, administered in escalating doses and applied repeatedly to the same application site, did not result in more episodes of orthostatic hypotension or any associated serious sequelae in elderly hypertensive subjects receiving thiazide diuretics compared to young healthy or elderly healthy subjects.

7.16 Drug-Disease Interactions

Drug-disease interactions assessed in the development program included hepatic impairment (Study BP97-0112), hypertension (Study BP97-0303), and fever/external heat application (Studies BP98-1204 and BP99-0204). No studies of the pharmacokinetics of buprenorphine have been conducted in patients with renal impairment. The Sponsor has conducted a single study evaluating the pharmacokinetics of buprenorphine in patients with mild or moderate hepatic impairment. Results of this study indicate that similar systemic exposures (AUC) but a 50% reduction in Cmax are observed when comparing systemic buprenorphine levels from healthy subjects to those of patients with mild or moderate hepatic impairment. Systemic exposure to norbuprenorphine did not appear to be affected by mild or moderate hepatic impairment. However, this analysis is based on pooling of subjects with mild and moderate impairment. Such pooling may obscure clinically important changes in subjects with moderate hepatic impairment (see Study BP97-0112). Fever (internal heat) does not alter the pharmacokinetics of buprenorphine with BTDS applications (see Study BP96-1102). However, external heat application results in a 26-55% higher Cmax relative to application without heat (see Study BP98-1204). There were no clinically signficant drug interactions in hypertensive patients receiving thiazide diuretics.

8 USE IN SPECIAL POPULATIONS

8.1 Adequacy of By-Gender Investigation and Analyses

The Sponsor has included adequate numbers of subjects and patients of both genders in the clinical development program. The Sponsor has also performed adequate by-gender analyses for both the efficacy data and the safety data. While some of the common opioid-related side effects are more common in women than in men, the overall safety and efficacy data do not suggest any substantial gender differences.

8.2 Pediatric Program Evaluation

On February 21, 2001, the Sponsor submitted proposed pediatric study requesting, consisting of the following general plan:

- (b) (4)
-
-

(b) (4)

The Agency responded to this proposal with a denial of the proposed pediatric study request, and cited the following clinical deficiencies:

1. The proposed plan does not address any pediatric age groups below (b) (4) old. The plan must address all pediatric age groups.

2. The plan must address the need and plans for age-appropriate formulations.

3. The proposed number of patients (b) (4) is not sufficient to provide an adequate safety database. The plan must include a sufficient number of patients (about 200 total) with adequate representation of all age subgroups.

4. The plan must justify the use of BTDS in the treatment of painful crisis (b) (4) While this condition often requires opioid analgesics, such opioid analgesics require rapid onset to relieve pain, the ability to be carefully titrated during the painful crisis, and tapering as the pain subsides. The 7-day BTDS patch may not be appropriate for this setting.

5. The plan must study BTDS in pediatric patients who have pain requiring continuous opioid analgesia. Examples of such patients could include those with chronic pain due to burns, trauma, or cancer. These studies must study safety and pain response in the multiple-dose setting. A formal demonstration of efficacy is not required.

6. The plan must study multiple-dose pharmacokinetics in all age subgroups.

7. The plan must addresses titration to higher doses, if the BTDS 5 is ineffective.

8. The plan must justify the large percent difference (b) (4) in proposed mean pharmacokinetic metrics between adults and children.

8.3 Abuse Liability

The Sponsor presents its analysis of overdose, abuse, or withdrawal for the Phase 2/3 studies in the "Abuse liability, overdose, and overdose management of buprenorphine transdermal system" section if the NDA (see NDA Section 8.15.6.2.).

The Sponsor used four methods to assess abuse liability from data from the Phase 2/3 studies. These four methods are summarized in the table below:

Method Description	Methodological Details
Review of patients with serious or significant adverse events	All available information on any patient who had a serious or significant adverse event (ie, death, other serious adverse event, or adverse events leading to drug discontinuation, drug interruption, or dose reduction) were reviewed by the Sponsor for evidence of overdose or abuse of BTDS, or withdrawal from BTDS or prestudy opioid medications.
Review of COSTART terms	The Sponsor reviewed a blinded list of all COSTART terms containing all adverse events, and terms with "any potential relationship to abuse or withdrawal were selected." Each of these events was assigned a score of 1, 2, or 3, based on the relative likelihood (with a higher score indicating a higher likelihood) that the "event would be anticipated to occur in a patient exhibiting opioid abstinence from BTDS or prestudy opioid medications." The sponsor further notes that abuse of a medication would be more likely to occur if abstinence symptoms were experienced after discontinuing prestudy opioid medication. A score was constructed for each patient based on the value of each term (with events scores being doubled if the event occurred within 7 days after initial application of the transdermal system or within 14 days of system removal). The Sponsor then reviewed all available information for the 10% of patients with the highest scores to ascertain if there was any evidence of overdose or abuse of BTDS, or abstinence following withdrawal of BTDS or pre-study opioid medication. This procedure was performed for controlled Phase 3 studies, as well as for the open-label study.
Review of comment fields for overdose or abuse	For the six blinded Phase 3 studies and for the open-label study, the Sponsor searched the investigator comment fields for the following terms: abstinence syndrome, abuse, addiction, compliance, dependence, drug abuse, drug addiction, drug dependence, near abuse, overdose, tolerance, toleration, withdrawal, and withdrawal syndrome. These terms were reviewed in a blinded manner as described above. In addition, a printout of the comments from the completion/discontinuation case report form was reviewed for every patient who discontinued. All available information was reviewed for any patient identified.
Survey of investigational sites for overdose, abuse or diversion	For two of the controlled Phase 3 studies (BP98-1201 and BP99-0203), the investigator or the principal study coordinator was surveyed using a 6-item questionnaire, either by telephone interview (35 sites) or by fax (6 sites). The six items assessed were: 1) overdose, 2) signs of addiction, 3) overuse, misuse, abuse, or near abuse, 4) diversion, 5) abuse liability, and 6) abuse risk of BTDS compared with oral combination analgesics.

The Sponsor concluded that there was no evidence of abuse, overdose, or withdrawal involved in the 2 deaths in the NDA studies.

After review of patient narratives of serious and significant adverse events (n=297), the Sponsor identified four cases that merited further discussion in Section 8.15.6.2.1.2 of the abuse liability section of the NDA. These four cases are briefly reviewed in the table below:

Study/ Patient	Brief Summary and Comments
BP96-0102/ 20226	25-year-old woman with low back pain who discontinued tramadol and propoxyphene napsylate/acetaminophen on Day –1. Started BTDS 5 on Day 0, and developed severe shakiness, headache, and weakness 3-5 hours after BTDS application. Judged by investigator to be probably related to study drug. Study medication was discontinued and the event resolved. Sponsor judged event to be related to withdrawal to prestudy opioids.
BP96-0102/ 21204	31-year-old man with low back pain whose pre-study oxycodone was discontinued on Day 0, at which time oxy/APAP was started. On Day 2, he noted mild restlessness and irritability, and awakening at night. These events were judged by the investigator to be possibly related to study medication. On Day 5, the restlessness resolved, but a rash developed, judged by the investigator to be possibly related to study medication. Because of the rash, study medication was stopped on Day 6, and the rash resolved on Day 8. The Sponsor judged the restlessness, irritability, and awakening to be possibly a manifestation of abstinence from prestudy opioids.
BP96-0102/ 21238	26-year-old woman with low back pain whose prestudy hydrocodone/APAP was discontinued on Day 0., who was started on BTDS 5 on Day 0. On Day 1, while on BTDS 5, she experienced mild hot flashes, judged by the investigator to be probably related to study drug. On Day 2, she reported "the shakes" and felt as if her skin was crawling, both of which were judged by the investigator to be possibly related to study medication, as was mild vomiting on that day. Medication was discontinued on Day 2 because of the skin crawling sensation and vomiting, and the events resolved that day. The Sponsor judged these events to be probably related to abstinence from prestudy opioids.
BP96-0103/ 24303	77-year-old man with low back pain, treated with placebo TDS in study BP96-0102. The patient entered the open-label study (Day 0), and was titrated to BTDS 20 on Day 62. He remained on this dose, but on Day 177 began to supplement the BTDS with his own oxycodone/APAP because of worsening back pain. On Day 182, he stopped the BTDS because of lack of efficacy and because of the concomitant use of oxy/APAP, which he continued taking. On Day 184, he reported dry heaves and weight loss. He required a one-day hospitalization on Day 188 for dehydration. On Day 192, he was found to have a 15-pound weight loss. On Day 196, he attempted suicide, probably with benzodiazepines (found on urine toxicology screen). After a hospitalization complicated by rhabdomyolysis and anemia, he was transferred to an inpatient psychiatric facility on Day 204. The Sponsor judged none of these events related to abstinence from BTDS.

Further review of the narratives (see Section 9.6 of 4-month safety update) was notable for two cases, not identified by the Sponsor, which describe instances of a withdrawal or possible withdrawal syndrome.

Study/ Patient	Brief Summary and Comments
BP96-0103/ 07309	70-year-old woman who interrupted BTDS 20 from Day 213 to Day 219 in order to have total knee replacement surgery. The narrative notes that "the patient reported mild restlessness judged possibly related to withdrawal of study medication." Of note, the AE data listing (8.14.3.8.1 in the 4-month safety update) notes that this event lasted for 243 days.
BP96-0104/ 00011	43-year-old man treating with placebo patch post-operatively after a right total hip replacement. Received placebo patch for 40 hours when it was prematurely discontinued due to rash. After patch removal, he developed shakiness, which ended 6.5 hours later.

The Sponsor's review of the COSTART terms identified 117 patients with the highest scores for abuse or withdrawal. The Sponsor then reviewed the available data for each of these patients. Based on this review, the Sponsor concluded that 5 patients "probably or definitely" experienced

"abstinence from prestudy opioids or benzodiazepines." These Sponsor-identified cases are summarized in the table below:

Study/ Patient	Brief Summary and Comments
BP98-1201/ 15106	66-year-old woman who discontinued prestudy analgesics (hydrocodone/APAP and fentanyl patch) two days prior (Day –2) to initiating BTDS 5 on Day 0. The daily dose of HCD and fentanyl total 180 mg of morphine equivalents/day. On Day 0, she reported mild hot flashes, mild diarrhea, moderate chills, and a severe headache, judged by the investigator to be definitely related to study medication. That same day, she discontinued the BTDS and resumed her prestudy medications, with resolution of her symptoms the next day. The Sponsor judged these events to definitely represent abstinence from prestudy opioids.
BP96-0604/ 16609	75-year-old man who discontinued prestudy oxycodone/acetaminophen one day prior (Day –1) to initiating BTDS 5 on Day 0. On Day 2, he developed moderate diarrhea and sneezing, and severe headaches and loss of appetite. These events were judged by the investigator to be possibly related to study medication. On Day 2, he discontinued the BTDS and restarted the oxycodone/acetaminophen with resolution of symptoms. The Sponsor judged these events to probably represent abstinence from prestudy opioids.
BP96-0604/ 16609	47-year-old man who discontinued prestudy bromfenac one day prior (Day –1) to initiating BTDS 5 on Day 0. On Day 2, he developed moderate headaches, palpitations, sweating, tremulousness, and related adverse events over the subsequent 10-day period as he proceeded from BTDS 5 to BTDS 20. These events were judged by the investigator to be probably related to study medication. On Day 21, he discontinued the BTDS due to lack of efficacy. The Sponsor judged these events to probably represent abstinence from prestudy opioids.
BP98-1201/ 16292	32-year-old man who discontinued prestudy hydrocodone/acetaminophen and oxycodone/acetaminophen two days prior (Day –2) to initiating BTDS 5 on Day 0. Prestudy diazepam was also discontinued on Day –2. On Day 0, he developed mild blurred vision, moderate facial muscle clenching, mild tachycardia, and moderate mental confusion. These events were judged by the investigator to be due to abstinence from diazepam. On Day 2, he discontinued the BTDS and resumed his prestudy medications. The Sponsor also judged these events to probably represent abstinence from prestudy diazepam.
BP99-0203/ 2052	46-year-old woman who discontinued prestudy hydrocodone/acetaminophen one day prior (Day –1) and alprazolam three days prior (Day-3) to initiating placebo TDS 5 on Day 0. On Day -1, she developed moderate weight loss, headache, insomnia, diarrhea, muscle cramps, and sweating. These events were judged by the investigator to be due to abstinence from alprazolam. On Day 2, he discontinued the TDS and was restarted on hydrocodone/acetaminophen. The Sponsor judged these events to probably represent abstinence from prestudy alprazolam.

In review of the above cases, it is possible that the adverse events in patients 16292 and 2052 could also represent withdrawal from prestudy benzodiazepines.

Further review of the adverse event listings indicates that two patients had adverse events whose COSTART term is "Withdrawal Syndrome", though these two patients appear not to have been identified by the Sponsor's algorithm for identifying patients with potential abuse of withdrawal based on COSTART terms.

Study/ Patient	Brief Summary and Comments
BP96-0101/ 11009	51-year-old woman randomized to Placebo, whose prestudy Vicodin was stopped on Day 0, who developed "drug withdrawal" (investigator term) on Day 0, leading to drug discontinuation on Day 2.
BP98-1201/ 2258	48-year-old woman who stopped BTDS 20 on Day 49. One day later, she developed a withdrawal syndrome (not further characterized), which lasted for 6 days. After she stopped study medication, she was instructed to take Tylenol #3 and to take Ativan for the withdrawal symptoms.

The Sponsor's review of the investigator comment fields identified six patients in whom there was a concern of overdose, abuse, or abstinence.

