CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	21306/S-027
Priority or Standard	Standard
Submit Date(s)	15 December 2016
Received Date(s)	15 December 2016
PDUFA Goal Date	13 October 2017
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE 2
Reviewer Name(s)	Robert A. Levin, MD
Review Completion Date	11 September 2017
Established Name	Buprenorphine Transdermal System
(Proposed) Trade Name	Butrans
Therapeutic Class	Opioids
Applicant	Purdue
Formulation(s)	2.5 (only for pediatric study), 5, 10, and 20 mcg/hour
Dosing Regimen	Butrans administered transdermally every 7 days
Indication(s)	For the management of pain severe enough to require daily, around-the-clock, long-term

	opioid treatment for which alternative treatment options are inadequate
Intended Population(s)	Pediatric

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approving this efficacy supplement for Butrans [Buprenorphine Transdermal System (BTDS)]. However, I do not recommend adding including pediatric patients 7 through 16 years of age into the approved indication. This recommendation not to add a pediatric indication is based on the limited number of pediatric patients and data that was collected in study BUP3031. The sample size included a total of 41 patients with six patients in the 7 to 11 year old age group and 35 patients in the 12 to 16 year old age group. A total of 37 patients in all age groups were exposed to Butrans for at least 2 weeks with 3 in the 7 to 11 year old age group and 34 in the 12 to 16 year old age group. At the time the PREA requirement was issued and the proposed study design was reviewed, a safety database of approximately 40 patients was considered adequate for approval of an extended-release/long-acting (ERLA) opioid analgesic for pediatric use. Since that time the requirements for approval have evolved. Following a Joint meeting of the Analgesic and Analgesic, Pediatric, and Drug Safety Advisory Committees in September 2016, Division now requests a total of 125 patients for the 12 to 17 year age group and 50 patients for the 7 to11 year age group to adequately assess safety. Also, the Division encourages the Applicant to enroll as many patients as possible with cancer-associated pain and carefully document the primary reason for chronic opioid treatment. There were no patients enrolled in study BUP3031 with a diagnosis of cancer as the primary pain etiology. There were several patients with diagnoses of migraine headache and low back pain as the primary pain etiology. Pediatric patients with these diagnoses are not currently typically treated with chronic opioids.

Expert opinion (Berde 2012) supports that the efficacy of opioids can be extrapolated from adults to children down to 2 years of age, based on the similarity of the underlying disease process and assuming the exposure response to buprenorphine in the pediatric age group is similar to adults. Therefore, for the indication of chronic pain, efficacy studies are not required by the Division for opioids in subjects two to less than 17 years of age. The open-label study design without a control group in study BUP3031 was considered acceptable since this was not intended to be an efficacy study. However, the Division now believes it is important to carefully collect information about rescue medication use, including dose and frequency of use to indirectly assess for efficacy. In the study, individual dosing or number of doses used of supplemental opioids and nonopioids were not required by protocol. The prescribed dose and frequency of rescue opioid and nonopioid pain medications were documented in the case report form as concomitant medications. Regarding pain scores, patient self-reported pain right now assessments were recorded once daily every evening during the first 4 weeks of study treatment and weekly thereafter. Pain scores were not required by protocol to be

documented in relation to use of supplemental analgesia, therefore pain scores prior to rescue medication use are not available for analysis. The data collected are insufficient to draw clear conclusions about the efficacy of BTDS in pediatric patients. Thus, per policy, any inferences about buprenorphine in the pediatric population age 2 years to <17 years is extrapolated from findings in adults.

The buprenorphine pediatric PK analysis dataset for Study 3031 which included 38 subjects and a total of 151 plasma concentrations, was used to characterize the pharmacokinetics of transdermal buprenorphine in pediatric patients. The final population PK model seemed to provide an adequate description of the pediatric PK data and could be used to perform simulations to identify the "target" pediatric BTDS dose which matches the steady-state exposures in adults following the recommended starting dose of BTDS 5 mcg/hr. A summary of simulated buprenorphine exposures in the younger age cohort (7 to 11 years) at a BTDS dose of 2.5 mcg/hr and the older age cohort (12 to 16 years) at a BTDS dose of 5 mcg/hr is provided in Table 2. From a clinical pharmacology perspective dosing recommendations could be derived in a pediatric population. However, there is inadequate safety experience from study BUP3031 (n = 6 in the age range of 6-11 years and n = 35 in the age range of 7-12 years) to support a pediatric indication and pediatric dosing information.
In summary, this submission does not contain the number of patients currently recommended for evaluation of a pediatric ERLA opioid indication. Also, many of the patient diagnoses for the primary cause of pain are not consistent with current guidelines for the use of ERLA opioids in pediatric patients. Although the Division does not consider this submission adequate to recommend a pediatric indication for Butrans, this study does fulfill Purdue's pediatric postmarketing requirements at the time of approval for NDA 21306. In a meeting on September 6, 2017, CDER's Pediatric Review Committee agreed with the DAAAP that the PREA requirement has been met.

1.2 Risk Benefit Assessment

Risk Benefit Assessment
The risk-benefit assessment does not support extension of the labeled indication to the new patient population, since an insufficient number of patients were studied to fully assess the risk-benefit profile. The safety profile for Butrans in pediatric patients was generally consistent with adults but the number of patients and exposure was limited. Generally, the overall ECG data did not suggest a safety signal regarding QTc interval prolongation.

Benefit
The Applicant conducted Study BUP3031, primarily a pharmacokinetic and safety study, as required by the PREA requirement. Study BUP3031 was an open-label, uncontrolled study and not designed to demonstrate the efficacy of BTDS. The efficacy of BTDS in pediatric patients is extrapolated from adults based on similar PK.

Risk
In the Butrans pediatric development program, a total of 41 patients were exposed to at least one dose of Butrans during Study BUP3031. The safety data obtained from this limited number of patients was consistent with findings observed in adults. Butrans is known to prolong the QT interval and includes a warning in the label on this risk of prolonged QTc interval. In study BUP3031, there were two patients who developed mild QT prolongation at doses of 10 mcg which may have been drug related. The approved label states, "A positive-controlled study of the effects of BUTRANS on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a BUTRANS dose of 10 mcg/hour; however, a BUTRANS dose of 40 mcg/hour (given as two BUTRANS 20 mcg/hour Transdermal Systems) was observed to prolong the QTc interval." The QT prolongation observed in these two patients was mild and an adequate warning already exists in the label.

No modifications are required to the existing Warnings and Precautions section of the label. The current label adequately informs prescribers to consider these conditions when prescribing Butrans, "…hypokalemia or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid the use of BUTRANS in 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), or other medications that prolong the QTc interval".

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Buprenorphine is a molecule with partial mu-opioid agonist and kappa-opioid antagonist activity approved as an analgesic and for medication assisted therapy for opioid use disorder. Butrans is a transdermal administration system indicated for the management

in adults of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate (not indicated for addiction). Butrans is available in doses of 5, 7.5, 10, 15, and 20 mcg/hour. Each Butrans patch is intended to be worn for 7 days.

Buprenorphine was initially approved as an injectable formulation, Buprenex, (NDA 018401) on December 29, 1981 for the treatment of moderate to severe pain. Buprenex is approved for use in pediatric patients aged 2-12 years. The approved label provides the following information on pediatric use:

> The safety and effectiveness of BUPRENEX have been established for children between 2 and 12 years of age. Use of BUPRENEX in children is supported by evidence from adequate and well controlled trials of BUPRENEX in adults, with additional data from studies of 960 children ranging in age from 9 months to 18 years of age. Data is available from a pharmacokinetic study, several controlled clinical trials, and several large post-marketing studies and case series. The available information provides reasonable evidence that BUPRENEX may be used safely in children ranging from 2-12 years of age, and that it is of similar effectiveness in children as in adults.

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. The safety and effectiveness of Subutex and Suboxone have not been established in pediatric patients. On October 7, 2002, the DEA rescheduled buprenorphine from Schedule V to Schedule III.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following are approved pediatric analgesics:

Nonopioid Analgesics
Acetaminophen
Aspirin
Ibuprofen

Opioid Analgesics
Buprenorphine injection
Fentanyl citrate injection
Fentanyl transdermal
Oxycontin

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine is approved as a transdermal system (Butrans), a buccal film and an injection for the treatment of pain, and a buccal film, sublingual tablet, and subdermal implant for the treatment of opioid dependence.

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, abuse, and diversion. Like methadone, buprenorphine has also been shown to prolong the QT interval.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 displays highlights of the regulatory activity that occurred during the clinical development program for Butrans in adolescents for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant

Date	Topics
June 30, 2010 NDA 21306 approved	• Butrans approved in adults for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. ○ Note: Due to opioid class labeling, the current indication is now for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. • At the time of approval, pediatric study requirements were waived for ages birth through six years because necessary studies were impossible or highly impracticable because the numbers of pediatric patients meeting the indication were too small in number to make pediatric studies feasible. • The pediatric study was deferred for ages 7 through 16 years because approval for the product was ready in adults. The PREA requirement at time of approval is listed below: 1655-1 Deferred pediatric study under PREA, a pharmacokinetic and safety study for the

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant	
	treatment of moderate to severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages 7 through 16. Final Protocol Submission: April 7, 2011 Study Completion: January 8, 2015 Final Report Submission: June 30, 2015
June 11, 2012 Advice Letter	The Division provided the following advice for Study BUB3031 • You propose that a conventional 12-lead ECG and 24-hour digital 12-lead ECG (Holter monitor) is to be performed 2 to 3 days after the up-titration to BTDS 20. However, the time required to reach the steady state plasma buprenorphine concentration in adults is greater than 72 hours post-dose. Revise the protocol to indicate that you will perform ECG monitoring at day 3-4 post-dose. • Add ECG monitoring as part of the end of study procedures for study drug premature discontinuations • Discontinue subjects if the average QTcF value of three post-screening ECG (30 minutes apart) is greater than 500 ms or greater than 480 ms with a concurrent increase in average QTcF value greater than 60 ms from the screening baseline. • Record and report the following adverse events of special interest: a. QTcF prolonged (> 500 ms), b. QTcF prolonged (> 480 ms with a concurrent increase in average QTcF value > 60 ms), c. Torsade de pointes (TdP), d. Sudden death, e. Ventricular tachycardia, f. Ventricular fibrillation and flutter, g. Syncope, and h. Seizures • Conduct a categorical analysis as follows: a. Number and percentage of individuals with: (1) Absolute QT/QTc values > 480 ms, and > 500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms (2) PR changes from baseline ≥ 25% and absolute PR values over the upper normal limit according to age (3) QRS changes from baseline ≥ 25% and absolute QRS values over the upper normal limit according to age b. Number and percentage of individuals with abnormal

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant	
	ECG findings c. Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death • Central tendency analysis should be conducted to generate mean and 90% two-sided confidence interval by each time points.
June 27, 2012 Advice Letter	We provided the following comments: 1. Protocol BUP3031 does not provide an adequate duration of treatment to sufficiently assess the long-term safety of Butrans. For a chronic pain indication, as noted in our September 20, 2011, Pediatric Written Request letter, you will need 40 completers with at least 6-months of exposure to assess safety. The proposed four-week treatment duration is acceptable for the pharmacokinetic (PK) aspect of your study, but additional patients must be studied to provide the necessary long-term safety data. 2. To ensure a precise estimate of the important PK parameters, Study BUP3031 should be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution in each pediatric subgroup, with at least 80% power. Patients must also be reasonably distributed within the age range and approximately evenly distributed between genders.
March 2, 2015 Deferral Extension Granted	• The Division agreed to extend the Final Report Submission date for PREA requirement 1655-1 to December 31, 2016
September 16, 2015 Advice on Pediatric Study Plan	Agreed Initial Pediatric Study Plan – No Agreement The Division said that an efficacy study would not be required and made the following comment: • The efficacy of opioids can be extrapolated from adults down to 2 years of age, based on the similarity of the underlying disease process and the exposure response to buprenorphine in adults and pediatric patients. Therefore, for the indication of chronic pain, efficacy studies will not be necessary in subjects 2 to less than 17 years. • Division did not agree with a waiver for doses greater than

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant	
	20 mcg/hour • The Division agreed with the following aspects of the proposed study design: ○ OL predominantly PK and safety study ○ Approximately 40 patients to be evaluated for up to 28 weeks with treatment for a minimum of 2 weeks ○ All patients in the younger age group (aged 7 to 11 years) will initiate treatment with BTDS 2.5; all patients in the older age group (aged 12 to 16 years) will initiate treatment with BTDS 5

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The 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

The Applicant reports that Study BUP3031 was performed in full compliance with the International Council for Harmonisation (ICH) and all applicable Good Clinical Practices (GCPs) and federal and local regulations. The study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects"), and all its accepted amendments to date concerning medical research in humans;
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use;
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use;

- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products;
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, and International Conference on Harmonization of Pharmaceuticals for Human Use;
- EurdaLex Volume 10 Clinical Trials Guidelines; and
- US Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including, but not limited to, parts 50, 56, and 312 concerning Informed Patient Consent, IRB and INVESTIGATIONAL NEW DRUG APPLICATION regulations).

Patients were informed that participation was voluntary and that they could withdraw from the study at any time. Informed consent was obtained at the screening visit before any study specific procedures were performed.

The Office of Scientific Investigation (OSI) inspected two sites for Study BUP3031, Site # 2493A (Sunny Hussain) and Site # 2527A (Jerry Tomasovic), based on these two sites enrolling the highest number of subjects. OSI concluded that the minor regulatory violations found during the inspections at both sites, were unlikely to impact the reliability of the data. The final clinical inspection summary dated August 4, 2017 stated, "The data from the CI sites submitted by the sponsor in support of the pending application are acceptable and the study was conducted adequately to support approval**."**

3.3 Financial Disclosures

Purdue submitted Debarment Certification and FDA form 3454 certifying that none of the financial interests or arrangements described in 21 CFR Part 54 exists for any of the clinical investigators who participated in Study BUP3031.

A copy of the completed Clinical Investigator Financial Disclosure Review form follows.

Clinical Investigator Financial Disclosure

Application Number: 21306

Submission Date(s): December 15, 2016

Applicant: Purdue

Product: Butrans (buprenorphine transdermal system)

Reviewer: Robert A. Levin, MD

Date of Review: August 27, 2017

Covered Clinical Study (Name and/or Number): BUP3031

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 33 (principle investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ____ Significant payments of other sorts: ____ Proprietary interest in the product tested held by investigator: ____ Significant equity interest held by investigator in sponsor of covered study: ____		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not Applicable	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: Not Applicable	Yes ☐	No ☐ (Request explanation from applicant)

Purdue has adequately disclosed financial arrangements with clinical investigators. The Applicant has submitted FDA form 3454 certifying that the clinical investigators who supervised studies in support of this application:

- 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)].

No financial arrangements were identified that would affect the approvability of this application. Potential bias was minimized by use of a contract research organization to implement and manage the study, and use of an independent Data Monitoring Committee to review the safety data from the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Not applicable

4.4 Clinical Pharmacology

A detailed discussion of the clinical pharmacology issues is contained in the review by Dr. Wei Qiu, the FDA clinical pharmacology reviewer.

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

Not applicable

4.4.3 Pharmacokinetics

The following summary of buprenorphine exposure in pediatric patients was obtained from the FDA Office of Clinical Pharmacology Review dated September 11, 2017. The

buprenorphine pediatric PK analysis dataset for Study 3031 which included 38 subjects and a total of 151 plasma concentrations, was used to characterize the pharmacokinetics of transdermal buprenorphine in pediatric patients. The pharmacologist concluded that the final population PK model seemed to provide an adequate description of the pediatric PK data and could be used to perform simulations to identify the "target" pediatric BTDS dose which matches the steady-state exposures in adults following the recommended starting dose of BTDS 5 mcg/hr. A summary of simulated buprenorphine exposures in the younger age cohort (7 to 11 years) at a BTDS dose of 2.5 mcg/hr and the older age cohort (12 to 16 years) at a BTDS dose of 5 mcg/hr is provided in Table 2. The pharmacology review team believes that from a clinical pharmacology perspective dosing recommendations can be derived in a pediatric population (up to age of 7 years) based on body weight that match the exposure in adults based on the final PopPK model. However, they do not provide recommendations due to the inadequacy of the safety experience from study BUP3031 (n = 6 in the age range of 6-11 years and n = 35 in the age range of 7-12 years) to support a pediatric indication. The current Butrans label contains a table summarizing buprenorphine pharmacokinetics in a study of healthy adults and is reproduced in Table 3.

Table 2: Exposures of Buprenorphine at Steady-state in Younger Age Cohort (7-11 Years) Receiving 2.5 mcg/hr Dose and Older Age Cohort (12-16 years) Receiving 5 mcg/hr Dose

Age Cohort	Pediatric subjects 7 - 11 years (n=5) following BTDS 2.5 mcg/hr (Median (Range))	Pediatric subjects 12-16 years (n=33) following BTDS 5 mcg/hr (Median (Range))
Buprenorphine Steady State Exposures [AUCss (ng.h/ml)]	15.7 (12.3, 23.2)	18.9 (13.3, 30.3)

Source: FDA Office of Clinical Pharmacology Review. Sept. 11, 2017, p.11

Table 3: Pharmacokinetic Parameters of Butrans in Healthy Adult Subjects, Mean

Single 7-day Application	**AUC_{inf} (pg.h/mL)**	**C_{max} (pg/mL)**
BUTRANS 5 mcg/hour	12087 (37)	176 (67)
BUTRANS 10 mcg/hour	27035 (29)	191 (34)
BUTRANS 20 mcg/hour	54294 (36)	471 (49)
Multiple 7-day Applications	**$AUC_{tau,ss}$ (pg.h/mL)**	**$C_{max,ss}$ (pg/mL)**
BUTRANS 10 mcg/hour, steady-state	27543 (33)	224 (35)

Source: Butrans Label, Table 7

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical data provided in this submission is from one trial (Study BUP3031).

5.2 Review Strategy

Efficacy
Study BUP3031 was an open-label study designed to primarily obtain safety and pharmacokinetic information in children from 7 to 16 years of age. The Applicant was not required to demonstrate efficacy, since the Division accepts that the efficacy of opioids can be extrapolated from adults to children down to 2 years of age. The open-label study design of Study BUP3031does not meet the Division's standard for determining efficacy and the data collected are insufficient to draw clear conclusions about the efficacy of BTDS in pediatric patients. Thus, per policy, any inferences about the efficacy of buprenorphine in the pediatric population age 2 years to <17 years is extrapolated from findings in adults.

Safety
Safety findings from the Study BUP3031 are discussed in Section 7 on Safety.

5.3 Discussion of Individual Studies/Clinical Trials

To support the safety and determine the pharmacokinetics of Butrans in children, the Applicant conducted Study BUP3031. The following summary of the design of Study BUP3031 was derived from final protocol Amendment # 6 dated January 13, 2014. The original protocol was dated April 12, 2011 and was amended six times. The first patient was enrolled July 23, 2012 after the first four protocol amendments. The following is the dates of the protocol amendments: Amendment 1 April 12, 2011, Amendment 2 June 13, 2011, Amendment 3 September 8, 2011, Amendment 4 November 23, 2011, Amendment 5 January 14, 2013 and Amendment 6 January 13, 2014. Relevant changes related to Amendment 5 and Amendment 6 are summarized at the end of this protocol review.

Protocol Number: BUP3031

Title: An Open-label, Multicenter Study of the Safety, Pharmacokinetics, and Efficacy of Buprenorphine Transdermal System (BTDS) in Children From 7 to 16 Years of Age, Inclusive, Who Require Continuous Opioid Analgesia for Moderate to Severe Pain

Dates Conducted: The first patient first visit was July 23, 2012 and the last patient last visit was April 12, 2016.

Objectives

The primary objective was to have been:

- To characterize the safety of BTDS in patients aged 7 to 16 years, inclusive, who require continuous around-the-clock opioid analgesia for moderate to severe pain.
- To characterize the PK of BTDS in patients aged 7 to 16 years, inclusive, who require continuous around-the-clock opioid analgesia for moderate to severe pain.

The secondary objective was to have been:

- To assess the efficacy (analgesic activity) of BTDS in patients aged 7 to 16 years, inclusive, who require continuous around-the-clock opioid analgesia for moderate to severe pain.

Overall Design: Study BUP3031 was an open-label, multicenter, multiple dose study primarily of the safety and PK of BTDS in patients aged 7 to 16 years, inclusive, who required continuous around-the-clock opioid analgesia for moderate to severe persistent pain. Pain assessments were completed once daily during the first four weeks of the study and weekly thereafter but no placebo arm was included for comparison. A total of 41 patients were treated with BTDS with 37 patients for a minimum of 2 weeks and up to 26 weeks (including the 14-day follow-up tapering period). Figure 1 below presents a schematic of the study design and Table 4 presents a schedule of activities for screening up to end of week 4, and Table 5 presents the schedule of activities for weeks 6 to week 24.

Patients may have been opioid naïve or opioid experienced. For patients treated with around-the-clock opioids, discontinuation of the around-the-clock opioid was required by visit 2 (prior to initiation with BTDS). Patients may have needed to have their around-the-clock opioids tapered down. If required, patients aged 12 to 16 years were tapered to a dose of 30 mg/day or less of morphine or equivalent and patients aged 7 to 11 years were tapered to a dose of 15 mg/day or less of morphine or equivalent. Once that dose was reached, the patient may have begun treatment with BTDS.

Patients who were opioid naïve or were receiving ≤ 10 mg/day oral morphine or equivalent (MEQ) during the 5 consecutive days prior to the initiation of BTDS treatment were required to be inpatients at the initiation of BTDS treatment and remain hospitalized for the first 48 hours of treatment.

All patients in the younger age group (aged 7 to 11 years) initiated treatment with BTDS 2.5; all patients in the older age group (aged 12 to 16 years) initiated treatment with BTDS 5. If the starting dose did not seem to be controlling the patient's pain, short-acting opioids were permitted during this time at the discretion of the investigator.

The dose of BTDS was allowed to be adjusted upward or downward as needed throughout the study. During the treatment period, patients may have used supplemental short-acting opioid (other than buprenorphine) or nonopioid medications.