Study/ Patient	Brief Summary and Comments
BP98-1201/ 10155	47-year-old man who discontinued prestudy medications (acetaminophen/caffeine and acetaminophen/codeine #3) one day prior (day –1) to starting BTDS 5 on Day 0. On Day 0 he developed mild headaches, nervousness, and mild loss of appetite. These symptoms were managed with diphenhydramine and amitriptyline starting from Day 2. He started BTDS 10 on Day 1 and BTDS 20 on Day 12, but went back to BTDS 10 on Day 13 and then down to BTDS 5 on Day 21 because of adverse events. He discontinued on Day 28 because of these symptoms, which the investigator judged to be due to withdrawal of his prestudy opioid medications. The Sponsor concurred with this assessment.
BP96-0103/ 7309	70-year-old woman who interrupted BTDS 20 from Day 213 to Day 219 in order to have total knee replacement surgery. The narrative notes that "the patient reported mild restlessness judged possibly related to withdrawal of study medication." Of note, the AE data listing (8.14.3.8.1 in the 4-month safety update) notes that this event lasted for 243 days.
BP96-0103/ 8303	The Sponsor notes that at the Day 28 visit, the patient was to have used three BTDS patches, but actually used two. The Sponsor further notes that the calculation for compliance was inverted, yielding a result of 150% instead of 67%. Because the protocol required any patients who was more than 125% compliant to be terminated from the study, the patient was discontinued because of a protocol violation with medication compliance. The investigator comment on the discontinuation from noted "drug seeking". The Sponsor contends that drug seeking is unlikely, given that two patches instead of three were actually used (and assumes that the compliance calculation is erroneous). It is equally likely, however, that the compliance calculation is accurate, but that the entries for numbers of patches used is erroneous.
BP98-1201/ 2022	32-year-old man on BTDS, who changes his patch every 2 to 4 days (rather than every 7 days), either due to lack of efficacy or to adverse events. He discontinued on Day 37 due to protocol violations for noncompliance with study visits, medication, and failure to return study drug (he failed to return 107 placebo tablets and 8 BTDS 10 patches). It is not known what medications he took after Day 37, though on Day 77 he developed anxiety and chills, which the study site attributed to withdrawal from study medication. The Sponsor also noted that these events may possibly be due to withdrawal of study medication. Of note, this case may also represent abuse of BTDS.
BP98-1201/ 2254	26-year-old woman who was frequently changing the patch (every 0-3 days, rather than every 7 days), and consumed twice as many placebo tablets as were recommended (232 vs. 108 recommended). This noncompliance was noted only at the final visit. She discontinued study medication on Day 15 because the patch would not remain in place. The Sponsor judged this to be a definite case of drug-seeking behavior.
BP98-1201/ 16292	32-year-old man who discontinued prestudy hydrocodone/acetaminophen and oxycodone/acetaminophen two days prior (Day –2) to initiating BTDS 5 on Day 0. Prestudy diazepam was also discontinued on Day –2. On Day 0, he developed mild blurred vision, moderate facial muscle clenching, mild tachycardia, and moderate mental confusion. These events were judged by the investigator to be due to abstinence from diazepam. On Day 2, he discontinued the BTDS and resumed his prestudy medications. The Sponsor also judged these events to probably represent abstinence from prestudy diazepam.

Review of the above narratives suggests that BTDS may be a drug sought out by those who seek to abuse opioid analgesics, though the strict drug dispensing standards in a clinical trial setting, relative to general clinical practice, preclude an assessment of how common this problem will be.

The Sponsor also conducted a survey of all investigators in Study BP98-1201 and BP99-0203, using a 6-item questionnaire, either by telephone interview (35 sites) or by fax (6 sites). The six items assessed were: 1) overdose, 2) signs of addiction, 3) overuse, misuse, abuse, or near abuse, 4) diversion, 5) abuse liability, and 6) abuse risk of BTDS compared with oral combination analgesics. Results of the survey are presented in Sponsor Table 8.15.6.2.2.2 in the Abuse Liability section of the NDA, which is reproduced below:

TABLE 8.15.6.2.2.2.
Abuse Liability, Overdose, and Overdose Management of BTDS
Responses of BP98-1201 and BP99-0203 Investigators to BTDS Abuse Potential Survey

Question No.	Item	Responses				Comments
		BP98-1201 (N = 22)		BP99-0203 (N = 24)		
		No	Yes	No	Yes	
1	Overdose	22	0	24	0	None
2	Signs of Addiction	20	2	24	0	At the Cesarec site in BP98-1201, patient 2022 reported withdrawal-type symptoms (anxiety, chills) after removing the last BTDS. At the Safdi site in BP98-1201, patient 17122 was always tired, in bed, and calling in a drowsy state. The site suspected addiction.
3	Overuse, Misuse, Abuse, or near abuse	20	2	24	0	At the Cesarec site in BP98-1201, patient 2254 had the BTDS constantly falling off due to sweating and humidity. The patient also did not return the study medication as instructed. The Safdi site in BP98-1201 suspected that patient 17117 was using the study medication for pain that was not as severe as initially reported.
4	Diversion	21	1	24	0	At the Safdi site in BP98-1201, patient 17122 was changing the BTDS too frequently without a valid reason.
5	Abuse Liability	20	2	24	0	At the T. Kelly site in BP98-1201, the investigator felt that the BTDS lasted 5.5 days, which might prompt patients to look for additional pain medications or to misuse the product. At the Safdi site in BP98-1201, it was felt that chronic opioid use always presents the possibility for abuse. Drs. Shergy and Lamb in BP98-1201 felt there was less abuse potential with BTDS.
6	Abuse risk of BTDS compared with oral combination analgesics	68.3% (28/41) = less 24.4% (10/41) = same 7.3% (3/41) = no opinion				Use of BTDS would be less likely to be distributed on the street. BTDS is a very useful, safe product.

Source: Sponsor Table 8.15.6.2.2.2 in Abuse Liability section of the NDA

Questions 1-4 in the above table asked the Investigator if he or she was aware of any overdose, signs of addiction, overuse, misuse, abuse, near abuse, or diversion in the patients treated at their sites. Question 5 and 6, on the other had, asked the Investigators about their opinions regarding abuse liability and abuse risk. For example, Question 5 reads “Have you any other concerns about the abuse liability of BTDS?” An answer of “No” to this question does not necessarily imply that an investigator has no concerns at all about the abuse liability or abuse risk of BTDS.

The above table is notable for two patients (17122 and 17117 in BP98-1201) who were not identified by any of the other methods to assess abuse or diversion. Patient 17122 was suspected of addiction and diversion, and Patient 17117 was suspected of possible abuse (ie, using it for pain that was not as severe an initially reported).

The Sponsor concludes that its methodology identified 9 patients with possible, probably, or definite abstinence from prestudy medications, 2 patients with possible or probable abstinence from BTDS, and possible, probable, or definite drug-seeking behavior in 3 patients. Review of the Sponsor’s methodologies, data and conclusions is notable for the following:

- The methodology is retrospective, and thus potentially relevant events that were not recorded are missed.
- Because all patients were followed immediately after study drug was started (and thus after prestudy opioids and/or benzodiazepines were discontinued), it is not surprising that some cases of possible or probable withdrawal from prestudy opioids and/or benzodiazepines were detected. Because the method for detecting these cases was based on symptoms, and not a standardized prospective evaluation for withdrawal, the true incidence of this finding is not known.
- Because patients were not followed in a standardized fashion after discontinuation of study medication, the frequency of withdrawal after BTDS can not be ascertained.
- The validity of the COSTART term-based algorithm to identify patients with possible abuse or withdrawal is not known. However, this method failed to identify the two patients in the AE database with an AE corresponding to the COSTART term "Withdrawal syndrome".
- A withdrawal syndrome after discontinuation of BTDS can occur (eg, patient 7309).
- BTDS may be a drug sought out by those who seek to abuse opioid analgesics, though the strict drug dispensing standards in a clinical trial setting, relative to general clinical practice, preclude an assessment of how common this problem will be.
- The relatively strict environment of a clinical trial, compared to actual clinical practice, precludes assessment of the abuse liability or abuse risk that may derive from the fact that the majority of the buprenorphine is still in the patch even after the patch has been worn for 7 days, and that the buprenorphine is easily extractable from the patch.

The Sponsor has also completed a BTDS abuse liability study in 9 non-opioid dependent volunteers, to determine the safety of BTDS 20 mg and the time course and magnitude of the subjective effects of buprenorphine administered transdermally compared with buprenorphine injectable (Buprenenx®) and with placebo given intramuscularly. Because a final study report for this study was received late into the review cycle (received June 29, 2001), a formal review of this study will not be included in the NDA. The Sponsor summary of the study design, in Section 8.15.6.2.4.1 of the Abuse Liability section of the NDA, is as follows:

> "The study involves 2 phases. The initial phase, a run-in practice session, exposes the subject to BTDS 20 mg. The second phase consists of a double-blind, double-dummy, randomized, 3-way crossover session to assess the subjective effects of BTDS (2 × 20 mg) transdermally compared with Buprenex® (0.9 mg) and with placebo administered intramuscularly. Each of 4 test sessions lasts approximately 26 hours. A washout period of at least 70 hours will be interposed between each test period. The total duration of the study for each subject will be approximately 18 days.
>
> Subjects will report to the clinical research unit approximately 48 hours before the scheduled dosing time on Day 1 of the practice session. On admission, subjects will undergo a urine drug screening, an alcohol breath test, a physical examination, and an interview and observation period for signs of opioid dependence conducted by trained site personnel.

> Each of the four 26-hour test sessions (practice session plus 3-way crossover) will consist of 1 day of dosing with 2 doses administered as follows: 2 BTDSs will be applied the morning of Day 1 and removed approximately 26 hours later, and a single injection will be administered in the hip within 2 minutes of the application time of the BTDS. Following dosing, subjects will complete a computer-aided battery of subjective assessments. Pupil diameter and vital signs will be measured at predose -1 hour (pupillometry only) and -0.5 hours, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 8, 24, 25, and 26 hours postdose on Day 1 of each test session. Oxygen saturation will be monitored continuously from -0.5 hours predose through 26 hours postdose on Day 1 of each test session at the same time points as the vital signs. On nights following administration of study drug, only oxygen saturation <92% or any results associated with symptoms of hypoxia will be documented. Exit evaluations will include a physical exam with vital signs, blood tests, and a 12-lead electrocardiogram (ECG)."

A potential problem with the above study design is that levels of buprenorphine are negligible for the first 12-15 hours after patch application, and do not reach steady state until beyond that time point. Intramuscular buprenorphine, however, reaches is maximum levels well within the protocol-specified observation period, so the planned comparison does not appear to be valid.

8.4 120-Day Safety Update

Review of all relevant material form the 120-Day Safety Update has been incorporated into the review of the ISS.

9 REVIEW OF PACKAGE INSERT

In view of the Agency's conclusion that the Sponsor has not provided substantial evidence of effectiveness of the product, no formal review of the package insert was conducted.

10 Appendices

10.1 Appendix A

Appendix A

NDA 21-306
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Summary of Clinical Questions for Sponsor

Feburary 22, 2001

Protocol BP99-0203:

1. What was the intent of the phrase "patients suffering with osteoarthritis pain ***secondary to a flare*** in the knee or hip" (emphasis added) in the protocol objective? How did investigators assess or record the presence of a flare, as the formal entry criteria do not specify a flare, and the CRFs have no place to record the presence of a flare?

2. How many patients were screened for the study? How many patients were screened but did not enter the ibuprofen Run-In Period? How many patients entered the ibuprofen Run-In period but were not randomized?

3. How many patients were enrolled at the time of each protocol amendment? (It appears that Amendment 1 occurred before enrollment began.)

4. It appears that the change of ibuprofen dose during the Run-In Period in Amendment 1 was from 200 mg QID to 400 mg TID. Amendment 2 also changed the dose of ibuprofen during the Run-In Period from 200 mg QID to 400 mg QID. Should not Amendment 2 have changed the dose from 400 mg TID to 400 mg QID?

5. Are the actual Case Report Forms the most recently corrected version? For example, Patient 100-2194 is listed in Data Listing 16.2.1 as having discontinued due to an adverse event related to test medication (itching), and the AE listing (Data Listing 16.2.7.1) indicates that the "TEST MED ACTION TAKEN" was "MED DISCONT". However, the AE CRF for this patient does not capture the fact that an episode of itching led to study drug discontinuation. Please explain.

6. How were protocol violations defined, apart from the definition in Section 10.2 of the Study report? Were they prospectively defined? Who determined if a protocol deviation constituted a protocol violation?

Study BP96-0604

7. How many patients were screened for this study?

8. Please provide a by-patient listing with the following information for all patients in Study BP96-0604:

Inv. No.	Pat. No.	Treatment Group	Study Completion	Completed or Reason for Discontinuation	Study Day of				LOCF Value	
					Completion or Discont.	Last Dose	Pain Scores Used in LOCF Analyses		Pain on Average	Pain Right Now
							Actual	Visit		

The "Study Completion" and "Completed or Reason for Discontinuation" should be the same data as are found in Data Listing 16.2.1. The "Study Day of Study Completion or Discont" and the "Study Day of Last Dose" should be the study days corresponding to the appropriate dates in Data Listing 16.2.1. The "LOCF Value – Pain on Average" and the "LOCF Value – Pain Right Now" should correspond to the LOCF values in Data Listing 16.2.6.1.2 and should be the LOCF values used in the primary and secondary analyses. There is no need to put values other than the LOCF values in this listing. The "Study Day of Pain Scores Used in the LOCF Analyses - Actual" should be the study day corresponding to the day the LOCF value was assessed, as noted in Data Listing 16.2.6.1.2. The "Study Day of Pain Scores Used in the LOCF Analyses - Visit" should be the study day corresponding to the Visit when the LOCF value was assessed, as noted in Data Listing 16.2.6.1.2. Please provide both a printed version of this listing as well as a SAS transport file.

General

9. The nature and content of many datasets, especially derived data sets, in the CRT folder is not apparent from their names. The "Description of Dataset" in the DEFINE.PDF folder generally is the same as the dataset name, and thus does not help to describe the dataset. Given that many start with "I1_", is there some system for interpreting the names of these datsets? If not, please provide more descriptions of these datasets that clarify the dataset name. In terms of priority, Studies BP99-0203 and BP96-0604, followed by the ISS datasets (including any new datasets submitted with the 120-Day Safety Update), should have the highest priority.

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March 7, 2001

Study BP96-0604

1. The datasets for the inclusion criteria (INCLUDE) and exclusion (EXCLUDE) criteria for Study BP96-0604, as well as the corresponding DEFINE.PDF files, can not be located. Please indicate their location in the submission, or provide these datasets if they were omitted form the submission

2. How extensively was the "Pain Site" evaluated and documented by the investigator? Were standard criteria used across all investigational sites?