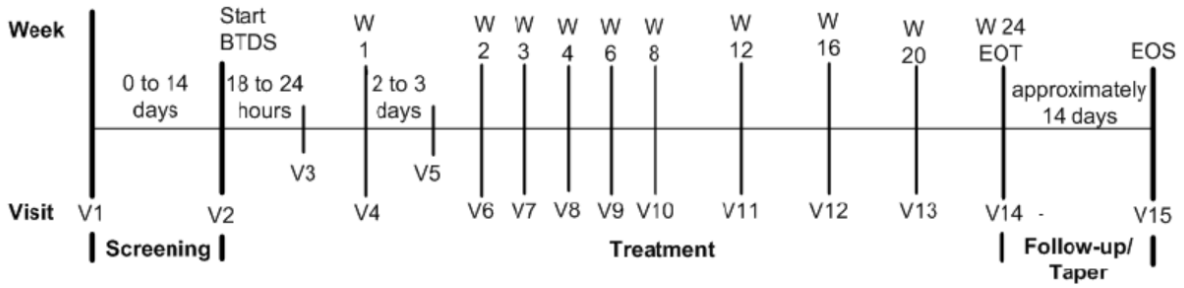
To minimize opioid withdrawal, patients underwent tapering of BTDS for up to 14 days at the completion of BTDS dosing. During this time, patients may have used supplemental short-acting opioids (other than buprenorphine) or nonopioid medications. If the patient continued to require opioid therapy, conversion to an appropriate opioid regimen based on the investigator's clinical judgment was performed.

The PK samples were drawn up to 5 times during the first 4 weeks of the study. PK was collected at the following timepoints:

- 18 to 24 hours after the application of the first BTDS patch (visit 3)
- End of week 1 (visit 4)
- 2 to 3 days after the end of week 1 (visit 5)
- End of week 2 (visit 6)
- End of week 4 (visit 8) or at discontinuation prior to visit 8.

A completer was defined as a patient who met any of the following conditions: (1) the patient completed at least 2 weeks of study drug dosing, did not meet any of the discontinuation reasons, and did not need additional treatment with opioid medication for pain relief at the minimum study drug dose (BTDS 2.5 mcg/h) or equivalent; (2) the patient completed the entire 24 weeks of study drug dosing; or, (3) the patient completed at least 2 weeks of study drug dosing and was being tapered down from his or her current BTDS dose in order to switch from BTDS to other opioid analgesic medication(s) for tapering purposes and did not meet any of the discontinuation reasons.

Figure 1: Study Design BUP3031



Source: CSR BUP3031. Figure 1, p. 25

Table 4: Schedule of Activities: Screening up to End of Week 4 (Visit 8)

Protocol Activity	Screen	Treatment							
	0 to 14 days	4 weeks							
	Visit 1	Visit 2 (Day 1)	Visit 3	Phone[a]/ Evaluation	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Study Day		Start BTDS 2.5 or 5	18h to 24h postdose	72h postdose	End of wk1 (+/- 3d)	2 to 3 days after v4	End of wk2 (+/- 3d)	End of wk3 (+/- 3d)	End of wk4 (+/- 3d)
Informed consent/assent	X								
Inclusion/exclusion criteria	X	X							
Contact IVRS/IWRS	X	X			X		X	X	X
Demography, med history, pain etiology, current med conditions	X								
Record prior opioids	X								
Pregnancy test	X[b]	X[b]					X[b]		X[b]
Physical examination, including Tanner staging	X								
Vital signs, weight, height[c]	X	X[c]	X	X[d]	X	X	X	X	X
Pulse oximetry (SpO_2)[c]	X	X	X	X[d]					
ECG (conventional)[e]	X				X		X	X	X
ECG (24-hour Holter)	X								
Laboratory evaluations	X						X		X
PK blood sample[i]			X		X	X	X		X
Distribute patient diary		X			X	X	X	X	X
Somnolence (UMSS)[f]	X	◄--►							
Assess/record pain right now (FPS-R or VAS)[g]		◄--►							
Collect and review patient diary					X	X	X	X	X

Protocol Activity	Screen	Treatment							
	0 to 14 days	4 weeks							
	Visit 1	Visit 2 (Day 1)	Visit 3	Phone[a]/ Evaluation	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Study Day		Start BTDS 2.5 or 5	18h to 24h postdose	72h postdose	End of wk1 (+/- 3d)	2 to 3 days after v4	End of wk2 (+/- 3d)	End of wk3 (+/- 3d)	End of wk4 (+/- 3d)
Assess current opioid needs and prescribe supplemental pain medications (as needed)	X	X	X	X	X	X	X	X	X
Taper/discontinue any incoming round-the-clock opioids[h]	X	X							
Dispense study drug		X			X		X	X	X
Conduct drug accountability / review for CSPCs					X	X	X	X	X
Assess abuse/diversion					X	X	X	X	X
Evaluate BTDS treatment			X	X	X	X	X	X	X
Apply/remove BTDS		◄--►							
Record concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	◄--►							
Parent and patient instructions/reminders	X	X	X	X	X	X	X	X	X

Abbreviations: BTDS = buprenorphine transdermal system; CSPC = clinical supply product complaint; d = days; ECG = electrocardiogram, FPS-R = Faces Pain Scale-Revised; h = hours; IVRS/IWRS = Interactive Voice Response System /Interactive Web Response System; PK = pharmacokinetics; SpO_2 = pulse oximetry; UMSS = University of Michigan Sedation Scale; VAS = Visual Analog Scale; v = visit; wk = week.

◄--► = procedure may be performed at any time (not just at visits).

a This evaluation may have been a phone call for outpatients.

b For female patients of childbearing potential only. During screening period, a serum pregnancy test was performed; if screening serum pregnancy test was performed more than 24 hours prior to start of study drug treatment, a urine pregnancy test was performed within 24 hours prior to start of study drug treatment. Urine pregnancy tests were done at visits 6 and 8.

c Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) and SpO_2 were recorded at: screening; before and after initial BTDS application; and before and after any up-titration. Vital signs (not SpO_2) were recorded at all scheduled and unscheduled visits. Height was collected only at visit 2. Weight was measured at every visit (including unscheduled and up-titration visits); during visit 2, weight was measured approximately 30 minutes before the initial BTDS application.

d For inpatients and outpatients who came to the clinic.

e Three readings of conventional 12-lead ECG, a minimum of 10 minutes apart. Patients whose BTDS was up-titrated to BTDS 20 had a conventional 12-lead ECG performed 2 to 3 days after the up-titration. In cases where both PK sampling and ECG examinations were planned, ECGs preceded PK sampling.

f UMSS was completed at: screening; 30 minutes before initial BTDS application on day 1; 1 hour after initial BTDS application on day 1; and thereafter once daily in the morning, 30 to 60 minutes, after the patient awakened, for the first 4 days of treatment with BTDS and the first 4 days following an up titration (30 to 60 minutes after the BTDS application for an up-titration). UMSS for inpatients was assessed by the investigator/designee for inpatients.

g Pain right now was assessed at: (1) 30 minutes before initial BTDS application on day 1; (2) 1 hour after initial BTDS application on day 1; and (3) thereafter once daily at approximately 8 PM for the first 4 weeks. Pain right now measured on FPS-R was assessed by patients aged 7 to 11 years, inclusive, and recorded by parent/caregiver and pain right now measured on 100-mm VAS was assessed and recorded by patients aged 12 to 16 years, inclusive.

h All incoming opioids were discontinued by visit 2. Patients aged 12 to 16 years who took > 30 mg/day morphine or equivalent or patients aged 7 to 11 years taking > 15 mg/day morphine or equivalent for at least the last 5 consecutive days prior to the screening visit had their incoming around-the-clock opioids tapered down, as deemed appropriate by the investigator. The tapering process occurred for up to 7 days and was completed before beginning treatment with BTDS.

i When scheduling visit 2, the site also scheduled visit 3 (PK draw) so that the PK blood sample was drawn 18 to 24 hours after the first patch was applied at visit 2.

Source: CSR BUP3031. Table 3, p. 46-48

Table 5: Schedule of Activities: Week 6 to Week 24

Protocol Activity	Treatment								
	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14[a]/EOT Early Discont.	Up-titration	Unsched. Visits[b]	Visit 15/EOS Taper[c] / F/U
	End of wk6 +/- 3 days	End of wk8 +/- 3 days	End of wk12 +/- 3 days	End of wk16 +/- 3 days	End of wk20 +/- 3 days	End of wk24 +/- 3 days	anytime	anytime	approximately 14 days
Pregnancy test[d]	X	X	X	X	X	X			
Physical examination						X			
Vital signs, weight[e]	X	X	X	X	X	X	X[f]	X	
Pulse oximetry (SpO_2)							X[f]		
ECG (conventional)[g]	X	X	X	X	X	X	X[h]		
Laboratory evaluations	X	X	X	X	X	X			
PK blood sample						X[i]			
Record concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	◄--►								
Apply/remove BTDS	◄--►								
Evaluate BTDS treatment	X	X	X	X	X	X	X	X	
Distribute patient diary	X	X	X	X	X	X			
Somnolence (UMSS)[j]	◄--►								
Assess/record pain right now (FPS-R or VAS)[k]	◄--►							X	
Collect and review diary	X	X	X	X	X	X			
Contact IVRS/IWRS	X	X	X	X	X	X[l]			

Protocol Activity	Treatment								
	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14[a]/EOT Early Discont.	Up-titration	Unsched. Visits[b]	Visit 15/EOS Taper[c] / F/U
	End of wk6 +/- 3 days	End of wk8 +/- 3 days	End of wk12 +/- 3 days	End of wk16 +/- 3 days	End of wk20 +/- 3 days	End of wk24 +/- 3 days	anytime	anytime	approximately 14 days
Dispense study drug	X	X	X	X	X	X			
Conduct drug accountability/ review for CSPCs	X	X	X	X	X	X		X	
Assess abuse and diversion	X	X	X	X	X	X	X	X	
Assess current opioid needs and prescribe supplemental pain medications (as needed)	X	X	X	X	X	X	X	X	X
Complete PGIC						X			
Assess patient's taper requirements						X			
Parent and patient instructions/reminders	X	X	X	X	X	X	X	X	

Abbreviations: BTDS = buprenorphine transdermal system; CSPC = clinical supply product complaint; Discont.= Discontinued; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment (prior to tapering off study treatment); FPS-R = Faces Pain Scale-Revised; F/U = follow-up; IVRS/TWRS = Interactive Voice Response System /Interactive Web Response System; PGIC = Parent/Caregiver-assessed Global Impression of Change; PK = pharmacokinetics; SpO_2 = pulse oximetry; UMSS = University of Michigan Sedation Scale; Unsched. = Unscheduled; VAS = Visual Analog Scale; wk = week.

a. Performed visit 14 procedures upon completing study drug treatment (ie, EOT) or at early discontinuation from the study.
b. Unscheduled visits occurred as necessary for dose changes or other reasons. Any procedure or drug dispensation may have been performed as needed except those mandatory procedures indicated.
c. Sites called caregivers for safety evaluations before permitting the patient to down-titrate to the next dose.
d. For female patients of childbearing potential only. Performed a serum pregnancy test (or urine pregnancy test if serum was not practical), except for visit 14/EOT when a serum pregnancy test was required.
e. Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) and weight (not SpO_2) were recorded at all scheduled and unscheduled visits, and before and after any up-titration. SpO_2 was also recorded before and after any up-titration.
f. For inpatients and outpatients who came to the clinic.
g. Three readings of conventional 12-lead ECG, a minimum of 10 minutes apart. Patients whose BTDS was up-titrated to BTDS 20 must have had a conventional 12-lead ECG performed 2 to 3 days after the up-titration. In cases where both PK sampling and ECG examinations were planned, ECGs preceded PK sampling.
h. Only for up-titration to BTDS 20.
i. PK sample was collected only if patient discontinued prior to visit 8 (end of week 4).
j. UMSS was assessed daily in the morning, 30 to 60 minutes after the patient awakened, for the first 4 days of treatment following an up-titration. UMSS for inpatients was assessed by the investigator/designee.
k. Pain right now was measured on FPS-R and VAS once a week at approximately 8 PM.
l. IVRS/IWRS did not dispense any more study treatment, however, IVRS/IWRS was contacted to indicate patient's status.

Source: CSR BUP3031. Table 4, p. 49-51

Inclusion Criteria:
Patients were to have met all of the following criteria:

1. Male and female patients, aged 7 to 16 years, inclusive, with malignant and/or nonmalignant moderate to severe pain requiring or anticipated to require continuous, around-the-clock, opioid treatment for at least 2 weeks (based on the investigator's judgment).
2. Patients must have written informed consent provided by the parent or legal guardian and assent provided by the patient, when appropriate.
3. Patients must have stable vital signs, including hemoglobin-oxygen saturation, measured by pulse oximetry (SpO2). Patients must have:
    - A normal respiratory rate for age.
    - Pulse oximetry (SpO2) ≥ 92% on room air.
    - No significant (grade 3 or 4) somnolence based on the University of Michigan Sedation Scale (UMSS).
4. Patients on incoming opioids must be taking ≤80 mg/day morphine or equivalent if aged 12 to 16 years or ≤40 mg/day morphine or equivalent if aged 7 to 11 years prior to the screening visit (visit 1).
5. Patients who are taking methadone must have a washout period of at least 4 days prior to the start of study drug.
6. Patients who are currently using transdermal fentanyl should have been on the patch for at least 3 days at the same dose before removing the patch.
7. Patients must have serum potassium, calcium, and magnesium levels within the reference range for age (defined by the testing laboratory).
8. Patients who have a history of cardiac repairs (e.g. ventricular septal defect [VSD]/atrial septal defect [ASD] repairs) must have no residual defects and no ECGs with clinically significant abnormalities as determined by the investigator [small residual VSDs, ASDs, and minor ECG abnormalities (axis shifts) will not be excluded].
9. Patients who have required continuous opioid treatment due to prolonged intubation without mechanical ventilation, either due to a medical condition or following surgery. Patients recently extubated on opioids may be included if their respiratory condition is stable.
10. Patients with post-operative pain may be included ≥ 48 hours after surgery.
11. Female patients who are sexually active must be using an acceptable method of birth control.
12. Female patients of childbearing age must have a negative pregnancy test within 24 hours prior to study drug administration and be nonlactating.
13. Patients and parent/caregiver must be compliant with the protocol and able to perform study assessments and understand and complete the age-appropriate scale to rate pain intensity. Patients must not have a cognitive developmental delay or any other condition that would prevent them from completing the pain scale.

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

1. Patients who are allergic to buprenorphine or have a history of allergies to other opioids.
2. Patients with a dermatological disorder, including burn and skin graft sites, at any relevant patch application site that would preclude proper placement and/or rotation of BTDS patches.
3. Patients with evidence of:
   a. Impaired renal function (serum creatinine > 2 times the upper limit of normal [ULN] for age).
   b. Hepatic impairment with serum alanine transaminase (ALT/SGPT) or serum aspartate transaminase (AST/SGOT) > 5 times the ULN for age.
4. Patients with the following conditions:
   a. Any history of seizures (patients with history of pediatric febrile seizures may participate after discussion with the sponsor)
   b. An increase in intracranial pressure
   c. A history of sleep apnea within the past year
   d. A current medical history of paralytic ileus.
5. Patients who require mechanical ventilation during study treatment period, are cyanotic, or who have unstable respiratory disease.
6. Patients with the following cardiac conditions:
   a. Clinically significant structural heart disease or a pacemaker.
   b. Syncope, near syncope, or palpitations requiring further investigation.
   c. Clinically unstable cardiac disease including but not limited to unstable congestive heart failure or active myocardial ischemia.
   d. Either short (QTc less than 340 msec) or long QT Syndrome or inherited arrhythmia (including but not limited to: Brugada Syndrome, Catecholaminergic Polymorphic Ventricular Tachycardia [CPVT], or Arrhythmogenic Right Ventricular Dysplasia [ARVD]) or any family member with these conditions.
   e. Family history of unexplained sudden death.
7. Patients with 3 conventional 12-lead ECGs (minimum of 10 minutes apart, prior to starting study drug treatment) having an average value of QTcB and QTcF of the 3 tracings > 460 msec or a single QTcB or QTcF value ≥ 480 msec.
8. Patients with clinically significant abnormal findings demonstrated on conventional 12-lead ECG that show any of the following:
   a. Significant supraventricular arrhythmias (history in the past 5 years or current) or ventricular arrhythmias (history in the past 5 years or current).
   b. QRS duration ≥ 110 msec (intraventricular conduction delay). *Reviewer's Note*: QRS duration changed from ≥ 90 msec to ≥ 110 msec in Amendment 6.
   c. Definite left or right ventricular hypertrophy based on voltage and repolarization measurements by age standard.

   d. Amplitude of U wave 25% greater than that of T wave or inverted T waves in leads V4 or V5.
   e. 1st degree atrioventricular (AV) block (P-R interval > 200 msec).
   f. Suspicion of pre-excitation syndrome (including Lown–Ganong–Levine syndrome [LGL] and Wolff-Parkinson-White syndrome [WPW]).
   g. 2nd degree AV block (Mobitz I); 2nd degree AV block (Mobitz II).
   h. 3rd degree AV block.
   i. Atrial flutter.
   j. Atrial fibrillation
   k. Marked sinus bradycardia (HR ≤ 40 bpm).
   l. Sinus tachycardia by age standard (HR > 130 bpm for patients aged 7 to 11 years; HR > 120 bpm for patients aged 12 to 16 years).
9. Patients with clinically significant abnormal findings demonstrated on 24-hour digital 12-lead ECGs (Holter monitor) that show any of the following:
   a. Significant supraventricular arrhythmias or ventricular arrhythmias
   b. Suspicion of pre-excitation syndrome (including Lown–Ganong–Levine syndrome [LGL] and Wolff-Parkinson-White syndrome [WPW])
   c. 2nd degree AV block (Mobitz II)
   d. 3rd degree AV block
   e. Atrial flutter
   f. Atrial fibrillation
   g. Marked sinus bradycardia by age standard (HR less than 40 bpm).
10. Patients receiving the following medications:
   a. Known or possible QTc prolongers within the last 7 days prior to the start of study drug treatment (visit 2) and/or will require such medications during study treatment
   b. Conditional QTc prolonger in combination with any other medications listed as a QTc prolonger (known, possible, or conditional), or patients taking more than 1 medication listed as a conditional QTc prolonger. Patients taking a medication listed as a conditional QTc prolonger must be on the medication at a stable dose for at least 5 days prior to the screening visit.
   c. Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide).
   d. Epidural opioids <2 hours prior to the application of the first BTDS patch or who have received epidural morphine <12 hours prior to the application of the first BTDS patch.
   e. Monoamine oxidase inhibitors (MAOIs) or who have been taking MAOIs within 2 weeks of start of study drug treatment.
11. Patients with any contraindication to blood sampling.
12. Patients with life expectancy less than 4 weeks.
13. Patients who use or who have an ongoing requirement for treatment with direct external heat sources such as heat lamps, electric blankets, saunas, heating pads, heated water beds, or other devices that increase body surface temperature.

14. Patients who have any planned surgery during the course of the study. Procedures will be allowed during the study period provided that they comply with the following:
    a. Procedures are for placement of central or peripheral venous access devices.
    b. Only routine procedures of patient care, e.g., wound dressing changes, lumbar punctures, bone marrow aspirations, and endoscopies.
    c. No major surgery that requires skin incision during the procedure necessitating entry into the abdomen, chest, skull, or musculoskeletal structures.
    d. Incremental increases or decreases in post-procedure analgesia requirements will not occur (those that would not otherwise be anticipated prior to the procedure).
    e. The patient will not have the patch removed for more than 24 hours.
    f. Investigators will contact the medical monitor to discuss the procedure prior to the event. Protocol-specified criteria for the occurrence of adverse events remain the same.
15. Patients who receive or anticipate to receive investigational medication/therapy during study drug treatment and follow-up periods:
    a. May be included if participating in standard-of-care protocols, observational protocols or those protocols using medication/chemotherapy already approved in children.
    b. May be included if participating in a trial in which the medication is approved for adults but not for children.
    c. Will not be included if they are receiving a purely investigational drug, i.e., one not approved in either adults or children.

Study Procedures

An overview of the visits and procedures for screening up to the end of week 4 is presented in Table 4, and Table 5 presents the schedule of activities for weeks 6 to week 24.

Treatments Administered

Patients were to have been treated for up to 26 weeks (including the 14-day follow-up tapering period) with at least 1 of the following BTDS doses: 2.5, 5, 10, or 20 mcg/hour. The parent/caregiver (for outpatient) or study site staff (for inpatient) were to have applied and replaced the BTDS. Each BTDS was to be worn no more than 7 days and the site of application was to have been rotated with each application (minimum of 3 weeks between applications to the same site). Each BTDS should have been applied to the upper arm/shoulder, upper chest (below collar bone), lower side (below armpit), or upper back. If the edges of the transdermal system started to loosen, use of hypoallergenic tape to hold loose edges down was to have been permitted. If any patch detached partially (2 or more corners) and could not be taped back, the patch should have been removed and a new patch applied to an alternate location.

Rationale for Tapering Prior Opioids

There is the potential for BTDS to precipitate withdrawal in patients who are already on opioids. Buprenorphine is a partial agonist at mu-opioid receptors with a high affinity for these receptors and an antagonist at kappa-opioid receptors. If an individual who is physically dependent on opioids receives an acute dose of a partial agonist, the partial agonist can displace the full agonist from the receptors, resulting in a decrease in agonist effect and a precipitated withdrawal syndrome.

Patients aged 12 to 16 years taking >30 mg/day morphine or equivalent, or patients aged 7 to 11 years taking >15 mg/day morphine or equivalent for at least the last 5 consecutive days prior to the screening visit were to have their around-the-clock opioids tapered. The tapering process was to have been determined by the investigator and taken up to 7 days and was to have been completed before beginning treatment with BTDS. Patients aged 12 to 16 years were to have been tapered down to a dose of 30 mg/day or less of morphine or equivalent and patients aged 7 to 11 years were to have been tapered down to a dose of 15 mg/day or less morphine or equivalent prior to beginning treatment with BTDS. Scheduled long-acting and short-acting opioids were to have been permitted if they were medications being tapered down but opioids used for supplemental analgesia (or breakthrough pain) were prohibited during the initial opioid tapering period. Tapering was not required for patients aged 12 to 16 years taking ≤ 30 mg/day morphine or equivalent or patients aged 7 to 11 years taking <15 mg/day morphine or equivalent. The patient's incoming opioids (both long and short-acting opioids) were permitted up to visit 2 (prior to the start of BTDS treatment). In addition, opioids used for supplemental analgesia (or breakthrough pain) were permitted if the patient did not require tapering.