3. How extensively was the "Disease/Condition Causing the Back Pain" evaluated and documented by the investigator? Were standard criteria used across all investigational sites?

4. Provide a table of laboratory values for Study BP96-0604 similar to Table 14.3.4.3 in Study BP99-0203 (ie, include N, Mean, Std. Error, Median, Min, Max for each lab test at Screening, Final Visit, and change from Screening to Final.) If such a table was included for Study BP96-0604 in the submission, provide its location.

5. Based on the inclusion criteria in Study Protocol BP96-0604, it appears that patients could be taking opiates at the time they were screened for the study. However, opiates for back pain were not permissible concomitant medications (Section 5.3.5.4 of the protocol). Were baseline opiate analgesics in patients who were "opiate-exposed" or "relatively opiate naïve" discontinued or "washed out" for a specified period of time before study medication was started? It appears from Data Listing 16.2.11.2 that the opiate was discontinued the day before the VISIT DATE. Does the VISIT DATE in Listing 16.2.11.2 refer to the date of the baseline visit. Where in the study protocol are the plans for discontinuing or otherwise managing baseline analgesics discussed?

CRTs

1. The file CRT/DATASETS/ndapool3/LAB3.xpt is 41,343 KB in size. Divide this file into two files, based on LAB TYPE (ie, chemistry, hematology, etc), so that each file is less than 25,000 KB in size. All lab tests (ie, LAB KEYs) for a specific LAB TYPE should be in the same file. The division of LAB TYPEs between the two files should be done so that the two files are roughly the same size.

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March 22, 2001

1) To analyze the occurrences of neutropenia in Phase 1 studies of BTDS in the NDA, provide the following information:

a) Create a line listing of all subjects in the Phase 1 studies who had any post-baseline (ie, after start of study treatment) absolute neutrophil count (ANC) less than 2,000/mm^3. Include the following information in the listing:

Pro-tocol	Inv	Pat	Treat-ment Group	Dose	Baseline				Lowest ANC Value					Final ANC Value				
					WBC (/mm^3)	Neutro-phil (%)	Band (%)	ANC (/mm^3)	Study Day*	WBC (/mm^3)	Neutro-phil (%)	Band (%)	ANC (/mm^3)	Study Day*	WBC (/mm^3)	Neutro-phil (%)	Band (%)	ANC (/mm^3)
*If necessary, specify the Study Day relative to first dose of study medication, as well as the duration from removal of last dose of study medication, if applicable																		

b) Was study drug prematurely discontinued because of neutropenia for any subject in Phase 1 studies?

c) Was specific treatment for neutropenia necessary for any subject in Phase 1 studies?

d) To analyze pre- and post-baseline ANCs in all subjects in Phase 1 studies, create the following shift table for each treatment group:

		Lowest Post-baseline ANC (/mm^3)				
		≥ 2,000	1,500 - <2,000	1,000 - <1,500	500 – <1,000	<500
Baseline AUC (/mm^3)	≥ 2,000					
	1,500- <2,000					
	1,000- <1,500					
	500- <1,000					
	<500					

2) Repeat analyses 1a-1d for the Phase 2/3 studies in the NDA.

3) Provide any additional follow-up (eg, results of tests pending in the hematologist's report) for the SAE of neutropenia reported on March 14, 2001and on March 20, 2001.

Submit paper copies of the responses to Questions 1-3 to IND 50,273.

Submit the responses to Question 1 and 2 to NDA 21-306, in either electronic or paper format. Regardless of the format of the responses, for each of the tables requested in 1a and 2a, also submit the data in a SAS transport file. In the SAS transport file, include visit number and visit date corresponding to the Study Days.

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April 3, 2001

1) For Study BP96-0604, analyze "Pain on Average" using the same statistical model as was used in Figure 11.1A in the BP96-0604 Study Report, but with no carry forward. Include the results of a repeated measures analyses from Study Day 21 through Study Day 84 (RM21-84). Present the LS mean results in a table and graphs similar to Figure 11.1A.

2) For Study BP96-0604, analyze "Pain Right Now" using the same statistical model as was used in Figure 11.1B in the BP96-0604 Study Report, but with no carry forward. Include the results of a repeated measures analyses from Study Day 21 through Study Day 84 (RM21-84). Present the LS mean results in a table and graphs similar to Figure 11.1B.

3) For Study BP96-0604, provide the SAS code for the PROC MIXED procedure used for the repeated measures analysis of both "Pain on Average" and "Pain Right Now."

4) For the pooled titration-to-effect studies (BP96-0604 and BP99-0203) in the Integrated Summary of Efficacy, repeat the repeated measures mixed model analyses for "Pain on Average" and "Pain Right Now" including a treatment-by-age interaction term as a potential covariate.

****

April 16, 2001

1) Were only "treatment-emergent" adverse events included in the adverse events tables listings? If an algorithm for treatment emergence was used, explain the algorithm.

2) For the titration-to-effect studies, it appears that adverse event incidence data are presented for all doses combined, while for forced-titration studies the adverse event incidence rates are presented for the assigned dose. It appears that there are no adverse event incidence rates presented by the dose at which the adverse event actually occurred. If such rates are included in the NDA, provide their location. If such rates are not included in the NDA, generate a table of adverse event rates by dose at which the event occurred. Include data from the forced-titration and the titration-to effect studies. The table can be similar in format to Table 8.14.2.2.1.4 in the 4-month safety update. The rows entitled "BTDS 5 mg", "BTDS 10 mg", and "BTDS 20 mg" should contain data for AEs that occurred at that dose level. The row "BTDS regimens combined" should be retained. For AEs occurring in the same patient at different dose levels, explain the method used to assign an AE to a given dose level. For AEs whose onset is after the discontinuation of study medication, explain the method of assigning these AEs to a specific dose level. For consistency with the rest of the safety data in the ISS, generate separate tables for the "worst case" of severity and seriousness, as well as for the "as reported" cases.

3) Explain how durations of adverse events and days relative to start of study medication were determined. Were all durations of less than 24 hours taken from the "Duration of Event (<24 hr)" field on the Adverse Experiences CRF, and converted to a fraction of a day? Were other durations determined by calculating the difference between two dates? If yes, was the calculation method used the same as the paradigm set forth in the Guidance for Industry "Providing Regulatory Submissions in Electronic Format – NDAs", Section IV.K, Item 11.6 (General considerations for datasets)? If not, justify the use of an alternative method of calculation.

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June 1, 2001

1) There appears to be a discrepancy in the two tables presenting subject disposition for the Phase 1 clinical studies in the ISS. The *Clinical Pharmacology Studies* subsection of section 8.13.3.2 of the ISS, as well as Table 8.13.A.2A in the Appendix, note that 21 subjects discontinued from a Phase 1 clinical study. Tables 8.14.1.1.1 and 8.14.1.1.2 also note that 21 subjects discontinued. In Table 8.14.1.1.3, the *All Studies* subheading indicates that 21 subjects discontinued. However, the sum of the patients in the six subgroups below in Table 8.14.1.1.3 totals 24. Specifically, under each of the subheadings of *Interaction Studies*, *Hepatic Impaired*, and *Elderly Hypertensives*, there is one patient who received BTDS 20 who is listed as Discontinued, though the corresponding percentage is 0. These three patients are not accounted for in Table 8.14.1.1.2. Please explain this apparent discrepancy.

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June 7, 2001

1) Please send Page 3 of Amendment No. 2 for Protocol BP96-0604, dated March 11, 1998. We note that pages 891-893 of the BP96-0604 clinical study report contain pages 1, 2, and 4 of the amendment.

2) Please complete the following table of patient-days of exposure in the Phase 2/3 studies. Please note that data for BTDS 5, BTDS 10, and BTDS 20 should be based on actual dose received. (We realize that some of the data, especially for BTDS, is in the application, but we were unable to locate all of the information requested below.)

	Patient-Days of Exposure						
	Treatment						
Study	BTDS 5*	BTDS 10*	BTDS 20*	BTDS (All)	Placebo	Oxy/APAP	HCD/APAP
BP96-0104							
BP96-0101							
BP96-0102							
All Forced-Titration Studies							
BP96-0604							
BP98-1201							
BP99-0203							
All Titration-to-Effect Studies							
BP96-0103							
All Placebo Controlled Studies							
All Controlled Studies							
All Phase 2/3							
*Based on actual dose received							

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June 11, 2001

1) Table 8.13.6.3.2 of the ISS indicates that the serious adverse event (SAE) "cerebrovascular accident" occurring in Patient 2165/2063 was reported to the FDA, but not included in the database. Explain why this SAE was not included in the database. What steps were taken to insure that all adverse events that were serious were reported in the NDA? Was an adverse event designated as serious based solely on the investigators' designation, or were all adverse events reviewed by the Sponsor for seriousness? Was the investigator's determination of seriousness re-classified by the Sponsor for any adverse event?

2) As was discussed briefly in a telephone conversation between the Division and the Sponsor on Friday, June 7, 2001, the assignment of COSTART terms (variable name ENGLISH in the CO_ADR3 dataset) is not always apparent when looking at the investigator verbatim term (variable name ADR in the CO_ADR3 dataset). The example of pruritus was discussed, and the Sponsor explained that an algorithm was used to classify pruritus-related AEs to either PRURITUS or to PRURITUS AT SITE. Review of several pruritus-related AEs reveals many whose coded term is not evident from the investigator verbatim term (see Attachment I). Some of these are presented in the accompanying table. While a few of the investigator verbatim terms corresponding to the coded term PRURITUS AT SITE can probably be explained by the algorithm briefly presented by the Sponsor in the phone conversation, many

can not be explained. Explain the algorithm for coding pruritus-related AEs, and explain how that algorithm results in the coding of AEs in the examples in Attachment I.

3) Review of the CO-ADR3 dataset indicates that most AEs of edema in the limbs were coded to the COSTART term PERIPHERAL EDEMA. However, the following terms were coded to EDEMA. Explain this choice of coding terms.

PROTOCOL	INO	PNO	ADR	ENGLISH
BP960101	1215	21005	RIGHT LEG SWOLLEN	EDEMA
BP960101	1248	3027	SWOLLEN LEGS	EDEMA
BP960101	1630	7004	BILAT DECREASED EXT. EDEMA	EDEMA
BP960101	1630	7014	EDEMA LOWER EXT.	EDEMA
BP960101	1630	7027	EDEMA LOWER EXT	EDEMA
BP960101	1692	5010	BILATERAL LE EDEMA	EDEMA
BP960604	1723	3607	SWELLING BOTH HANDS	EDEMA
BP990203	1995	1101	1+ EDEMA LEFT FOOT	EDEMA
BP990203	2062	1057	1+ PITTY EDEMA PRE-TIBIAL	EDEMA
BP990203	2062	2058	LOWER LEG EDEMA	EDEMA

4) Explain the variable coding if investigator terms “cold”, “cold symptoms”, and related terms:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP960101	131	8023	COLD	CHILLS	BODY	
BP960101	131	8023	COLD	CHILLS	BODY	
BP960102	1627	20230	COLD	CHILLS	BODY	
BP960102	1756	29201	COLD	CHILLS	BODY	
BP960102	302	28213	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960102	1721	26217	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960604	1820	16607	COLD SYMPTOMS	FLU SYNDROME	BODY	RUNNY NOSE, SORE THROAT, CONGESTED
BP960604	1820	16619	COLD SYMPTOMS	FLU SYNDROME	BODY	
BP960101	100	4021	COLD-LIKE SYMPTONS	INFECTION	BODY	
BP981201	1878	2022	COLD	PHARYNGITIS	RES	PT. TOOK NYQUIL FOR RELIEF
BP990203	1215	2017	COLD	PHARYNGITIS	RES	
BP990203	2061	1161	COLD	PHARYNGITIS	RES	
BP981201	2032	6231	COLD LIKE SYMPTOMS	PHARYNGITIS	RES	
BP981201	1215	5044	COLD SYMPTOMS	PHARYNGITIS	RES	
BP981201	1878	2256	COLD SYMPTOMS	PHARYNGITIS	RES	
BP990203	1741	1137	COLD SYMPTOMS (NASAL CONGESTION & DRAINAGE)	PHARYNGITIS	RES	COLD & FLU RELEIF ANTIHISTAMINE

5) Explain the variable coding of the investigator verbatim term “blurred vision” and related terms:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP981201	1740	19167	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	1944	16292	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	1944	16292	BLURRED VISION	ABNORMAL VISION	SS	
BP981201	2032	6178	BLURRED VISION	ABNORMAL VISION	SS	
BP990203	2061	2136	BLURRED VISION	ABNORMAL VISION	SS	
BP990203	2067	2153	BLURRED VISION	ABNORMAL VISION	SS	
BP960101	1139	6012	BLURRED VISION	AMBLYOPIA	SS	
BP960101	1693	2020	BLURRED VISION	AMBLYOPIA	SS	REPORTED TO DR. MILLER
BP960101	1741	29008	BLURRED VISION	AMBLYOPIA	SS	
BP960102	302	28203	BLURRED VISION	AMBLYOPIA	SS	
BP960102	302	28213	BLURRED VISION	AMBLYOPIA	SS	
BP960102	1214	25206	BLURRED VISION	AMBLYOPIA	SS	
BP960604	1215	7612	BLURRED VISION	AMBLYOPIA	SS	
BP960101	1630	7011	BLURRY EYES	AMBLYOPIA	SS	
BP981201	2048	17118	BLURRY VISION	ABNORMAL VISION	SS	BLURRY VISION PT HAD BEFORE HER ER VISIT. IT WAS NOTED AT HE
BP990203	2060	1080	BLURRY VISION	ABNORMAL VISION	SS	
BP960101	1248	3018	BLURRY VISION	AMBLYOPIA	SS	
BP960101	1630	7009	BLURRY VISION	AMBLYOPIA	SS	
BP990203	2060	1079	BLURRY VISION IN THE A.M.	ABNORMAL VISION	SS	DATE ENDED UNKNOWN, UNABLE TO CONTACT PATIENT.

6) Explain the variability in the coding of the following gastrointestinal adverse events:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP960102	302	28207	ACID REFLUX	DYSPEPSIA	DIG	
BP981201	2032	6178	ACID REGURGITATION	VOMITING	DIG	SUBJECT REPORTS AE ENDED WITH PREVACID TREATMENT
BP960604	1139	5601	ACID STOMACH	GASTRITIS	DIG	
BP960102	302	28203	GASTRIC UPSET	DYSPEPSIA	DIG	
BP990203	2060	1078	GASTRIC UPSET	DYSPEPSIA	DIG	
BP960102	1139	6209	GASTROINTESTINAL VIRUS	GASTRITIS	DIG	
BP960102	1574	22215	GASTROINTESTINAL VIRUS	GASTRITIS	DIG	
BP960102	131	8201	GI DISCOMFORT	DYSPEPSIA	DIG	
BP960102	1255	24219	GI DISTRESS	DYSPEPSIA	DIG	
BP960102	1721	26209	GI UPSET	GASTROINTESTINAL DISORDER	DIG	
BP981201	1740	19167	GI UPSET	GASTROINTESTINAL DISORDER	DIG	
BP981201	2035	11094	NERVOUS STOMACH	DYSPEPSIA	DIG	
BP960101	1630	7014	STOMACH ACID	GASTRITIS	DIG	

7) Explain the variable coding of adverse events related to numbness:

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP990203	2067	1052	NUMB LIPS	PARESTHESIA	NER	
BP960102	302	28207	NUMBNES FROM LOWER BACK-KNEES	HYPESTHESIA	NER	
BP960101	1692	5020	NUMBNESS	PARESTHESIA	NER	
BP960102	1215	21212	NUMBNESS	PARESTHESIA	NER	
BP960102	1574	22208	NUMBNESS +TINGLNG IN BOTH HAND	PARESTHESIA	NER	
BP960102	1723	27204	NUMBNESS AROUND LIPS	PARESTHESIA	NER	
BP990203	2063	2165	NUMBNESS BILAT HANDS	PARESTHESIA	NER	
BP990203	2067	1052	NUMBNESS BOTH HANDS	PARESTHESIA	NER	
BP960604	1215	7616	NUMBNESS IN ARMS AND HANDS	HYPESTHESIA	NER	
BP960102	1627	20205	NUMBNESS IN FACE	HYPESTHESIA	NER	
BP960101	1248	3001	NUMBNESS IN HAND (RT)	HYPESTHESIA	NER	
BP960101	1248	3001	NUMBNESS IN HANDS	HYPESTHESIA	NER	
BP990203	2065	1064	NUMBNESS IN HANDS	HYPESTHESIA	NER	
BP960102	1627	20204	NUMBNESS IN LEGS	HYPESTHESIA	NER	
BP990203	2064	1092	NUMBNESS LEFT ARM	HYPESTHESIA	NER	
BP960102	1708	23218	NUMBNESS OF LEGS AND BUTTOCKS	HYPESTHESIA	NER	
BP981201	2042	21241	NUMBNESS ON LIPS	PARESTHESIA	NER	
BP981201	2032	6173	NUMBNESS RIGHT ARM	HYPESTHESIA	NER	
BP981201	2042	21083	NUMBNESS RIGHT HAND	HYPESTHESIA	NER	
BP960102	1215	21210	NUMBNESS TO ARM	HYPESTHESIA	NER	
BP960102	1215	21204	NUMBNESS-TOP OF THIGH TO KNEE	HYPESTHESIA	NER	NUMBNESS- FROM TOP OF THIGH TO BOTTOM OF KNEE

8) Explain the coding of the following two AEs. Should the gastrointestinal hemorrhage have been a serious adverse event, or was the bleeding not a gastrointestinal hemorrhage?

PROTOCOL	INO	PNO	ADR	ENGLISH	BODYSYS	COMMENT1
BP981201	1878	2028	BLEEDING	GASTROINTESTINAL HEMORRHAGE	DIG	PT. WENT TO ER FOR PRESSURE DRESSING PT. SCRATCHED HIS LEG S
BP960604	100	2601	DIVERTICULITIS	PERIODONTAL ABSCESS	DIG	FLAGYL AND CIPRO

Attachment I – Pruritus-related AEs with unclear relationship between investigator verbatim term and COSTART term

Protocol	Inv	Pat	English	ADR	Comment1
BP960101	1248	3008	PRURITUS	ITCHING	PATCH SITES ITCH AFTER BATHING NECK SCAR ITCHES
BP960102	1574	22201	PRURITUS	ITCHING	AT PATCH SITE
BP960102	1574	22202	PRURITUS	ITCHING	AT PATCH SITES
BP960102	1574	22205	PRURITUS	ITCHINESS	AT PATCH SITES
BP960102	1627	20203	PRURITUS	ITCHING	AT PATCHES
BP960102	1627	20209	PRURITUS	ITCHING	ON BACK AT PATCH SITE
BP960102	1708	23210	PRURITUS	ITCHINESS	ITCHINESS AT ANTERIOR THORAX PATCH
BP960102	1723	27208	PRURITUS	ITCHINESS	AT PATCH SITE
BP960102	1723	27221	PRURITUS	ITCHING	UNDER LARGE AND MEDIUM PATCHES
BP960102	1723	27223	PRURITUS	ITCHING	AT PATCH SITES
BP960604	1627	4606	PRURITUS	ITCHING	ITCHINESS IS AT PATCH SITE ONLY DURING LAST 2-3 DAYS OF
BP960101	1215	21006	PRURITUS AT SITE	ITCHING BODY	
BP960101	1630	7027	PRURITUS AT SITE	ITCHINESS ON CHEST	
BP960102	100	4206	PRURITUS AT SITE	ITCHING ALL OVER	
BP960102	131	8206	PRURITUS AT SITE	ITCHY	
BP960102	302	28203	PRURITUS AT SITE	ITCHING OF FACE AND CHEST	
BP960102	1215	21234	PRURITUS AT SITE	ITCHY	
BP960102	1215	21239	PRURITUS AT SITE	NECK AND CHEST ITCH	
BP960102	1708	23218	PRURITUS AT SITE	ITCHY	
BP960604	1803	6604	PRURITUS AT SITE	ITCHING TORSO	
BP981201	100	22315	PRURITUS AT SITE	ITCHINESS	
BP981201	100	22315	PRURITUS AT SITE	ITCHINESS	
BP981201	1215	5039	PRURITUS AT SITE	ITCHINESS BODY	
BP981201	1215	5185	PRURITUS AT SITE	ITCHING BODY	
BP981201	1215	5307	PRURITUS AT SITE	ITCHING	
BP981201	1215	5307	PRURITUS AT SITE	ITCHING RIGHT ARM	
BP981201	1627	23294	PRURITUS AT SITE	ITCHING	
BP981201	1627	23296	PRURITUS AT SITE	ITCHING	
BP981201	1740	19165	PRURITUS AT SITE	GENERALIZED ITCHING	
BP981201	1807	12269	PRURITUS AT SITE	ITCHING	
BP981201	1820	4005	PRURITUS AT SITE	ITCHING	
BP981201	1825	1045	PRURITUS AT SITE	GENERALIZED ITCHING	

Protocol	Inv	Pat	English	ADR	Comment1
BP981201	1825	1047	PRURITUS AT SITE	ITCHING	
BP981201	1825	1052	PRURITUS AT SITE	ITCHING	
BP981201	1825	1052	PRURITUS AT SITE	ITCHING	
BP981201	1825	1207	PRURITUS AT SITE	ITCHING	
BP981201	1825	1207	PRURITUS AT SITE	ITCHING	
BP981201	1825	1209	PRURITUS AT SITE	ITCHING	
BP981201	1825	1211	PRURITUS AT SITE	ITCHING	
BP981201	1825	1211	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1825	1212	PRURITUS AT SITE	ITCHING	
BP981201	1878	2028	PRURITUS AT SITE	ITCHING	
BP981201	1878	2255	PRURITUS AT SITE	GENERALIZED BODY ITCHING	
BP981201	1878	2257	PRURITUS AT SITE	ITCHING	
BP981201	1890	8054	PRURITUS AT SITE	UPPER BODY PRURITIS	
BP981201	1890	8054	PRURITUS AT SITE	ITCHING	
BP981201	1944	16141	PRURITUS AT SITE	ITCHING	
BP981201	2032	6174	PRURITUS AT SITE	ITCHINESS	
BP981201	2032	6174	PRURITUS AT SITE	ITCHINESS	
BP981201	2032	6176	PRURITUS AT SITE	ITCHINESS	
BP981201	2034	10149	PRURITUS AT SITE	ITCHES	
BP981201	2034	10149	PRURITUS AT SITE	ITCHES	SEEMS WORSE IN SUN WITH PERSPERATION
BP981201	2034	10152	PRURITUS AT SITE	ITCHING	PT STATES THE ITCHING HAPPENS THE SAME TIME EVERY DAY.. AT
BP981201	2035	11093	PRURITUS AT SITE	ITCHING	
BP981201	2035	11093	PRURITUS AT SITE	ITCHING	
BP981201	2035	11097	PRURITUS AT SITE	ITCHING	
BP981201	2035	11281	PRURITUS AT SITE	ITCHING	PT. WASHED AREA WITH CLEAR WATER ONLY SEEMED TO HELP.
BP981201	2036	13109	PRURITUS AT SITE	LEFT KNEE ITCHY	
BP981201	2036	13109	PRURITUS AT SITE	SLIGHT ITCHING	
BP981201	2036	13112	PRURITUS AT SITE	ITCHING	
BP981201	2039	18128	PRURITUS AT SITE	ITCH	
BP981201	2039	18130	PRURITUS AT SITE	ITCHING IN BODY ARMS & LEGS	
BP981201	2039	18131	PRURITUS AT SITE	FACIAL ITCHINESS	
BP981201	2039	18131	PRURITUS AT SITE	ITCHY ALL OVER BODY	

Protocol	Inv	Pat	English	ADR	Comment1
BP981201	2042	21079	PRURITUS AT SITE	ITCHING	
BP981201	2043	15102	PRURITUS AT SITE	ITCHY SKIN	
BP981201	2048	17123	PRURITUS AT SITE	ITCHY AROUND PATCH	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	CONDITION CONTINUING WILL BE FOLLOWED POST DOSE
BP981201	2048	17124	PRURITUS AT SITE	PRURITIS	CONDITION CONTINUING WILL BE FOLLOWED POST DOSE
BP990203	100	1029	PRURITUS AT SITE	ITCHING	
BP990203	100	1031	PRURITUS AT SITE	ITCHING	
BP990203	100	1148	PRURITUS AT SITE	ITCHING	
BP990203	100	2029	PRURITUS AT SITE	ITCHING	
BP990203	100	2030	PRURITUS AT SITE	ITCHING	
BP990203	100	2031	PRURITUS AT SITE	ITCHING	
BP990203	100	2194	PRURITUS AT SITE	ITCHING	
BP990203	302	1005	PRURITUS AT SITE	ITCHING	
BP990203	302	1005	PRURITUS AT SITE	ITCHING	
BP990203	1215	1013	PRURITUS AT SITE	ITCHINESS	
BP990203	1721	1189	PRURITUS AT SITE	ITCHING	
BP990203	1721	2086	PRURITUS AT SITE	ITCHING	PATIENT NOTED ON SIDE EFFECT LOG THAT THE ITCHING STARTED IN
BP990203	1721	2192	PRURITUS AT SITE	ITCHING	
BP990203	1721	2192	PRURITUS AT SITE	ITCHING	
BP990203	1741	2138	PRURITUS AT SITE	ITCHING	
BP990203	1820	1022	PRURITUS AT SITE	ITCHING	
BP990203	1937	1070	PRURITUS AT SITE	ITCHING	
BP990203	1937	2069	PRURITUS AT SITE	ITCHING	
BP990203	1944	2036	PRURITUS AT SITE	ITCHING	
BP990203	1944	2129	PRURITUS AT SITE	ITCHING	
BP990203	1944	2130	PRURITUS AT SITE	ITCHING	
BP990203	1944	2132	PRURITUS AT SITE	ITCHING	

Protocol	Inv	Pat	English	ADR	Comment1
BP990203	1995	2081	PRURITUS AT SITE	ITCHY	
BP990203	1995	2101	PRURITUS AT SITE	ITCHY	ACCORDING TO PATIENT "FEELS BUMPY"
BP990203	2060	1079	PRURITUS AT SITE	ITCHING	
BP990203	2060	1080	PRURITUS AT SITE	ITCHING	
BP990203	2060	2077	PRURITUS AT SITE	ITCHING	
BP990203	2060	2077	PRURITUS AT SITE	ITCHING	
BP990203	2061	1163	PRURITUS AT SITE	ITCHING LEFT ARM	
BP990203	2067	1153	PRURITUS AT SITE	ITCHING	
BP990203	2068	2055	PRURITUS AT SITE	ITCHING	
BP990203	2068	2055	PRURITUS AT SITE	ITCHING	

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Appears this way on original

June 12, 2001

1) Please send the case report forms (CRFs) for Patient 20209 (Investigator No. 1627) in Study BP960102. (This patient died while participating in open-label study BP96-0103 [patient no. 20304, investigator no, 1627], and CRFs were sent only for the open-label study.)

2) The narrative of the death of patient 20304 (investigator no. 1627) in Study BP96-0103 notes that on Study Day 481, she fell at home, and was admitted to the hospital with shortness of breath and a lumbar fracture. Review of adverse event data for this patient indicates that the shortness of breath and lumbar fracture were not reported as either adverse events or serious adverse events. Similarly, the post-hospitalization events leading to her deterioration (atrial fibrillation, anteroseptal infarct, inferior wall infarct, pulmonary edema, and myopathy) are mentioned in the narrative, but are not recorded as serious adverse events in the adverse event dataset. What is the source of this information, and why were these events not in the adverse event database as serious adverse events?

3) Some of the clinical studies have a case report form (CRF) for Intercurrent Diseases and Conditions, in addition to CRFs for adverse events. What is the definition of an "intercurrent disease or condition", and how does this differ from an adverse event? What instructions were investigators given to distinguish between "adverse events" and "intercurrent diseases and conditions"? For example, in Study BP96-0103, Patient 4302 (Investigator No. 100) had an intercurrent illness of "kidney infection" which started on August 4, 1998. This event, which started before the patient's last dose of study medication on August 31, 1998, was not recorded on the adverse event CRF. At baseline, this patient had no urogenital medical conditions reported. Why was this kidney infection counted as an "intercurrent illness" and not as an adverse event? How many studies (Phases 1, 2, or 3) used both an "Intercurrent Illness" CRF and an "Adverse Event" CRF? How many patients in each such study had at least one intercurrent illness recorded? How many intercurrent illnesses were recorded in each study? Were these intercurrent illnesses reported in the adverse event database and were they counted in the adverse event frequency tables? Why or why not? Apart from the brief discussion of intercurrent illnesses on page 53 of the ISS, are intercurrent illnesses discussed elsewhere in the ISS?