Dose Initiation

The starting dose for patients 7 to 11 years old was to have been BTDS 2.5 and the starting dose for patients 12 to 16 years was to have been BTDS 5. Each BTDS patch was to have been worn no more than 7 days (± 12 hours) with a minimum of 3 weeks between applications to the same site. Patients using transdermal fentanyl should have been on the patch for at least 3 days at the same dose before removing the patch. BTDS was only to be initiated at least 18 hours after removing the transdermal fentanyl patch.

Patients who were opioid naïve or were receiving ≤10 mg/day oral morphine or equivalent (MEQ) during the 5 consecutive days prior to initiation with BTDS treatment were to have been inpatients at the time of initiation and were to remain hospitalized for the first 48 hours of the treatment.

Dose Titration

Upward or downward titration of the BTDS dose was to have been allowed throughout the study. Downward titrations were allowed at any time, not just at scheduled visits. However, upward titrations, were to occur only after a minimum of 72 hours of treatment

at the current dose level. The goal of BTDS dose titration was a level that provides adequate analgesia with no or tolerable side effects. Patients unable to tolerate any dose of BTDS were to have been discontinued from the study drug treatment.

Up-titration
The BTDS dose was allowed to be increased if the dose was tolerated but did not provide adequate pain control. The investigator was allowed to up-titrate BTDS dose to the next higher dose after at least 72 hours of treatment with BTDS at a particular prior dose level. The BTDS dose may have been increased until a tolerable and efficacious dose was reached or until the maximum dose allowed (BTDS 20) was reached. The investigator's assessment should have taken the following into considerations:

- Pain scores and somnolence recorded in the diary by the parent/caregiver or the patient.
- Information regarding concomitant and supplemental pain medication use.
- Parent/caregiver calls to the study center indicating that the patient's pain is not being adequately controlled.
- Results of tests or observations made at the study visit or tests or observations not specified in the study protocol (e.g., tolerability of BTDS, vital signs, hemoglobin-oxygen saturation, ECGs, AEs, somnolence, and routine laboratory tests).

If possible, up-titration should have been performed at the clinical site. If a dose up-titration was made at home, the parent/caregiver was to have contacted the study center immediately prior to administering the dose to the patient. Every time a patient's BTDS dose was up-titrated to BTDS 20, the patient was to have a conventional 12-lead ECG examination performed 2 to 3 days after the up-titration. The upward BTDS dose titration scheme is shown in Table 1 below. Up-titration is allowed only to the next higher dose. The maximum dose allowed in the study is BTDS 20.

Down-titration
The investigator was allowed to adjust BTDS dose downward at any time to establish the safest and most effective dose. A downward titration was to have been considered when unacceptable opioid adverse effects occurred. The BTDS dose was to have been down-titrated to the next lower dose level immediately after removal of the current patch, unless in the clinical judgment of the investigator a still lower dose was more appropriate. For patients not tolerating the current dose of BTDS and whose BTDS should be down-titrated to a lower dose, the investigator was to have spoken to the parent/caregiver before down-titrating to a lower dose. The parent/caregiver was to have called the clinical site immediately prior to applying the first down-titrated BTDS patch. The parent/caregiver after removing the current BTDS patch was to apply the next lower dose BTDS patch at a different application site. The parent/caregiver was to have recorded the patch removal/application information (dose/date/time/site of application) in the diary.

Maintenance Therapy
During maintenance therapy with BTDS, the investigator was to have periodically reassessed the continued need for around-the-clock opioid analgesic therapy. The BTDS patch was to have been removed after it had been worn for 7 days (± 12 hours) and the parent/caregiver was to have applied a new BTDS patch of the same dose at a different application site. The parent/caregiver was to have recorded the patch removal/application information in the diary.

Rescue Medication
All patients were to have been allowed nonopioid analgesic medications during the screening period and opioid tapering period. Opioid analgesic medications used for supplemental analgesia (or breakthrough pain) were not to have been permitted during the initial opioid tapering period. However, scheduled short-acting and long-acting opioids were permitted for opioid tapering purposes if these were the medications that were being tapered down. If a patient did not require tapering of their incoming opioids, the patient's incoming opioid regimen (long and short-acting opioids) was permitted up to visit 2, prior to the patient starting BTDS. Opioids used for supplemental analgesia were to have been permitted for those patients who do not require a taper. The dose of supplemental pain medication allowed was to have been at the discretion of the investigator and within appropriate dose ranges for patients' age and weight. During treatment with BTDS supplemental short-acting opioids (other than buprenorphine) and/or non-opioid pain medication may be prescribed by the investigator. Other than study drug, long-acting opioid medications were to have been prohibited throughout the study starting prior to initiation of BTDS.

During the follow-up tapering period, short-acting opioid (other than buprenorphine) and/or nonopioid pain medications were to have been allowed as needed at the end of treatment tapering period, to minimize the risk for withdrawal and inadequate pain control.

Tapering of BTDS at end-of-treatment
To minimize opioid withdrawal, a follow-up/taper period of up to approximately 14 days was to have started at the end of the treatment period or upon early discontinuation. BTDS was to have been down-titrated a minimum of every 3 days to the next lower dose level. If the patient continued to need opioid therapy, the patient was to have been converted to an appropriate opioid regimen based on the investigator's clinical judgment.

Prohibited Medications
QTc Prolongers
Known QTc prolongers and possible QTc prolongers were to have been excluded within 7 days of starting study drug and throughout study treatment. Conditional QTc prolongers, drugs that carry a risk of TdP and/or excessive QT prolongation under certain conditions, such as drug overdose or co-administration of interacting drugs were

allowed during the study, as long as the patient was taking only 1 drug in this class. Patients taking a conditional QTc prolonger must have been on the medication at a stable dose for at least the last 5 days prior to the screening visit.

Long-acting opioids are prohibited from the time of first BTDS application and throughout the study.

Pharmacokinetic Blood Sampling
The PK samples were drawn up to 5 times during the first 4 weeks of the study for determining plasma concentrations of buprenorphine and its metabolites. PK was collected at the following timepoints:

- 18 to 24 hours after the application of the first BTDS patch (visit 3)
- End of week 1 (visit 4)
- 2 to 3 days after the end of week 1 (visit 5)
- End of week 2 (visit 6)
- End of week 4 (visit 8) or at discontinuation prior to visit 8.

Efficacy Assessments
Efficacy variables included the following:

- Pain right now assessed by patients using Faces Pain Scale-Revised (FPS-R), for patients aged 7 to 11 years
- Pain right now assessed by patients using 100-mm Visual Analog Scale (VAS), for patients aged 12 to 16 years
- Parent/caregiver-assessed Global Impression of Change (PGIC), for patients aged 7 to 16 years

Pain intensity measures were to have been recorded daily during weeks 1 to 4 and weekly after week 4. Pain intensity was to have been summarized using descriptive statistics within the age groups. Parent/caregiver-assessed Global Impression of Change (PGIC) rating score was summarized using the number and the percentage of patients in each category.

Safety Assessments
Safety variables included adverse events, vital signs (blood pressure, pulse rate, and respiratory rate), hemoglobin-oxygen saturation, clinical laboratory tests, somnolence assessed by University of Michigan Sedation Scale (UMSS), 12-lead ECGs, and Holter monitoring. The safety variables were summarized descriptively. All safety analyses were performed using the safety/full analysis population which is the group of patients who received at least 1 dose of study drug during the study.

Clinical Laboratory Tests

Clinical laboratory tests are presented in Table 6. Laboratory tests were to have been obtained at screening and end of weeks 2, 4, 6, 8, 12, 16, 20 and 24/early termination. For women of childbearing potential, pregnancy testing was to have been performed at the same timepoints as other laboratory evaluations except if the serum pregnancy test at screening was performed more than 24 hours prior to start of study drug treatment a urine pregnancy test was to have been obtained within 24 hours prior to start of study drug treatment.

Table 6: Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, and WBC count with differential (segmented neutrophils, band neutrophils, lymphocytes, monocytes, eosinophils, basophils) count in percentages (%) and absolute counts
Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium, magnesium, and bicarbonate
Liver function tests	Alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin
Renal function parameters	Blood urea or BUN, creatinine
Other	Glucose, albumin, phosphorus, LDH, total protein, uric acid
Urinalysis	Qualitative analysis was performed for the following analytes: specific gravity, pH, ketones, glucose, leukocytes, nitrite, blood, protein, urobilinogen, and bilirubin. If nitrite, blood, leukocytes, or protein tests were positive, a microscopic examination was performed.
Pregnancy test	
Serum	For all female patients of childbearing potential
Urine	For all female patients of childbearing potential

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; RBC = red blood cell; WBC = white blood cell.
Source: CSR 3031, Table 7, p. 59

Vital Signs and Pulse Oximetry

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) were to have been recorded at screening, before and after initial BTDS application at all scheduled and unscheduled visits, and before and after the first up-titrated BTDS application for any up-titration. All patients were to remain at the clinical site for 2 hours after the initial BTDS application for vital signs and hemoglobin-oxygen saturation measured by pulse oximetry (SpO2). Vital signs and SpO2 were to be recorded at 30, 60, 90, and 120 minutes post initial BTDS application and up-titration. Additionally, for inpatients only, vital signs and SpO2 were to have been recorded at 4, 6, 8, 12, 24, 48, and 72 hours post initial BTDS application and up-titration. Pulse oximetry was to have been assessed at screening, before and after initial BTDS application and before and after the first BTDS application of any up-titration.

Electrocardiograms
Electrocardiograms during the study were to have consisted of 3 ECGs per analysis, a minimum of 10 minutes apart. 12-lead ECGs were to have been performed at screening, end of weeks 1, 2, 3, 6, 8, 12, 16, 20, and 24/early discontinuation, and 2 to 3 days after up-titration to BTDS 20. A prolongation of QTc interval based on 12-lead ECG results was considered an adverse event in the following cases: Average QTc prolonged (≥ 460 msec), QTcB prolonged (≥ 480 msec), QTcF prolonged (≥ 480 msec), QTcB prolonged (increase in QTcB value ≥ 50 msec from baseline), and QTcF prolonged (increase in QTcF value ≥ 50 msec from baseline).

Protocol Amendments
No patients were enrolled under the original protocol or prior to Amendment 4 of the protocol.

Amendment 5 (January 14, 2013)
This amendment implemented the following changes:

- Duration of treatment extended from 4 weeks to 24 weeks
- Increase in number of patients from 30 to 40
- Number of PK samples required was revised from 6 to 5 samples

Amendment 6 (January 13, 2014)
This amendment implemented the following changes:

- Screening period and subsequent visits: Average QTc value > 460 or single value ≥ 480 msec would result in a screen failure or discontinuation.
- QRS duration changed from ≥ 90 msec to ≥ 110 msec.
- P-R interval from > 180 msec (6 to 11 years) to > 200 msec (for all ages).
- Bradycardia: HR from 50 bpm to 40 bpm.
- Sinus tachycardia: HR from > 110 bpm to > 120 bpm (patients 12 to 16 years).
- Reduce time of surgery to enrollment from 2 weeks to 48 hours.
- Classification of QT prolonging drugs into known, possible or conditional (conditional QT prolongers are permitted as long as patient is on a stable dose and is only taking one drug).
- Removed all follow-up 24-hour Holter based on the thorough QT study results (Study BUP 1025).

Efficacy Results
Refer to Section 6 for a discussion of efficacy.