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June 29, 2001

1) If adverse events (AEs) that led to discontinuations were analyzed and summarized by dose at which the AE occurred in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Tables 8.14.2.2.20.1 and 8.14.2.2.20.2 in the ISS, Table 8.14.2.2.20.4 in the 120-Day Safety Update, and Table 14.3.2.5 in the BP96-0103 Study Report with additional columns for BTDS 5, BTDS 10, and BTDS 20, so that the incidence of adverse events that led to study discontinuation is presented by dose level at which the AE occurred. In addition, regenerate Table 12.3.1.3C in Study Report BP960103 to include the dose at which the AE occurred, and the dose at which study drug was discontinued.

2) If adverse events (AEs) that led to discontinuations were analyzed and summarized by dose at which the study medication was discontinued in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Tables 8.14.2.2.20.1 and 8.14.2.2.20.2 in the ISS, Table 8.14.2.2.20.4 in the 120-Day Safety Update, and Table 14.3.2.5 in the BP96-0103 Study Report with additional columns for BTDS 5, BTDS 10, and BTDS 20, so that the incidence of

adverse events that led to study discontinuation is presented by dose level at which study drug discontinuation occurred. (This table will be similar to the table requested in #1 above if the study drug was discontinued at the same dose at which the AE occurred. If, for example, a patient developed moderate nausea on BTDS 5, which continued at the same severity while on BTDS 10, and the drug was discontinued while on BTDS 10, then the event will be assigned to BTDS 5 in the first table and to BTDS 10 in the second table.)

3) If adverse events (AEs) that led to drug interruption were analyzed and summarized by dose at which the AE occurred in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.21.1 in the ISS so that the BTDS dose under the TREATMENT heading corresponds to the dose received at the time of the AE that led to drug interruption. Regenerate Table 8.14.2.2.21.2 the ISS and Table 14.3.2.6 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to drug interruption is presented by dose level at which the AE occurred.

4) If adverse events (AEs) that led to drug interruption were analyzed and summarized by dose at which study medication was interrupted in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.21.1 in the ISS so that the BTDS dose under the TREATMENT heading corresponds to the dose received at the time of drug interruption. Regenerate Table 8.14.2.2.21.2 the ISS and Table 14.3.2.6 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to drug interruption is presented by dose level at which drug interruption occurred. (This table will be similar to the table requested in #3 above if the study drug was interrupted at the same dose at which the AE occurred).

5) If adverse events (AEs) that led to dose reduction were analyzed and summarized by dose which required dose reduction in the Phase 3 trials, identify the location of these analyses in the NDA. If not, regenerate Table 8.14.2.2.22.2 the ISS and Table 14.3.2.7 in the BP96-0103 study report with three additional columns (BTDS 5, BTDS 10, and BTDS 20), so that the incidence of AEs that lead to dose reduction is presented by dose level which required reduction.

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July 5, 2001

1) Apart from the section on "Post-study Analgesics" in each of the Phase 3 protocols, did any of the Phase 3 protocols specify any further directions for post-study treatment with opioid or non-opioid analgesics? Did any of the Phase 3 studies have protocol-specified visits after treatment was discontinued to evaluate patients for withdrawal?

2) Explain in more detail the algorithm used to identify patients with suggestions of overdose, abuse, or withdrawal based on COSTART terms (see Section 8.15.6.2.1.1 of the Abuse Liability section of the NDA, page 57). Specifically, explain the phrase "and then dividing by the maximum adverse event score in that body system." Does this refer to the single highest AE score in that body system among all patients? Does this refer to the highest possible AE score in that body system?

3) The comment on the Discontinuation page (dataset: DISCON) for Patient No. 4313 in Study BP96-0103 notes "Patient discontinued from study per sponsor request." What was the reason for this request?

4) Adverse events for the Phase 3 studies are presented separately for the forced-titration and titration-to-effect studies in the main body of the NDA. In a follow-up submission on May 4, 2001, pooled adverse event data for the Phase 3 studies are presented, including BTDS dose-specific rates for adverse events. None of these analyses, however, provides for an analysis of pooled Phase 3 placebo-controlled studies (BP96-0101, BP96-0102, BP96-0604, and BP99-0203, but excluding BP98-1201). Please provide tables similar in format to those in Attachment 3 and Attachment 4 of the May 4 submission for the pooled Phase 3 placebo-controlled studies.

5) Generate a table similar to Table 8.13.5.3D in the ISS for the pooled Phase 3 placebo-controlled studies (BP96-0101, BP96-0102, BP96-0604, and BP99-0203). Include columns for "BTDS 5", "BTDS 10", "BTDS 20" (where those labels refer to the dose at which the AE occurred), "BTDS Total", "Placebo", and "% BTDS Minus % Placebo" (using the BTDS Total value for this comparison). Include all AEs occurring in 2% or more of patients in any of the four BTDS groups listed above, sorted by descending order of frequency in the "BTDS Total" group.

6) Generate a table similar to Table 8.13.5.3E in the ISS for the open-label Phase 3 study (BP96-0103). Include columns for "BTDS 5", "BTDS 10", "BTDS 20" (where those labels refer to the dose at which the AE occurred), and "BTDS Total". Include all AEs occurring in one or more patients in any of the four BTDS groups listed above, sorted by descending order of frequency in the "BTDS Total" group.

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July 10, 2001

1) For the Phase 2/3 controlled studies, the open-label study BP96-0103, and the clinical pharmacology studies, generate data listings of all clinically significant abnormal laboratory values (see Section 8.13.7.2.3 of the ISS). Include columns for lab test, protocol number, investigator, patient, normal range, baseline value, most abnormal post-baseline value, final value, study day of most abnormal value, study day of final value, name of study medication, and for BTDS the dose of study medication at the time of the most abnormal value. For each of the three study groupings above, generate two versions of the listing: the first sorted by protocol, investigator, patient, and lab test, and the second sorted by lab test, protocol, investigator, and patient number.

2) Review of Table 8.14.2.3.3.1 of the ISS (Laboratory Tests and Their Change From Screening – Summary Statistics) reveals that the mean change from baseline for Specific Gravity in the Placebo group in the forced titration studies is 234.65. Other clinically implausible values include a maximum final value of 20000, a screening mean value of 19.15, and final mean value of 248.69. The minimum and maximum values at screening are 3 and 31, respectively. By way of example, review of the patient data listings (Data Listing 16.2.8 in Study BP96-0101) reveals that Patient 4001 (Investigator 100) had an End of Study specific gravity of 25.00, with normal range for that test reported as L0W – 1.00 and HIGH – 30.00. That patient's case report form (CRF), however, indicates a specific gravity value at that time of 1.025, with no normal ranges reported on the CRF. Further review of the LAB3_A dataset reveals that certain studies, such as BP96-0101 and BP96-0102 have LOW values ranging from 0.00 to 15.00, while the LOW value for BP960104 is 10.00 and the corresponding value for BP96-0604 is 1.00. Similarly, the HIGH values for studies BP96-0101 and BP96-0102 range from 25.00 to 35.00, while the HIGH value for study BP96-0104 is 30.00 and the HIGH

value for study BP96-0604 is 1.03. Explain the deviation of the specific gravity results in the data listings from those on the CRFs. Also, explain the clinical interpretation of specific gravity measures that do not use the standard 1.000-1.030 scale.

3) In the analysis of mean change from baseline for urinalysis values, how were qualitative values such as GLUCOSE – 3+ handled?

4) Review of Tables 8.14.1.3.3.1, 8.14.2.3.3.1 (ISS) and 14.3.4.5 (BP96-0103) reveals some values suggestive of data entry errors, which might affect the summary statistics. Address these values, examples of which are presented in the table below:

Table	Laboratory Test	Summary Statistic	Time Point	Value
8.14.1.3.3.1 (ISS)	Globulin	Maximum	Final	38
8.14.1.3.3.1 (ISS)	Phosphorus Inorganic	Maximum	Final	547.99
8.14.2.3.3.1 (ISS)	Hematocrit %	Maximum	Final	399
8.14.2.3.3.1 (ISS)	Chloride	Maximum	Screening	711
14.3.4.5 (BP96-0103)	Calcium	Maximum	Worst Case High Value	94.0
14.3.4.5 (BP96-0103)	Phosphate	Maximum	Baseline	43.0

5) Section 8.13.7.2.1 of the ISS notes that "There were no clinically meaningful changes in mean values for any laboratory parameter." Reference is made to Table 14.3.4.2C in Clinical Study Report BP96-0104. That table is a shift table, not a table of mean changes from baseline. Indicate the location in the NDA of the supporting data for this statement. If a table of mean changes from baseline for laboratory values exists for Phase 2 study BP96-0104, indicate its location in the NDA. If not, generate a table for this study, similar information to Table 8.14.2.3.3.1 in the ISS.

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July 16, 2001

1) Does Table 8.13.7.2.2E in the ISS (Shift Tables of Subject changes in the Clinical Pharmacology Studies) include both placebo-treated and BTDS-treated patients? The ISS methodology (page 267 of the ISS) notes that a "Shift table of screening vs final (end-of-study) values by treatment group" will be provided. The Shift tables provided in Tables 8.14.1.3.1.1 through 8.14.1.3.1.7 appear to be for "All Treatments". Please explain.

2) Were data from Study BP96-0104 included in ISS Table 8.13.7.2.3.1A, since the data listings in Table 8.14.2.3.5.1 in the ISS includes patients from Study BP96-0104?

3) Review of hepatic function data from Study 96-0103 indicates that two subjects had isolated marked abnormalities of total bilirubin: Subject 21361 had and end-of-study value of 6.9 mg/dl (no follow-up values available), and Subject 2307 has a value of 7.3 mg/dl, which returned to normal (0.5 mg/dl) at the end of the study. In each case, review of the CRFs revealed that these values were recorded in the "Value Within Normal Range" column, not in

the “Abnormal Value” Column. In each case there was no entry in the “Indicate Clinical Significance of Abnormal Value”. In each case, the patient’s total protein value (in g/dl) at the visit was identical to the total bilirubin value (in mg/dl). Is it possible that these two total bilirubin values are data entry errors – for example, transcription errors from the original lab report form to the CRFs? Why was there no comment for such markedly abnormal values? Is there a follow-up total bilirubin value for Subject 21361?

4) What was the cut-off time period after the last dose of study medication for including abnormal laboratory values in the analysis of hepatic function tests? For example, Patient 2119 in Study BP99-0203 had mildly elevated AST and ALT at screening (72 and 77 U/L, respectively), which increased to 120 and 122 U/L, respectively, at the end of the study. Neither of these values is more than 3 X ULN (ULN = 48). However, repeat values measured about one week later were above 3 X ULN (AST and ALT were 154 and 152 U/L, respectively). No additional measurements were reported. This patient is not reported in Table 8.14.2.3.5.1 in the ISS – is this because of a time cut-off? Is there any further follow-up laboratory data for this patient?

5) Is any further information regarding hepatic function known for the following subjects in the clinical pharmacology studies: Subject 9 in Study BP95-0901, Subject 22 in Study BP95-0901, Subject 8 in Study BP96-1102, and Subject 76 in Study BP98-0201?

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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/

Gerald DalPan
8/10/01 04:17:30 PM
MEDICAL OFFICER

Bob Rappaport
8/10/01 04:27:32 PM
MEDICAL OFFICER
I completely concur with Dr. Dal Pan’s conclusions and recommendations
.

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 24, 2001

To: Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care and Addiction
Drug Products (HFD-170)

Through: Deborah B. Leiderman, M.D.
Director, Controlled Substance Staff (HFD-009)

From: Ann-Kathryn Maust, M.D., Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Silvia Calderon, Ph.D., Chemist
Controlled Substance Staff (HFD-009)

Subject: Abuse Liability Assessment of NDA 21-306 Norspan (buprenorphine transdermal system, BTDS)
Treatment for pain
Sponsor: Purdue Pharma L.P.

Background:

Buprenorphine Transdermal System (BTDS) is a patch that contains 5, 10 and 20 mg of buprenophine. Buprenorphine, a partial agonist at the mu opioid receptor, and an antagonist at the kappa opioid receptor, is currently controlled in Schedule V of the Controlled Substances Act (CSA). BTDS is intended for use as an analgesic for chronic pain over a period of 7 days of use.

I. Executive Summary:

The classification of buprenorphine substance in Schedule V of the CSA is presently under review based upon pharmacological, clinical trial, and epidemiological data that have become available since approval of the original parental buprenorphine formulation. It is probable that buprenorphine will be placed into Schedule III once FDA and the Department of Health and Human Services (DHHS) complete the CSA mandated review; however, the Drug Enforcement Administration (DEA) makes the final determination on the control level. NDA 21-306 (Norspan or buprenorphine transdermal system – BTDS) provided insufficient information to fully characterize the abuse liability of BTDS (b) (4) Nonetheless, available data on marketed formulations of buprenorphine, especially combined with the ready extractability of buprenorphine substance from the BTDS patch, lead to the conclusion that the Norspan product has at least moderate abuse liability with consequent safety concerns if abused and/or overdosed. This product, if approved, should have a risk management program that addresses safety, prevention of abuse and diversion. Restricted distribution may be appropriate for this product.

Conclusions:

- Available epidemiological data suggest that once the transdermal dosage form becomes available, buprenorphine is likely to gain more extensive use than the original parenteral product. Buprenorphine abuse/overdose appears to be a significant problem in countries where buprenorphine is available to the general public. Since approval of the high dose sublingual buprenorphine formulation in France in 1996, more than 100 reports of death from abuse of buprenorphine have been received. Particularly vulnerable are adolescents and young adults who are likely to experiment with a readily available opiate for recreational purposes. The United States experience with other partial opiate agonists supports the probability that an accessible outpatient dosage form significantly increases misuse, abuse, and morbidity.

- Buprenorphine is readily extracted from BTDS matrix and most of the drug (b) (4) remains in the dosage form after seven days of use. Studies conducted by the Sponsor show that greater than (b) (4) of the drug substance can be extracted from the BTDS. Simple physical manipulations of the patch, including heat application, chewing, or otherwise disrupting the patch matrix, readily increase the available buprenorphine and the plasma concentration of buprenorphine and could lead to misuse and overdose.

- Discontinuation of BTDS and potential withdrawal phenomena are not fully characterized in the submission. The clinical trial data suggest issues of drug accountability that may indicate abuse and diversion.

Recommendations:

1. Completion of the effort to reschedule buprenorphine substance prior to approval of BTDS. BTDS product would be controlled under the same class as buprenorphine substance.

2. Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation.

3. Explore modification of the BTDS matrix to reduce the ease of extractability and potentially reduce the quantity contained in the weekly patch.

4. A complete Risk Management Program acceptable to the Agency should be required prior to approval of this product.

II. Chemical Extractability:

The buprenorphine transdermal system (BTDS) is a transdermal patch formulated to deliver buprenorphine over a seven day period. BTDS is a matrix system in which the active component [redacted] It is a five layer patch that consists of 1) an outermost backing layer that prevents the patch from sticking to clothing, 2) an adhesive matrix without active drug substance, 3) a separating foil that prevents diffusion of the buprenorphine-containing matrix into the drug free adhesive matrix, 4) a buprenorphine containing matrix and 5) a [redacted] release liner, which is removed prior to the application of the patch to the skin. Three strengths of patches are being developed: 5 mg, 10 mg and 20 mg. Bioavailability studies (BP98-0201 and BP97-0501) showed that about 15% of the drug substance in each BTDS is absorbed during a 7-day treatment. Thus, after 7-day use, a 20 mg BTDS will still contain 17 mg of buprenorphine base.

Extractability of buprenorphine was studied under various pH conditions and as a function of time. Buprenorphine base is a white, crystalline powder very slightly soluble in water, freely soluble in acetone, soluble in methanol, and slightly soluble in cyclohexane. It dissolves in dilute acid solutions. The study performed by the Sponsor showed that 10 ml of deionized water (pH=5.1) resulted in extraction of approximately 6 mg of the base after shaking at room temperature for 2 hours. (The amount of base extracted was quantified by HPLC.)

Although extractive procedures using organic solvents were not performed as part of the abuse liability characterization of the drug, the test procedure used to determine the amount of buprenophine base in the TDS, described in Vol. 7, page 55, could be viewed as an effective method for the extraction of the drug substance. The procedure recommends the following: [redacted] Greater than [redacted] of buprenorphine contained in an intact (unused) BTDS patch was extractable using this method.

Significant quantities of buprenorphine drug substance are readily extracted from both used and unused BTDS units.

III. Preclinical Pharmacology:

Abuse liability resulting from oral or buccal administration was tested using beagle dogs. For oral administration, BTDS patches were cut into pieces and mechanically pounded with a meat tenderizer before placement into gelatin capsules for oral dosing. This test was designed to simulate chewing and swallowing of BTDS patches. For buccal administration, BTDS patches were cut in half and pierced 15 times before application to the right and left buccal surfaces of the dogs. According to the summarized data submitted, a 20 mg BTDS patch gave the following Cmax values:

Species	Route	Cmax (ng/ml)
Dog	Oral	0.51
	Buccal	176
Human	Transdermal	0.47 (after 7 day administration)

IV. Pharmacokinetics:

The Sponsor states that following removal of BTDS, plasma buprenorphine concentrations decline gradually with an apparent terminal half-life of 26 hours. A graph shows that plasma buprenorphine levels persist for an extended period following removal of BTDS, presumably from residual absorption of buprenorphine from skin depots. In this graph, it is shown that following 7 day administration of a 10 mg BTDS patch, buprenorphine levels are not reduced completely until almost 4 days after removal of the patch.

A chart is provided showing Cmax and AUC levels and comparing transdermal BTDS (at 5, 10 and 20 mg) to buprenorphine administered at 25 ug/hr intravenously. The Sponsor notes that these pharmacokinetic data show that bioavailability of buprenorphine from BTDS is approximately 15% across all doses. As expected, time to maximum buprenorphine plasma levels are slower with BTDS than with intravenous administration. The narrative states that the amount of buprenorphine remaining in a patch following 7 day application is:

Patch dose	Amount left after 7 days	Percent left in patch
5 mg		(b) (4)
10 mg		
20 mg		

The Sponsor references a study with healthy subjects (BP96-0501) showing that following placement of the patch to different parts of the body (upper outer arm, upper chest, upper back, side of chest), there can be “less than” 18% difference in buprenorphine exposure. These differences were “not considered clinically significant” by the Sponsor.

V. Human Pharmacology Abuse Liability Study

A single study examined the subjective effects of BTDS compared with intramuscular buprenorphine in opiate-experienced, non-dependent volunteers. The safety, time course, and magnitude of subjective effects of two BTDS patches (40 mg total), placed transdermally and worn for 26 hours, were compared to 0.9 mg of i.m. buprenorphine and placebo by using a variety of standard subjective assessment instruments and measurements of physiological parameters.

The design of the study was inadequate to characterize the abuse potential of BTDS due to the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Additionally, the failure to use a standard comparator, such as morphine, as well as the failure to obtain plasma levels of buprenorphine makes interpretation of the study results impossible.

Attachments:
Appendix A: Controlled Substance Medical Reviewer's Notes
Appendix B: Controlled Substance Pharmacology Reviewer's Notes

Appendix A:
Controlled Substance Medical Reviewer's Notes

The information reviewed includes the following: preliminary report for study BP98-1202, abuse liability submissions dated 11/3/00 and 3/9/01, volume 2 of the NDA, parts of the BP98-1204 Clinical Study Report, case report forms from several studies, and other sections of the NDA. Topics that are discussed below are as follows: the human abuse liability study conducted by the Sponsor (BP98-1202); Sponsor's review of the clinical database to detect overdose, abuse, or withdrawal; drug accountability; Sponsor and Controlled Substance Staff (CSS) summaries of buprenorphine overdose cases; response to opioid antagonists after buprenorphine overdose; and comments regarding the Sponsor's March 9, 2001 submission.

"A Study to Characterize the Abuse Potential of BTDS in Non-Opioid Dependent Volunteers" (Study BP98-1202)

Information regarding one human abuse liability study was given to CSS to review. CSS reviewed the preliminary report for this study, which was submitted on May 4, 2001.

The study was conducted at the Behavioral Pharmacology Research Unit of Johns Hopkins University. It was a double-blind, double-dummy, randomized 3-way crossover (placebo, dose, active control) study preceded by a single-blind, double-dummy, single dose safety evaluation and practice session. The study was performed in compliance with Good Clinical Practice regulations.

The study tested the safety, time course, and magnitude of subjective effects of two BTDS patches (40 mg total) placed transdermally on nine African American male volunteers with histories of opioid use but without current physical dependence on opioids. The effects of the BTDS patches, which were worn for 26 hours, were compared to 0.9 mg of i.m. buprenorphine and placebo by using a variety of standard subjective assessment instruments and measurements of physiological parameters.

The design of the study is inadequate for the following reasons.

- The only dose of BTDS tested was 40 mg (2-20 mg patches). There should be a full range of doses tested (if this can be done safely), with the application of a sufficient number of patches to produce low, moderate, and high reinforcing responses to buprenorphine.

- Because plasma levels were not measured, it is unclear how the doses of BTDS and i.m. buprenorphine compare to each other. It is possible that 0.9 mg of i.m. buprenorphine produces higher acute plasma levels and thus higher acute subjective effects than the 2-20 mg patches. Indeed, the Sponsor's conclusion—p. 5 of the preliminary report—is "These results support the hypothesis of a lower opioid effect and thus a lower abuse potential of buprenorphine administered transdermally (BTDS) compared to acute administration (i.m. buprenorphine)."

- Because the subjects wore the patches for only 26 hours, the maximum buprenorphine plasma levels possible might not have been reached. The Sponsor states on p. 98 of volume 2 of the NDA,

  > *The concentration of buprenorphine…was observed to rise steadily for up to approximately 48 hours to levels that are maintained for 7 days. With the BTDS 10, mean concentrations of 100 pg/ml were usually attained at approximately 24 to 48 hours and remained in the range of 100 to 200 pg/ml for 7 days….pharmacokinetic data …support dose proportionality and multiple application of BTDS 5, 10, and 20. The BTDS 5, 10, and 20 provide dose-proportional increases in total exposure (AUC) over the 7-day application period.*

  In addition, on p. 115 of the same volume, a graph shows that the maximum concentration of buprenorphine was reached after BTDS 10 was worn for 3 to 5 days, and that at the end of one day, the concentration appears to be half the maximum concentration. This information may explain why the scores for general drug effect, drug liking, and heroin feeling appeared to be increasing and the pupil measurements appeared to be decreasing after the subjects wore the patches for 26 hours. (See graphs on pp. 50, 52, 54, and 48 of the preliminary study report.)

- Finally, it is not clear to CSS why the Sponsor designed a study to show that a large dose of i.m. buprenorphine leads to higher acute subjective effects than two BTDS 20 mg patches. Demonstrating this phenomenon does not eradicate the fact that buprenorphine can be easily extracted from BTDS and that BTDS can be altered in other ways so that higher acute subjective effects are experienced.

CSS concludes that buprenorphine is the same substance, regardless of whether it is administered by injection or patch or in another manner, and buprenorphine in any form has abuse potential. Abuse related to BTDS could occur in several ways. Buprenorphine can be easily extracted from BTDS and used orally or parenterally (p. 34 of the 11/3/00 Abuse Liability Submission, or ALS). In addition, the plasma concentration of buprenorphine can be increased by applying heat to BTDS, by applying BTDS to a site that has recently been a BTDS application site, by applying multiple BTDS patches, and by chewing or altering BTDS in other ways and then allowing absorption of the drug to occur through the buccal mucosa (p. 11, ALS).

Sponsor's Review of Clinical Database to Detect Overdose, Abuse, or Withdrawal

The Sponsor states that they reviewed data to detect cases of overdose, abuse, or withdrawal from discontinuation of BTDS or prestudy opioids (p. 56 of ALS). However, it is not clear from the information submitted that patients in the clinical studies were routinely assessed for evidence of withdrawal after BTDS was discontinued. For example, in study BP96-0101, BTDS was given every six days for sixty days and the patients were evaluated only on days 9, 15, 30, 45, and 60. It appears that patients were evaluated only while using BTDS in the following Phase 3 studies: BP96-0101, BP96-0102, BP96-0604, BP98-1201, and BP99-0203 (vol. 2 of NDA). CSS recognizes that it may be difficult to assess patients for opioid withdrawal symptoms after the study medication is discontinued because the patients might immediately be placed on another opioid for pain management. CSS would like to note that if patients were not

assessed after BTDS was discontinued, it is not possible to conclude that "BTDS was associated with possible or probable abstinence syndrome in only 2 of 658 BTDS-treated patients in Phase 3 studies" (vol. 2 of NDA).

The Sponsor states that they evaluated whether withdrawal occurred in 16 of 20 "healthy subjects who had two weeks' exposure to BTDS (2 consecutive, separate 7-day exposures in BP98-1204)" (p. 41, ALS). On pages 3 and 27 of the BP98-1204 Clinical Study Report, the Sponsor says that a washout period of at least 10 days occurred between each BTDS treatment. The two treatments were one BTDS 10 worn for 7 days without the application of heat and one BTDS 10 worn for 7 days while a heating pad was applied intermittently on Day 2 and intermittently on Day 4. The subjects were asked by telephone three months after study completion whether they experienced any of the following symptoms.

1. "At any time, were you tense, jittery, or nervous?"
2. "At any time after the study did you get chills and sweating, clammy, or goose flesh?"
3. "At any time after the study did you get face blushing, watery eyes, or runny nose?"

One subject felt "jittery and nervous" for 24 hours during the day after study drug was stopped. Another had watery eyes, which began three weeks after discontinuation and lasted two weeks.

The subjects were not asked whether any of the following diagnostic criteria for opioid withdrawal (as per DSM-IV-TR) occurred: dysphoric mood (although they were asked about feeling tense), nausea or vomiting, muscle aches, diarrhea, yawning, fever, or insomnia. Also, perhaps more of the subjects would have experienced withdrawal symptoms if they had used BTDS for a longer period of time. According to the literature, "clinically significant withdrawal usually requires daily use of an adequate amount (of opioid) for at least 3 weeks," or requires use that has lasted several weeks or longer (1, 2).

CSS would like to note that another concern regarding the BP98-1204 study is that an effect appeared that was consistent with previous studies—"applying a new BTDS to a skin site recently used for a previous BTDS application may result in increased buprenorphine absorption" (p. 109, NDA vol. 2).

Four Methods Used to Detect Overdose, Abuse, or Withdrawal

The Sponsor describes four other methods that were used to review the clinical database for reports of overdose, abuse, or withdrawal.

First Method

The first method was a review of "all available information on any patient who died, had other serious adverse events, or other significant adverse events." Based on this review of 297 patients, the Sponsor concluded that three cases (involving patients 20226, 21204, and 21238—all from study BP96-0102) possibly represented abstinence from prestudy opioids. The investigators stated that the problems observed in these cases were probably or possibly related to the study drug. The fourth case deserves more discussion and is summarized below.

Patient 24303 (BP96-0103)
The BTDS dose was titrated to 20 mg over the course of 62 days. This dose was continued from days 62-177. On day 177 the patient began supplementing BTDS with his own Percocet (oxycodone/acetaminophen) because of worsening back pain. On day 182 BTDS was discontinued due to lack of efficacy and concomitant use of Percocet. The patient continued Percocet and on day 184 reported dry heaves and weight loss. On day 188 the patient was hospitalized for dehydration. The Sponsor judged that the events were unlikely to represent abstinence from BTDS. However, CSS believes that the dry heaves and possibly related decreased appetite could have represented a BTDS abstinence syndrome.