Safety Results
A detailed discussion of the safety findings is presented in Section 7.

6 Review of Efficacy

Efficacy Summary

In this open-label study, the data collected are insufficient to draw definitive conclusions about the efficacy of BTDS in pediatric patients. Thus, per policy, any inferences about buprenorphine in the pediatric population age 2 years to <17 years is extrapolated from findings in adults.

6.1 Indication

Proposed Indication: Purdue is not requesting a pediatric pain indication.

Approved Indication: Butrans is approved in adults for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

6.1.1 Methods

Assessment of efficacy was a secondary objective in open-label Study BUP3031 and included the following:

- Pain right now assessed using the Faces Pain Scale-Revised (FPS-R) for patients 7 to 11 years.
- Pain right now assessed using a 100-mm Visual Analog Scale (VAS) for patients 12 to 16 years.
- Parent/caregiver-assessed Global Impression of Change (PGIC) for all patients.

Pain intensity measures were recorded daily for the first four weeks and then weekly. Pain intensity was summarized using descriptive statistics within the age groups. No formal hypothesis testing was performed. Parent/caregiver-assessed Global Impression of Change was summarized using the number and the percentage of patients in each category.

6.1.2 Demographics

The demographic and baseline characteristics are summarized in Table 7.

Table 7: Demographics and Baseline Characteristics

Category	Age Group		Total
	7 to 11 years N=6 n (%)	12 to 16 years N=35 n (%)	N=41 n (%)
Age (years)			
N	6	35	41
Mean (SD)	10.3 (1.21)	14.6 (1.31)	14.0 (1.99)
Median	11.0	15.0	14.0
Min, Max	8, 11	12, 16	8, 16
Gender			
Male	3 (50)	12 (34)	15 (37)
Female	3 (50)	23 (66)	26 (63)
Race			
White	3 (50)	18 (51)	21 (51)
Black	2 (33)	15 (43)	17 (41)
Other	1 (17)	2 (6)	3 (7)
Weight (kg)			
Mean (SD)	31.7 (7.2)	64.4 (18.3)	59.6 (20.7)
Median	33.0	60.0	57.0
Min, Max	22.2, 42.2	29.4, 111.5	22.2, 111.5
Height (cm)			
Mean (SD)	137.0 (12.1)	162.6 (8.6)	159.3 (12.4)
Median	144.8	162.0	160.0
Min, Max	121.9, 147.0	139.8, 182.9	121.9, 182.9
Body Mass Index (kg/m^2)			
Mean (SD)	16.7 (1.9)	24.5 (7.3)	23.5 (7.3)
Median	16.0	22.3	21.2
Min, Max	14.9, 19.9	15.0, 47.7	14.9, 47.7

Source: CSR 3130. Table 14, p.95

Table 8 summarizes the reasons for pain at the time of study entry.

Table 8: Reasons for Pain at Study Entry			
System Organ Class Preferred Term	**Age Group**		**Total N=41 n (%)**
	7 to 11 years N=6 n (%)	**12 to 16 years N=35 n (%)**	
Congenital, Familial and Genetic Disorders	**1 (17)**	**6 (11)**	**7 (17)**
Sickle Cell Anemia	1 (17)	4 (11)	5 (12)
Amniotic Band Syndrome	0	1 (3)	1 (2)
Hemoglobin C Disease	0	1 (3)	1 (2)
Gastrointestinal Disorders	**0**	**4 (11)**	**4 (10)**
Abdominal Pain	0	2 (6)	2 (5)
Crohn's Disease	0	2 (6)	2 (5)
General Disorders And Administration Site Conditions	**0**	**1 (3)**	**1 (2)**
Pain	0	1 (3)	1 (2)
Injury, Poisoning and Procedural Complications	**0**	**3 (9)**	**3 (7)**
Gun Shot Wound	0	2 (6)	2 (5)
Limb Crushing Injury	0	1 (3)	1 (2)
Investigations	**1 (17)**	**0**	**1 (2)**
Epstein-Barr Virus Antibody Positive	1 (17)	0	1 (2)
Musculoskeletal and Connective Tissue Disorders	**3 (50)**	**13 (37)**	**16 (39)**
Back Pain	0	8 (23)	8 (20)
Musculoskeletal Pain	0	2 (6)	2 (5)
Arthralgia	1 (17)	0	1 (2)
Arthritis	0	1 (3)	1 (2)
Juvenile Arthritis	1 (17)	0	1 (2)
Osteonecrosis	1 (17)	0	1 (2)
Pain in Extremity	0	1 (3)	1 (2)
Systemic Sclerosis	0	1 (3)	1 (2)
Nervous System Disorders	**0**	**6 (17)**	**6 (15)**
Migraine	0	6 (17)	6 (15)
Reproductive System Disorders	**0**	**1 (3)**	**1 (2)**
Pelvic Pain	0	1 (3)	1 (3)
Surgical and Medical Procedures	**1 (17)**	**1 (3)**	**2 (5)**
Chest Wall Operation	0	1 (3)	1 (2)
Hemiplevectomy	1 (17)	0	1 (2)

Source: CSR 3130. Table 15, p.96

In addition to the primary pain condition for study entry provided in the table, many subjects had additional relevant medical history with respect to the cause of their pain. For the five patients listed with sickle cell disease as the primary reason for pain at study entry, the patients also had the following diagnoses: avascular necrosis of the hips and headaches (1), migraines (1), headaches (1), no additional diagnoses (2). The patient listed with hemoglobin C also had pain in arms, legs and hip. The subject listed with Epstein Barr had spasm due to Epstein Barr and headache. For the two subjects listed with Crohns Disease, one subject had oral mouth ulcers and migraines, and the other subject had no additional relevant medical history. For the two subjects with abdominal pain as the primary reason for pain, one subject had Crohn's Disease and the one subject had irritable bowel disease and low back pain.

Two clinical investigator inspections were conducted as a routine part of the review process. Medical records for the seven patients enrolled at one site were collected and reviewed to provide detail around the coded diagnoses. All of patients enrolled at this site had complex medical histories. One patient was coded with fibromyalgia, one with EBV-related neuralgia, and the remainder had migraine or chronic headache. Two of the patients had pain so debilitating that they could not attend school. All patients had been previously treated with a variety of non-narcotic drugs used for pain and migraine such as gabapentin, pregabalin, fioricet, clonidine, topirimate, divalproex sodium, verapamil, NSAIDs, cyclobenzaprine, propranolol, tricyclic antidepressants, corticosteroids, ergots, botulinum toxin injections, and milnacipran. Several patients had comorbid psychiatric conditions, particularly depression, for which some were on SSRIs. Other patients were on trazodone or benzodiazepines for insomnia. The number of discrete non-narcotic analgesics tried before enrollment in the study ranged from 1 to 14 with most patients having tried at least 7 non-opioid drugs. Of the five patients with migraine, two had not been treated with a triptan. With regard to prior opioid therapy, six out of seven patients had prior exposure to tramadol and three were on scheduled vs. prn tramadol. The one patient who had never taken tramadol had failed butorphanol nasal spray.

6.1.3 Subject Disposition

Subject Disposition

Screening Period
Of the 70 subjects enrolled for this study, 41 received treatment and 29 were screen failures. In the 7 to 11 year old age group, all four screening failures were due to not meeting the inclusion/exclusion criteria. Screening failures in the 12 to 16 year old age group were due to the following: 21 patients failed to meet inclusion/exclusion criteria, 3 patients 'subjects choice' and 1 patient for an SAE.

Treatment Period
The reasons for patient discontinuation from the study are summarized in Table 9. Adverse events were the most common reason for study discontinuation which is not unexpected for an opioid. Only one subject was reported to discontinue the study due to lack of efficacy. A patient was considered as completing the study if he/she met any of the following conditions:

1. Completed at least 2 weeks of study drug dosing, did not meet any of the discontinuation reasons, and did not need additional treatment with opioid medication for pain relief at the minimum study drug dose or equivalent.
2. Completed 24 weeks of study drug dosing (Note: Amendment #5 extended the treatment duration from 4 weeks to 24 weeks).
3. Completed at least 2 weeks of study drug dosing and was being tapered down from his or her current BTDS dose in order to switch from BTDS to other opioid analgesic medications for tapering purposes and did not meet any of the discontinuation reasons.

Table 9: Patient Disposition and Reasons for Discontinuation of Study

Category	Age Group		Total
	7 to 11 years N=6 n (%)	12 to 16 years N=35 n (%)	N=41 n (%)
Completed Study	2(33)	21 (60)	23 (56)
Discontinued study	4 (67)	14 (40)	18 (44)
Adverse event	4 (67)	7 (20)	11 (27)
Subject's Choice	0	3 (9)	3 (7)
Administrative	0	2 (6)	2 (5)
Lack of Therapeutic Effect	0	1 (3)	1 (2)
Confirmed or Suspected Diversion	0	1 (3)	1 (2)
Administrative	0	2 (6)	2 (5)

N=number of patients; n=number of patients in category.
Source: CSR Protocol 3031. Table 11, p91

6.1.4 Analysis of Primary Endpoint(s)

Efficacy was a secondary objective in the study and no formal hypothesis testing was performed. Efficacy variables included pain right now scores and PGIC scores and were summarized descriptively. All efficacy analyses were performed using the full analysis population (FAP), which was defined as all patients who received at least one dose of study drug.

Pain Scores for Patients 7 to 11 years
In general, pain scores during the study appeared similar to pain scores at baseline for subjects aged 7 to 11 years (Table 10). At baseline, the mean FPS-R score was 2.80, with a range of 0 to 8 for the 5 patients assessed. At week 1, the mean score was 3.49

with a range of 0.4 to 9.6 for the 5 patients assessed, and at week 2, the mean score was 2.98 for the 3 patients assessed. No definitive conclusions regarding efficacy of Butrans alone can be made in this age group, given the small sample size, open-label study design, lack of a comparator group, and use of rescue medication. Supplemental opioid analgesics were used by all the patients in the 7 to 11-year age group.

Table 10: Mean Pain Scores for Patients Aged 7 to 11 Years

	Number of patients assessed	**FPS-R score, mean (SE)**
Baseline	5	2.80 (1.50)
Week 1	5	3.49 (1.77)
Week 2	3	2.98 (1.88)
Week 3	2	0.29
Weeks 4-12	1	0

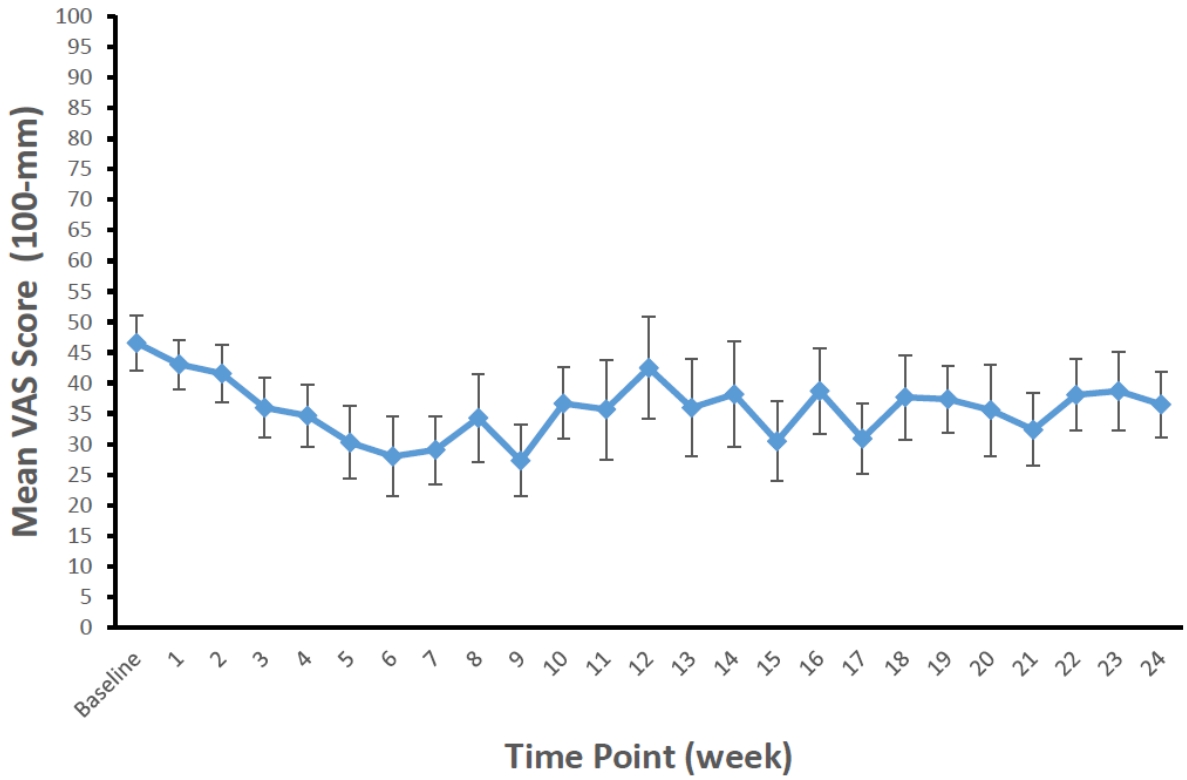
Source of data: CSR BUP3031. p. 106-107

Pain Scores for Patients 12 to 16 years

The mean pain scores in the older age group are summarized by week in the graph below (Figure 2). At baseline, the mean VAS score was 46.6, with a range of 0 to 85 for the 33 patients assessed. At week 1, the mean VAS score was 43.1, with a range of 2 to 85 for the 35 patients assessed; at week 4 the mean VAS score was 34.7, with a range of 2 to 92 for the 29 patients assessed; at week 10, the mean VAS score was 36.7 with a range of 3 to 81 for the 17 patients assessed; at week 20 the mean VAS score was 35.6 with a range of 4 to 93 for the 12 patients assessed and; at week 24 mean VAS score was 36.5 with a range of 9 to 59 for the 11 patients assessed.

The scores fluctuated slightly throughout the study with the highest pain score present at baseline of 46.6, the lowest of 27.3 at week 9 and the highest during the study of 42.5 at week 12. As with the younger age group, no definitive conclusions regarding efficacy of Butrans alone can be made, given the small sample size, open-label study design, lack of a comparator group and use of rescue medication. Supplemental opioid analgesics were used by 89% (31 patients) in the 12 to 16-year age group.

Figure 2: Mean Pain Score from Baseline to Week 24 for patients aged 12 to 16



Source: Purdue's Advisory Committee Briefing Materials. p.34, Figure 2.

Patient/Caregiver-assessed Global Impression of Change

The PGIC score assessed at the end of the study treatment was summarized using the number and percent of patients in each of the 7 possible response categories: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." Table 11 provides a summary of the results of the PGIC. Interpretation of the results in the younger age group is limited due to the small sample size of only four patients. In the older age group, 18 patients (53%) were either very much improved or much improved and three patients (9%) were either minimally worse or much worse.

Table 11: Summary of Parent/Caregiver-Assessed Global Impression of Change

PGIC	Age Group 7 to 11 years (N = 5)	Age Group 12 to 16 years (N = 35)	Total (N = 40)
By PGIC Category, n (%)			
Total Number of Patients Responding (n)	4	34	38
1. Very Much Improved	1 (25)	6 (18)	7 (18)
2. Much Improved	0	12 (35)	12 (32)
3. Minimally Improved	0	8 (24)	8 (21)
4. No Change	2 (50)	5 (15)	7 (18)
5. Minimally Worse	1 (25)	2 (6)	3 (8)
6. Much Worse	0	1 (3)	1 (3)
7. Very Much Worse	0	0	0
Very Much Improved/Much Improved	1 (25)	18 (53)	19 (50)
No Improvement[a]	3 (75)	16 (47)	19 (50)

[a] No Improvement defined as minimally improved, no change, minimally worse, much worse, or very much worse.

Source: CSR Protocol 3031. Table 22, p. 110

Efficacy Conclusions

No definitive conclusions about the efficacy of Butrans can be made from Study 3031 due to the small sample size, open-label study design, lack of a comparator, and use of supplemental opioids. However, Study 3031 suggests that Butrans in combination with supplemental analgesics maintains or improves the mean weekly pain scores and for children 12 to 16 years, over 50% had PGIC scores either very much improved or much improved. As discussed previously in this review, the efficacy of buprenorphine in the pediatric population age 2 years to <17years is extrapolated from findings in adults.

6.1.5 Analysis of Secondary Endpoints(s)

Refer to Section 6.1.4 Analysis of Primary Endpoint

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

No formal analyses of efficacy by subgroup were performed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not Applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not Applicable

6.1.10 Additional Efficacy Issues/Analyses

Not Applicable

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Butrans in pediatric patients was evaluated in Study 3031, an open-label multicenter primarily pharmacokinetic and safety study of BTDS in children 7 to 16 years of age who required continuous opioid analgesia for moderate to severe pain.

7.1.2 Categorization of Adverse Events

Adverse events were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA, version 15.0) terms.

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

Not applicable since only one study was conducted.

7.2 Adequacy of Safety Assessments

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

Exposure for Study BUP3031
A summary of exposure by age group is shown in Table 12. Of the 41 patients exposed to at least one dose of Butrans, only six patients were in the 7 to 11 year age group and those patients were in the older portion of that stratum with a mean age of 10.3 and median age of 11. There were 35 patients in the 12 to 16 year age group with a mean age of 14.6 and median age of 15. Older children had a longer duration of treatment

with over 90% of patients in the older age group receiving treatment for at least 2 weeks and over 80% for at least 4 weeks. In the younger age group only 3 patients received treatment for at least 2 weeks and one patient for at least four weeks. Also, exposure to the highest dose occurred only in the older age group and was of limited duration with only 10 subjects receiving treatment for at least 2 weeks.

The duration of exposure was less than previously requested from the Applicant. In an advice letter dated June 27, 2012, the Division said that for a chronic pain indication Study 3031 would need 40 completers with at least 6-months of exposure to assess safety. The proposed four-week treatment duration was considered acceptable for the pharmacokinetic aspect of the study, but additional patients would need to be studied to provide the necessary long-term safety data. Since that advice letter was issued the thinking of the Division has changed and, consistent with advice from the 2016 Advisory Committee meeting, the Division now accepts a 2 to 4 week study duration but requests 125 patients for the 12 to 17 year age group and 50 patients for the 7 to 11 year age group to adequately assess safety instead of the smaller database previously requested.

Table 12: Number of Days on BTDS

Cumulative Number of Days on BTDS	Age Group		Total N=41 n (%)
	7 to 11 years N=6, n (%)	12 to 16 years N=35, n (%)	
Any Exposure	6 (100)	35 (100)	41 (100)
≥ 1 week	5 (83)	35 (100)	40 (98)
≥ 2 weeks	3 (50)	34 (97)	37 (90)
≥ 3 weeks	2 (33)	32 (91)	34 (83)
≥ 4 weeks	1 (17)	30 (86)	31 (76)
≥ 6 weeks	1 (17)	21 (60)	22 (54)
≥ 8 weeks	1 (17)	20 (57)	21 (51)
≥ 12 weeks	1 (17)	17 (49)	18 (44)
≥ 16 weeks	0	16 (46)	16 (39)
≥ 20 weeks	0	16 (46)	16 (39)
≥ 24 weeks	0	13 (37)	13 (32)
Cumulative Number Days of BTDS			
Mean (SD)	25.8 (30.4)	100.8 (72.6)	89.9 (72.9)
Median	15.0	73.0	57.0
Min, Max	3, 86	11, 188	3, 188

Source: CSR 3031. Table 23, p.113

7.2.2 Explorations for Dose Response

Too few subjects were exposed to various doses for assessment of a dose response.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the pediatric clinical trials for Butrans appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology Review.

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 adverse events include nausea, vomiting and constipation. A thorough QT study in adults on Butrans showed evidence of QT prolongation at the supratherapeutic dose.

7.3 Major Safety Results

7.3.1 Deaths

In Study 3031 there were no deaths reported in patients who received BTDS.

7.3.2 Nonfatal Serious Adverse Events

Of the 41 patients treated with BTDS in Study 3031, a total of eight patients (20%) experienced the following eight treatment emergent SAEs: chronic osteomyelitis, appendicitis, two cases of vaso-occlusive crisis due sickle cell disease, Crohn's disease exacerbation, first degree heart block, migraine, and hypersomnia. Also a nontreatment-emergent SAE of worsening bilateral avascular necrosis of the hip was reported. The narratives of all SAEs were reviewed. BTDS may have exacerbated the severity of the SAE of hypersomnia. The SAE of first degree heart block as initially reported in the NDA submission appeared to be related to study drug but after obtaining additional information from Purdue, it appeared unlikely that this SAE was due to BTDS. Summaries of the SAEs of hypersomnia and first degree heart block are provided below. Study drug was not considered by this reviewer to be a cause of any of the other reported SAEs.

Individual Patient Summaries of Nonfatal Serious Adverse Events

Patient Number: 0024003
Study: BUP3031
Serious Adverse Events: Fatigue/hypersomnolence

Patient 0024003 was an 11-year-old female with a history of pain due to sickle cell anemia. The patient's past medical history included: splenectomy, obstructive sleep apnea and snoring (2011), adenoidectomy and tonsillectomy (2011), and headaches (2013). Prestudy opioids included oxycodone 5 mL (no information on dosing frequency).

On 03 February 2015, she began the screening period and on 17 February 2015 she began treatment with open-label BTDS 2.5. On (b) (6) she was hospitalized after she fell while sleeping in the classroom. Study drug was discontinued the same day in the hospital. The patient complained of increased fatigue and sleepiness for the previous 3 to 4 weeks. She was subsequently diagnosed with hypersomnolence which was considered by the investigator to be not related to the study drug. No treatment was reported. The patient stated that study drug made her feel sleepier than usual.

Vital signs were the following in the hospital: pulse rate 86 beats/minute, respiratory rate 24 breaths per minute, temperature 37˚C and SpO2 98%. A computerized tomography scan of the head was normal and magnetic resonance imaging of the brain with contrast was negative. An ECG revealed normal sinus rhythm.

On (b) (6) the event of hypersomnolence resolved and the patient was discharged. On March 3, 2015, the patient discontinued the study due to hypersomnolence. O (b) (6) the patient experienced another SAE of fatigue while not on BTDS and was hospitalized. The next day the fatigue resolved and the patient was discharged from the hospital. She was seen in a pediatric sleep disorder clinic and the symptoms were not considered consistent with narcolepsy.