Second Method
The second method used to review the clinical database for reports of overdose, abuse, or withdrawal is described as a "review of COSTART terms." The Sponsor states, "For the 10% of patients with the highest total patient (adverse event) scores in the 6 double-blind clinical studies" and for "the 10% of patients with the highest total patient (adverse event) scores in the open-label continuation safety study," all available information was reviewed in a blinded manner for evidence of BTDS overdose or abuse, or of abstinence following discontinuation of BTDS or prestudy opioids (p. 57, ALS). (The total patient score is defined as the sum of body system adverse event scores for that patient.) However, in answer 3a on page 4 of the 3/9/01 submission, the 10% of patients whose information was reviewed is defined in a different manner.

CSS assumes that the first method noted above was used, or that the data of patients with the highest total body adverse event scores was screened for COSTART terms related to abuse or withdrawal. Using this method would not necessarily identify all the patients who experienced abuse or withdrawal. For example, Patient A could have a lower total body adverse event score than Patient B, but all the points for Patient A's total body adverse event score might have resulted from problems related to abuse or withdrawal.

Five patients out of (presumably) the 117 with the highest total patient scores were identified when the Sponsor used the method described in the preceding paragraph. (The term "presumably" is used because on pp. 60-61 of ALS, the 10% of patients whose information was reviewed again seems to be defined differently from how it is defined under the description of the method on p. 57 of ALS.) The Sponsor judged that three of these cases definitely or probably represented abstinence from prestudy opioids. The investigators stated that one of these three cases represented abstinence from prestudy opioids and that two of these cases possibly or probably involved events due to BTDS. The Sponsor and investigators seemed to agree that the other two cases probably represented abstinence from prestudy benzodiazepines. CSS believes that one of the last two patients mentioned could have also been experiencing abstinence from the prestudy opioid. The adverse events that this patient experienced were moderate weight loss, headache, insomnia, diarrhea, muscle cramps, and sweating. (This patient received placebo BTDS during the trial.)

Third Method
The third method used to review the clinical database for reports of overdose, abuse or withdrawal was a review of investigator comment fields. All investigator comment fields in the six double-blind studies and the open-label continuation study were searched to screen for terms associated with overdose, abuse, or withdrawal. As per the Sponsor, Appendix 6 of ALS lists all patients whose comment fields contained a word that could reflect misuse, abuse, or overdose. In addition, Appendix 6 lists all patients who dropped out of the studies, regardless of whether their comment fields contained words that reflect misuse, abuse, or overdose. The Sponsor states, "The case report forms of patients identified were reviewed for clinical evidence of overdose, abuse, or abstinence. From this review, 6 patients were identified…." The criteria used to choose these 6 patients is not described in further detail. The patients are presented below.

Pt. 16292 (study BP98-1201) has already been mentioned and probably experienced abstinence from a prestudy benzodiazepine.

Pt. 10155 (BP98-1201) received Fioricet (butalbital/ acetaminophen/caffeine) and Tylenol With Codeine prior to beginning the study. These medications were stopped on Day –1. On Day 0 the patient began using BTDS 5 and developed moderate nervousness, headaches, and mild loss of appetite. BTDS dose was increased to 10 on Day 1 and to 20 on Day 12. On Days 13 and 21 the BTDS dose was decreased to 10 and 5, respectively, because of "adverse events" (p. 62, ALS). The patient discontinued the study on Day 28. The investigator and Sponsor judged that the adverse events probably represented abstinence from prestudy opioids. CSS believes it is also possible that the nonspecific symptoms noted on Day 0 were symptoms of butalbital withdrawal. Anxiety, nausea or vomiting (2), and possibly headache due to increased blood pressure can be symptoms of sedative-hypnotic withdrawal. In addition, when the BTDS dose was decreased, the patient could have been experiencing BTDS withdrawal—BTDS might have at least partially substituted for the prestudy codeine.

Pt. 7309 (BP96-0103) was judged by the Sponsor to have had restlessness due to BTDS withdrawal.

Pt. 8303 (BP96-0103)-The Sponsor's and investigator's conclusions regarding this patient were inconsistent.

Pt. 2022 (BP98-1201) changed BTDS frequently, was noncompliant with visits, and failed to return 107 placebo tablets and 8 BTDS patches. He stated that he developed chills and anxiety 40 days after BTDS was discontinued. The site prescribed chlordiazepoxide for anxiety and tramadol for pain. The study coordinator attributed these symptoms to abstinence from BTDS and the Sponsor judged that they "possibly represented abstinence from BTDS." CSS agrees with the study coordinator and would like to note that this case may also represent abuse of BTDS.

Pt. 2254 (BP98-1201) said that she frequently changed BTDS (every 0 to 3 days) because it repeatedly fell off due to humidity and sweating. She took more than twice as many (232 vs.

108) placebo tablets as were recommended. On Day 15 she discontinued the study because BTDS would not remain in place. The patient did not return the study medication. The Sponsor judged that this case definitely represented drug-seeking behavior.

CSS would like to note that the following terms were used while the Sponsor was using the third method (during the search of investigator comment fields): "abstinence syndrome, abuse, addiction, compliance, dependence, drug abuse, drug addiction, drug dependence, near abuse, overdose, tolerance, toleration, withdrawal, and withdrawal syndrome" (p. 58, ALS). It might have been helpful if the Sponsor had also used the following terms: lost patches, did not return patches, lost to follow-up, did not return study medication/drug.

Fourth Method
The fourth method used to review the clinical database for reports of overdose or abuse— whether withdrawal occurred was not assessed with this method— was an abuse potential survey of investigators/study coordinators for studies BP98-1201 and BP99-0203. BP98-1201 was an active-controlled 56 day study. The patients were titrated to their effective dose levels during the first 21 days, and then the effective dose was maintained during the last 35 days. BP99-0203 was a placebo-controlled 28 day study. The patients were titrated to their effective dose levels during the first 21 days, and then the effective dose was maintained during the last 7 days.

The principal investigators or study coordinators for all the sites involved in these two studies were surveyed after the studies were completed. The Sponsor states, "The survey was conducted separately from the monitoring process for the clinical trial. For this reason, the statements made regarding individual patients may not totally reflect entries in the case report forms" (p. 63, ALS).

Three of the 22 principal investigators/study coordinators for BP98-1201 answered positively to the following questions. (The survey consisted of six questions.)

- "Were you aware of (or did you suspect) any signs of addiction to buprenorphine by any of the patients in this trial?"

- "Were you aware of (or did you suspect) any 'overuse,' misuse, abuse or 'near abuse' of buprenorphime by any of the patients in this trial?"

- "Have you any other concerns about the abuse liability of BTDS?"

One study coordinator for BP98-1201 answered affirmatively to the following question.

- "Were you aware of (or did you suspect) any diversion of buprenorphine by patients or others to any use other than that which was intended in the trial protocol?"

Thirteen of the 41 investigators/study coordinators for the two studies answered "same" or "no opinion" to a question that asked them to rate the abuse risk of BTDS relative to oral combination analgesic products, such as Percocet or Percodan.

The patients that were recalled during the abuse potential survey all participated in study BP98-1201 and are presented below.

Pt. 2022 was suspected of being addicted to BTDS and is described earlier in this paper –see *Third Method* section.

Pt. 17122 received BTDS 20 as maintenance treatment. The study coordinator stated that the patient changed BTDS too frequently (every two to seven days) without a valid reason and appeared drowsy. The patient "was always tired, in bed, and calling in a drowsy state" (p. 64, ALS).

Pt. 2254 is described in the *Third Method* section.

Pt. 17117 titrated on Day 7 to BTDS 10. On Day 11, she developed disorientation and slurred speech. BTDS dose was increased to 20 on Day 14 because the patient complained of inadequate pain control. On Day 17, BTDS and placebo tablets were discontinued because of opioid side effects. Disorientation and slurred speech resolved on Day 20. The study site suspected the patient overstated her pain level, which she described as an 8 out of 10 throughout the study. The patient's satisfaction score was zero throughout the study.

To conclude, instead of conducting a retrospective survey of investigators, the Sponsor could have asked the investigators to write answers to questions related to abuse/dependence during each of the study visits. This type of questioning might have provided more reliable information because it would not have relied on memory.

Summary of the Four Methods
The Sponsor identified 16 cases using the four methods described above and did not believe that each case represented a problem with BTDS. (CSS does not agree with all of the Sponsor's comments regarding each case.) Each method used by the Sponsor has its limitations—some are noted above—and often the methods identified different cases. The fact that different cases were identified using different methods shows that the methods were not reliable ways to identify BTDS abuse/dependence. To reiterate, having the investigators note on the CRFs during each study visit whether there seem to be abuse/dependence problems might be a more reliable way to detect these problems than conducting a retrospective analysis of various kinds of data.

Drug Accountability

In December 2000, CSS asked the Sponsor to provide the location of the CRFs of patients who lost their patches or did not return them. CSS believed that reviewing these CRFs might also be a way to detect abuse or dependence problems. The Sponsor's reply was as follows.

> *No CRFs or narratives for subjects who lost their patches or did not return them were included because these occurrences were not felt to be related to abuse or misuse. Compliance was assessed in 4 protocols (BP96-0101, BP96-0102, BP96-0604, and BP96-0103), and 57 patients who used >100% of their allotment of patches were identified from 1037 patients, and explanatory comments were available on 10. All comments had to do with the subject using more than the expected number of patches, generally because of*

patches falling off early. In one case, a subject reportedly used extra patches to avoid AEs. None of these comments related to misuse, abuse or diversion. Comments on the discontinuation page(s) of the case report form(s) from the 872 subjects who discontinued identified 13 subjects who lost or did not return one or more patches, usually because of losing patches or having them fall off. In one case, patches were reportedly stolen out of a truck and in another they may have been inadvertently taken. Attachment 7 of this submission (3/9/01) includes patient profiles for these 13 patients, as narratives are not available….

To reiterate, the Sponsor identified 13 patients who lost their patches or did not return them by searching the discontinuation pages of the CRFs of the 872 patients who discontinued. This reviewer manually searched most but not all of the investigator comments that appear in Appendix 6 of ALS (most of the comments from study BP99-0203 were not reviewed) and concluded that it seems that at least 32 patients lost their patches or did not return "study medication." Of these patients, 17 were using true BTDS (as opposed to placebo BTDS). The 32 patients were

1021 (BP96-0101)	3604 (BP96-0604)	2033 (BP99-0203)
20218 (BP96-0102)	3605 (BP96-0604)	2131 (BP99-0203)
27303 (BP96-0103)	1026 (BP99-0203)	2081 (BP99-0203)

and the following patients from BP98-1201

2022	7089	21079	21080	21081	21196	5035
5041	5043	5181	4004	4213	4216	4217
16141	10151	21082	21083	21084	21190	21192
21237	2254					

Also determined by manual review of most of the comments in Appendix 6—comments from study BP99-0203 were not reviewed—was that at least 14 patients did not return for follow-up, refused to return, or were lost to follow-up. This group of 14 patients does not include any of the 32 patients mentioned above. Eleven of these 14 patients used true BTDS. Perhaps the patients who were lost to follow-up also did not return their study medication. These patients were

BP96-0102	BP96-0103	BP96-0604	BP98-1201
6206	20310	8603	19169
6210	20315		18311
6218	20322		21195
27215	21307		21240
27218			

As stated above, the Sponsor assessed compliance by noting the number of patients—57 of 1037 patients—who used >100% of their allotment of patches during the four studies that are discussed below. (The Sponsor does not specify whether these patients were using placebo or

true BTDS.) It does not appear that return or failure to return patches was consistently noted in the CRFs. There are "Study Drug Compliance Check" pages in the CRFs. On these pages of the CRFs for studies BP96-0101 and BP96-0102, the lines regarding BTDS are the following:

# of Patch Sets Patients Should Have Used (A)=
# of Complete Patch Sets Used (B)=
B/A x 100 =____%
Any patient <75% or > 125% compliant will be terminated from the study.

The compliance pages of the CRF for study BP96-0103 essentially contain what is noted above also.

The investigators noted in some of the completed CRFs when patches were not returned, but there does not always appear to be a specific place in the CRFs to record whether patches (used or unused) were returned. A question in the CRF from study BP96-0604 does pertain to return of unused BTDS—see below.

A line regarding the comparator drug (e.g., oxycodone / acetaminophen), which appears on the "Study Drug Compliance Check" pages of the CRFs for studies BP96-0101 and BP96-0102, specifically asks about return of tablets and appears below.

# of Tablets Dispensed=
# of Tablets Returned=
# of Tablets Lost/Ruined=

The "Study Drug Compliance Check" pages in the CRFs for study BP96-0604 contain more detailed questions regarding BTDS and less detailed questions regarding oxycodone/acetaminophen. Lines from these pages appear below.

<u>Buprenorphine TDS</u>
Number of TDS Dispensed (Include Extra TDS)=____(A)
Number of Unused TDS Returned=_____(B)
Number of TDS Lost or Ruined=____(C)
Number of TDS Expected to be Used (Include Extra TDS Used)=____(D)
<u>A-B-C</u>
D X 100%=_____% Compliant
If compliance is <75% or >125% the pt will be terminated from the study

<u>Oxycodone/Acetaminophen Tablets</u>
No. of Tablets Taken=____(A)
No. of Tablets the Pt Should Have Taken=____(B)
A/B X 100%=____% Compliant
If compliance is <75% or >125% the pt will be terminated from the study

In the lines above, there is no question regarding the number of used TDS returned. This may be because the Sponsor instructed the patients to flush TDS patches that were used. However, perhaps even used patches should have been returned, since (b) (4) of the buprenorphine remains in the patch after it has been used for seven days.

To conclude, the amount of study medication that was not returned appears to be unknown. This information should have been clearly noted in the CRFs.

Sponsor's Summary of Buprenorphine Overdose Cases

This section of the ALS is separated according to whether the cases occurred in the U.S. or other countries and whether the cases involved buprenorphine only or multiple drugs.

Domestic Experience—Buprenorphine Only and Mixed Exposures (Sponsor's Summary)
Volunteers who were current i.v. users of heroin but not physically dependent received sublingual buprenorphine in doses ranging from 1 to 32 mg. A statistically significant decrease (by 4 breaths per minute) in respiratory rate (RR) was noted at doses of greater than or equal to 4 mg. However, beyond the 16 mg dose, no further decrease in RR was noted. After subjects received 8, 16, or 32 mg, a statistically significant decrease in arterial oxygen saturation occurred.

In study BP96-0304 (Phase 1), one subject who was receiving BTDS 20 and who had received promethazine 25 mg experienced a significant decrease in RR to 3 breaths per minute. Recovery occurred after BTDS was removed.

Fullerton et al (1991--p. 76, ALS) reported that four healthy male volunteers who received 0.3 mg/70 kg of buprenorphine via rapid i.v. infusion experienced severe nausea and vomiting.

International Experience—Buprenorphine Only Exposure (Sponsor's Summary)
The Sponsor states that in the medical literature they found seven cases of buprenorphine overdose that occurred outside the U.S. and outside of clinical trials, and which involved no concurrent medications. Tracqui et al (1998—p. 76, ALS) described four cases of buprenorphine only overdose that occurred in France. One of these people (31 year old male with a history of i.v. drug abuse) died. The death was reported as an unintentional overdose.

Decocq et al (1997—p. 77, ALS) described two nonfatal cases of buprenorphine overdose that occurred in France and involved i.v. injection of ground sublingual tablets. Cracowski et al (1999—p. 77, ALS) reported that a 22 y.o. male from France had a myocardial infarction after self-administering 8 mg of buprenorphine by insufflation.

Adelhoj et al (1985—p. 77, ALS) reported a RR of 2 to 4 breaths per minute in a 30 y.o research volunteer after he received 0.004 mg/kg of i.v. buprenorphine.

In a study done by Gal (1989—p. 77, ALS), six healthy volunteers received 0.3 mg/70 kg of buprenorphine, and measurable respiratory depression occurred. Orwin (1977—p. 77, ALS) administered buprenorphine i.m. (0.15, 0.3, 0.6 mg) to 6 volunteers and i.v. (0.3 mg) to 5 volunteers to produce respiratory depression. None of the subjects in the Gal and Orwin studies suffered permanent adverse effects.

Umbricht et al (1998—p. 77, ALS) gave 6 experienced opioid users sublingual buprenorphine 12 mg or placebo and i.v. buprenorphine (0, 2, 4, 8, 12, 16 mg). A decrease in oxygen saturation of 7.3% and a slight increase in systolic blood pressure occurred at the 8 mg i.v. dose only. One subject discontinued because of nausea at the 12 mg dose.

International Experience—Mixed Buprenorphine Exposures (Sponsor's Summary)
The Sponsor states that according to their review (as of 11/3/00), 21 deaths associated with buprenorphine have been reported (Tracqui—1998—p. 78, ALS). One of the cases did not involve concurrent medication and was discussed above. The mean buprenorphine postmortem plasma concentration from the 20 people who used concurrent medication was 9.6 ng/ml. Plasma concentrations for the concurrent medications were reported only in one case. In this case the postmortem plasma concentrations were as follows: buprenorphine-12.6 ng/ml, norbuprenorphine—2.1 ng/ml, desmethyldiazepam-612 ng/ml (which indicates a dose of ~20 to 30 mg of diazepam), and ethanol-0.13 ng/ml. The concurrent medications involved in all the cases were the following: dipotassium clorazepate (75%), oxazepam (40%), ethanol (35%), flunitrazepam (25%), morphine (15%), cyamemazine (10%), diazepam (10%). The following medications were used in one (5%) of the 20 cases: propoxyphene, alimemazine, meprobamate, paroxetine, amitriptyline, and bromazepam.

The Sponsor found 31 individual patient reports from international sites of nonfatal mixed buprenorphine overdoses and a Danish report of 12 patients who received buprenorphine i.v. (30-40 ug/kg) preoperatively along with other medications. In all but one of the 12 patients, the RR decreased. In greater than half of these patients, the RR decreased to less than 8 breaths per minute.

Of the 43 patients noted above, 18 were in a surgical setting. The concurrent medications of the 43 patients were as follows: benzodiazepines (67%), ethanol (19%), and cannabis (19%). Barbiturates, LSD, opioids, acetaminophen, and antidepressants were concurrent medications in less than 10% of the 43 cases.

In a group of 24 nonfatal mixed overdose cases reported by Tracqui et al (1998—p. 79, ALS), two people required mechanical ventilation and one received naloxone that was deemed ineffective. The doses of buprenorphine in 12 of these 24 cases ranged from 2 mg i.v. to 40 mg p.o.

Sponsor's Conclusion Regarding Overdose Information
Use of buprenorphine with other drugs that depress respiration worsens the prognosis for buprenorphine overdose. Most (20 of 21) lethal overdoses of buprenorphine described by the Sponsor occurred when concurrent medications were used. Seventeen of these cases involved benzodiazepine use. Concurrent benzodiazepine use enhances the buprenorphine respiratory depressant effect (Jain and Shah, p. 82, ALS).

Controlled Substance Staff's Summary of Buprenorphine Overdose Cases

Buprenorphine has been abused in multiple countries, including France, Spain, India, England, Scotland, Ireland, Australia, New Zealand, Germany, and Norway. The Sponsor acknowledges

abuse of buprenorphine in many countries—see pages 47 through 50 of ALS. The following information was presented at the 2000 AAFS (American Association of Forensic Science) meeting.

> *In 2000 Kintz reported on 117 buprenorphine fatalities. Information was based on data from the Institute of Legal Medicine of Strasbourg and 13 other forensic centers in France. The actual number of fatalities was believed to be higher, as there was a lack of full response to inquiries from forensic centers, and in many overdose cases, autopsies were not performed. When autopsies were conducted, buprenorphine and norbuprenorphine levels in postmortem blood varied widely: 0.1 to 76.0 ng/ml and <0.1 to 65 ng/ml, respectively. All but one case involved a concomitant intake of psychotropics, which is not unexpected in the opioid-addicted population. Cause of death was often listed as tracheobronchial inhalation. Benzodiazepines were frequently associated with the buprenorphine deaths; they were present in 91 observations, 64 of which involved nordiazepam. Other cases involved neuroleptics, tricyclic antidepressants, SSRIs, and other narcotics. Four fatalities involved ethanol and buprenorphine* (3).

France has limited the distribution of sublingual buprenorphine after initial post-marketing experience with buprenorphine because of abuse, diversion, and deaths due to overdose. By regulation, only a seven day supply is dispensed at one time.

CSS concludes that buprenorphine abuse/overdose appears to be a significant problem in some countries where buprenorphine is available to the general public. Because of this problem, because buprenorphine is easily extracted from BTDS, and because (b) (4) of the drug remains in BTDS after it has been used, CSS recommends that the Agency consider whether the distribution of BTDS should be restricted.

Response to Opioid Antagonists After Buprenorphine Overdose

Near the end of the main text of the ALS, the Sponsor provides the following information regarding the treatment of buprenorphine overdose.

The effect of naloxone after buprenorphine administration differs from the effect of naloxone after the administration of other u-agonists. In a study done by Gal (1989—p. 79, ALS) naloxone (1, 5, or 10 mg i.v.) was given two hours after 0.3mg/70 kg of i.v. buprenorphine had been administered to six male volunteers. (This dose of buprenorphine caused a significant decrease in respiration.) Naloxone 1 mg did not significantly affect respiratory parameters until 3 hours after its administration. Naloxone 5 and 10 mg significantly reversed respiratory depression as early as 30 minutes after administration, and this effect continued for the duration of the three hour study.

Orwin et al (1976—p. 80, ALS) demonstrated that naloxone is needed in doses ranging from 8 to 12 mg to overcome the respiratory depression produced by buprenorphine 0.3 mg i.v. In a study done by Knape (1986—p. 80, ALS), a 42 y.o. male received 0.3 mg of buprenorphine epidurally and then 0.2 mg of i.v. naloxone followed by 0.1 mg doses of i.v. naloxone. (Total dose of

naloxone received was 1.0 mg.) No detectable reversal of respiratory depression occurred until 54 minutes after apnea started.

Doxapram reversed respiratory depression when it was administered to six male volunteers one hour after they had received buprenorphine 0.3 mg i.v. The reversal was short-lived. However, using a doxapram infusion after the bolus prolonged the reversal. Doxapram is no longer used to treat drug overdoses because of its toxic effects.

To summarize, in the Gal study, higher doses of naloxone were required to reverse respiratory depression due to buprenorphine than are required to reverse depression due to other opioid agonists. In addition, the onset of action of naloxone is delayed when it is used to treat buprenorphine overdose. By contrast, naloxone displays an almost immediate effect when it is used to reverse respiratory depression due to u-agonists such as morphine. Thus, it may be more difficult to treat patients who have respiratory depression due to buprenorphine than patients who have respiratory depression due to other opioids. The Sponsor states, "Treatment of a massive buprenorphine overdose may require even larger doses of naloxone (than were used in the Gal study), and the time course for the naloxone effect in this setting is not known" (p. 82, ALS).

Comments Regarding the 3/9/01 Submission

CSS submitted a list of questions regarding the ALS to the Sponsor in December 2000. The Sponsor's replies were contained in their March 9, 2001 submission, and parts of that submission are discussed below.

Error
The Sponsor was asked to provide the location of CRFs/narratives of patients who had a history of drug or alcohol abuse or dependence prior to participating in the studies. The Sponsor stated, "A history of drug or alcohol abuse or dependence prior to the study was an exclusion criterion, so such patients would not have been entered into the study." This statement is incorrect. For example, an exclusion criterion for study BP98-1201 was that the patient could have no history of substance abuse during the five years preceding the study. Also, as per Appendix 6 of ALS, multiple patients from study BP96-0102 had histories of substance abuse—e.g., patients 6206, 8201, 8209, 21201, 21233, 22201, 26204, 28203, 28205. In addition, there are other patients from the clinical studies who had histories of substance abuse/dependence.

Buprenorphine Reapplication
The Sponsor was asked to submit data testing the removal and reapplication of BTDS. The Sponsor answered that (b) (4) of the buprenorphine remains in the patch following a 7-day application and that "it is likely that reapplication of a used BTDS that has been previously worn for 7 days would result in further delivery of buprenorphine." From an abuse liability point of view, these characteristics of BTDS are concerning.

Appendix B:
Controlled Substance Pharmacology Reviewer's Notes

Epidemiology

The Sponsor states that buprenorphine substance is in Schedule V under the CSA and that there have been no reports of buprenorphine abuse in the Drug Abuse Warning Network (DAWN) database since parenteral buprenorphine was introduced into the US in 1985. However, buprenorphine has appeared as a mentioned drug in the DAWN database during 1995-1999 (the last years for which data are available by individual drug). The low numbers for most years are probably related to the fact that the only currently marketed drug product containing buprenorphine (Buprenex) is available solely as a parenteral preparation in hospital settings. It is unclear why there were 67 mentions for buprenorphine in 1997, which is 10 times the number of mentions of the next highest number of mentions (6 mentions in 1999).

Emergency Department Visits Where Buprenorphine Was Mentioned (DAWN database)

Year	Number of Mentions	Recreation	Dependence	Other/OD
1999	6	3	2	1
1998	0			
1997	67	66	1	
1996	1			1
1995	2			2

The Sponsor acknowledges that BTDS is vulnerable to intentional misuse through multiple patch applications, chewing patches to increase buccal absorption, or through extraction of buprenorphine from the patch for parenteral use. Because buprenorphine can be extracted from BTDS, the Sponsor recommends that BTDS be controlled under the CSA in Schedule V. Extracted buprenorphine can be abused intravenously or through other routes of administration.

Disposition of Used BTDS Patches

The Sponsor recommends disposal of used BTDS by flushing the patch down the toilet.

Conclusions:

There is insufficient information provided to CSS by the Sponsor to fully assess the abuse liability of BTDS (b) (4)
However, upon review of the information that was submitted and the available epidemiological data received by the Agency, it is clear that BTDS does have a significant abuse liability.

The greatest risk of abuse stems from the large amount of buprenorphine that is left in the BTDS patch after 7 days of administration. Depending on the BTDS patch dose, (b) (4) mg of buprenorphine can remain in the matrix of the patch following proper medical usage.

Extraction of the drug from the patch is time-consuming but not difficult with appropriate solvents. Thus, the availability of buprenorphine extracted from a patch for intravenous use is a serious risk associated with BTDS.

References

1. *Treatments of Psychiatric Disorders,* 2nd Edition, Volumes 1 & 2. Gabbard GO, Editor-in-Chief. Washington, DC, American
Psychiatric Press, 1995.

2. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

3. Kintz, P. Deaths involving buprenorphine: a compendium of French cases. American Association of Forensic Science meeting, Reno, Nevada, 2000.

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

/s/

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Medical Officer's Review and Evaluation of Clinical Data

NDA # (serial):	**21-306 (000)**
Drug Name (generic):	**Norspan™ (buprenorphine transdermal system, BTDS)**
Sponsor:	**Purdue Pharma, LP**
Type of Submission:	**NDA**
45 Day Filing Date:	**03JAN00**
Type of Review:	**45-day Filing Review**
Material Reviewed:	**NDA 21-306 (000)**
Reviewer:	**Gerald J. Dal Pan, MD, MHS**
Project Manager:	**Sara Shepherd, MS**

1 Background

The Sponsor has submitted a New Drug Application (NDA) for Norspan™ (buprenorphine transdermal system, BTDS). This review assesses the fileability of the submission.

1.1 On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?

Yes.

1.2 Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?

Yes.

1.3 On its face, is the clinical section of the NDA legible so that substantive review can begin?

Yes.

1.4 If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (ie, appropriately designed dose-ranging studies)?

Yes.

1.5 On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?

Yes.

1.6 Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

Yes.

1.7 Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?

Yes.

1.8 Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

Yes.

1.9 Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

Yes.

1.10 Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the US population?

Yes.

1.11 Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?

Yes.

1.12 Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?

Yes.

1.13 Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?

Yes.

1.14 Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?

1.15 Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?

Yes.

1.16 From a clinical perspective, is this NDA fileable? If "no", please state below why it is not?

Yes.

Gerald J. Dal Pan, MD, MHS Medical Officer	Date	Bob Rappaport, MD Deputy Division Director	Date

NDA# 21-306
Division File
HFD-170: C. McCormick, MD
HFD-170: B. Rappaport, MD
HFD-170: G. Dal Pan, MD, MHS
HFD-170: S. Shepherd

/s/

Gerald DalPan
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MEDICAL OFFICER

You've already signed a hard copy of the checklist.

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