Impression
Fatigue and sleepiness preceded the patient starting BTDS and occurred after BTDS was discontinued but the SAE of hypersomnolence may have been exacerbated by study drug as noted by the patient. Increased sleepiness is a known side effect of opioids.

Patient Number: 0010005
Study: BUP3031
Serious Adverse Events: First degree heart block

Subject 0010005 was an 11-year-old white female with a history of pain due to Epstein Barr antibody positive enrolled in Study 3031. Prestudy medications included tramadol 50 mg qid.

She was diagnosed with asymptomatic 1st degree AV block on day 8 (BTDS 5 mcg/hour). From the narrative provided in the initial NDA submission, it appeared as though the first degree heart block may have not resolved until several days after BTDS was discontinued. However, after receiving additional information from Purdue in response to an information request it was clear that the AV block resolved prior to removal of the patch. The patient began study drug treatment with BTDS 2.5 mcg/hour on 25 June 2013 and had the dose increased to 5.0 mcg/hour on 28 June 2013. On July 2nd at the week 1 study visit the subject was diagnosed with asymptomatic 1st degree AV block with a PR interval 196 msec (normal < 180 msec for patients 7 to 11 years of age). The 5.0 mcg/hour patch was removed on 05 July 2013 at 10:45 am and ECGs performed on the same day, approximately one hour prior to removal of the patch, showed that the PR interval had returned to baseline (144 msec).

Impression
The SAE of first degree heart block was unlikely due to BTDS since the PR interval returned to baseline prior to removal of the patch. Also, the first degree heart block did not require clinical intervention, as would higher degrees of AV block.

7.3.3 Dropouts and/or Discontinuations

A summary of subject disposition and the reasons for study discontinuation is provided in Table 9. The main reason for discontinuation was adverse event, 11 patients (27%) in both age groups; in the 7 to 11 year age group, 4 patients (67%) discontinued due to an adverse event and in the 12 to 16 year age group, 7 patients (20%). All 4 discontinuations in the younger age group were due to an adverse event. Since there was no control group in the study, it is difficult to assess the relevance of the number of discontinuations due to adverse events. The next highest cause for discontinuation was 'subject's choice', 3 patients (7%). One patient discontinued due to lack of 'therapeutic effect'.

Discontinuations Due to Adverse Events
Table 13 lists the adverse events leading to study drug discontinuation. The 12 reported adverse events occurring in 11 patients that resulted in study drug discontinuation are the following: increased migraine pain (2); QT prolongation (2); worsening pain due to neuroma (1); application site irritation (1); sinus tachycardia (1);

sickle cell anemia with vaso-occlusive crisis (1); hypersomnia (2); first degree AV block (1) and; prolonged QRS complex (1). Patient 0010011 was reported as having two adverse events (prolonged QT and somnolence) that resulted in study drug discontinuation but review of this patient's narrative suggested that only the adverse event of prolonged QT resulted in study drug discontinuation.

The narratives of all the treatment discontinuations due to adverse events were reviewed. BTDS may have caused 4 of the 12 adverse events leading to study drug discontinuation: QT prolonged (2), application site irritation (1), and QRS complex prolonged (1), and exacerbated the adverse event of hypersomnia in patient 0024003 which resulted in study drug discontinuation.

Table 13: Adverse Events Leading to Study Drug Discontinuation

Patient Number	Verbatim Term	Preferred Term	Number with AE
0008002 0010010	Increased Migraine Pain	Migraine	2
0008003, 0010011[1]	QTCB Prolonged, Prolonged QT	ECG QT Prolonged	2
0030003	Worsening pain due to neuroma	Pain	1
0030004	Skin irritation on patch site	Application site irritation	1
9009004	Worsening sinus tachycardia	Sinus tachycardia	1
0024002	Vaso occlusive crisis	Sickle cell anemia with crisis	1
0024003[2] 0010011[1]	Hypersomnolence[2], somnolence[1]	Hypersomnia[2], somnolence	2
0010005	First degree heart block	Atrioventricular block first degree	1
0010006	QRS complex prolonged	ECG QRS complex prolonged	1

[1]Patient 0010011 was recorded as having 2 AEs (prolonged QT and somnolence) resulting in study drug being stopped
[2]Patient 0024003 was recorded as having the SAE of hypersomnolence and is reviewed in Section 7.3.2 on SAEs

The following are patient summaries of adverse events possibly related to BTDS or exacerbated by BTDS that resulted in study drug discontinuation.

Individual Patient Summaries of Adverse Events Resulting in Discontinuation

Patient Number: 0030004
Study: BUP3031
Discontinuation from Study Drug due to AE: skin irritation on patch site

This 12-year-old white female with a history of chronic back pain was enrolled in study BUP3031. Her relevant past medical included: lupus (2014), Sjogren's syndrome (2014), chronic generalized joint pain, and cushingoid. The patient was taking the following medications: hydroxychloroquine, meloxicam, methotrexate, and prednisone.

On 03-Nov-2015, the patient began treatment with open-label BTDS 5, which was up-titrated on 17-Nov-2015 to BTDS 10. On 08-Mar-2016, the patient began experiencing skin irritation at the patch site which was considered by the investigator to be mild in severity and definitely related to the study drug. No treatment was reported for the event. Patch administration sites were rotated. On 12-Apr-2016, the patient discontinued the study drug due to skin irritation. On 23-May-2016, the adverse event of skin irritation was reported as resolved.

Impression
The skin irritation resulting in discontinuing study drug was due to BTDS. The skin irritation resolved without treatment except for discontinuing the patch.

Patient Number: 0008003
Study: BUP3031
Discontinuation from Study Drug due to AE: QTcB prolonged (>480 msec)

This was a 13-year-old white male with pain related to a Nuss procedure for repair of pectus excavatum. The narrative pertaining to relevant past medical history states, "…prolonged QTc interval [related to pectus excavatum as indicated by the PI] (Sep-2014)".

Prestudy opioids included: hydromorphone hydrochloride continuous intravenous infusion and hydromorphone (100mcg) IV prn. The patient was taking the following medications during the treatment period: Obetrol, methocarbamol, oxycodone, Oxycocet, and ibuprofen.

This patient was diagnosed with QTc prolongation on day 28 (BTDS 10-mcg/hour; QTcF 451 msec with ΔQTcF 47msec and QTcB 489 with ΔQTcB 48 msec). He was withdrawn from the study and recovered on day 34. At baseline, the patient's QTcF was 403 msec and QTcB was 441 msec. On 22-0ct-2014, the patient began treatment with open-label BTDS 5, which was up-titrated on 27-0ct-2014 to BTDS 10. On 27-0ct-2014, the patient's QTcF was 420 msec and QTcB was 461 msec. On 03-Nov-2014, the patient's QTcF was 428 msec and QTcB was 462 msec. On 12-Nov-2014, the patient's QTcF was 425 msec and QTcB was 463 msec. On day 28 (18-Nov-2014), the patient was reported to have QTcB prolonged (>480msec) with a QTcB of 489 msec and QTcF of 451 msec which was considered by the investigator as mild in intensity and probably related to the study drug. The dose was down-titrated to 5-mcg/hour on day 28 and the subject was discontinued on day 30. Four days after discontinuation, the QTcF fell to 418 msec and the QTcB 462 msec.

Impression
This case was reviewed by the FDA cardiologist, Dr. Fred Senatore, from the Division of Cardiovascular and Renal Products who commented that the temporal relationship

between drug administration and QTc prolongation followed by drug discontinuation with QTc resolution suggested that the prolonged QTcF was drug-related. Dr. Senatore focused on the QTcF data since the QTc data calculated from the Fridericia formulation (QTcF) is considered superior to that calculated from the Bazett formulation (QTcB) for predicting 30-day and 1-year mortality.

Patient Number: 0010006
Study: BUP3031
Discontinuation from Study Drug due to AE: QRS complex prolonged

This was a 15-year-old white female with a history of pain due to chronic migraines enrolled in study BUP3031 with QRS complex prolongation on day 57 (BTDS 20-mcg/hour). Her past medical history included: obesity, seasonal allergies, asthma, migraines (2007), acid reflux, depression, generalized anxiety, hypothyroidism, polycystic ovarian syndrome, and vitamin D deficiency. Prestudy opioids included tramadol 50 mg, TID. The patient was taking the following medications from screening to the start of study drug: montelukast sodium, respiratory inhalation salbutamol, respiratory inhalation budesonide w/ formoterol fumarate, cetirizine hydrochloride, clonazepam, duloxetine hydrochloride, gabapentin, imipramine hydrochloride, propranolol, colecalciferol, lansoprazole, levothyroxine sodium, tramadol hydrochloride, and metformin hydrochloride. The patient was taking the following medications during the treatment period in addition to the previously listed medications: ibuprofen, paracetamol, meloxicam, pregabalin, and promethazine.

On 19-Sep-2013, the patient began the screening period. On the same day (at baseline), the patient's QRS was 86 msec. On 02-0ct-2013, the patient began treatment with open-label BTDS 5, which was increased on 08-0ct-2013 to BTDS 10. On 08-0ct-2013, the patient's QRS was 86 msec. Up-titration of BTDS dose occurred on 14-0ct-2013 to BTDS 20. On the same day, the patient's QRS was 85 msec. On 22-0ct-2013, the patient's QRS was 85 msec. On 31-0ct-2013, the patient's QRS was 88 msec. On 25-Nov-2013, the patient's QRS was 95 msec and an AE of QRS complex prolonged (QRS duration >90 msec) was reported. Two days later, on 27-Nov-2013, the patient's QRS was 91 msec at which time study drug was discontinued. One week later on 03-Dec-2013, the QRS returned to baseline (85 msec).

Impression
This case was reviewed by the FDA cardiologist, Dr. Fred Senatore, who commented that the temporal relationship between study drug administration/titration and QRS prolongation followed by drug discontinuation and subsequent resolution of the QRS prolongation suggested that this adverse event may have been drug-related. It is noted that the maximum prolongation of QRS for this patient of 95 msec is within the normal range for a 15 year old.

Patient Number: 0010011
Study: BUP3031
Discontinuation from Study Drug due to AE: Somnolence and prolonged QT

This was a 16-year-old white female with a history of pain due to migraine headache enrolled in study BUP3031. She was diagnosed with QTc prolongation on day 11 (BTDS 10-mcg/hour; QTcF 459 msec with ΔQTcF 41 msec) and was withdrawn from the study on that day.

The patient's past medical history included: intermittent constipation, appendectomy, asthma, seasonal allergies, frequent fever, intermittent anxiety, nausea, sleep disturbance, hemorrhagic ovarian cyst, tremors, exploratory laparoscopy with adhesion removal (May-2015), generalized body aches, intermittent lethargy, and vertigo. Prestudy opioids included tramadol 50 mg, TID. The patient was taking the following medications at the start of the study drug: respiratory inhalation salbutamol sulfate, tramadol, diphenhydramine, eszopiclone, and meloxicam. In addition to the medications previously reported, the patient was taking meclizine during the treatment period.

At baseline the patient's QT was 435 msec and QTcB was 409 msec. On 21-Jul-2015, the patient began treatment with open-label BTDS 5. On 27-July-2015, the patient experienced an AE of somnolence, which was considered by the investigator to be moderate in intensity and definitely related to the study drug. On the same day, the patient's dose was up-titrated to BTDS 10. On 27-Jul-2015, the patient's QT was 413 msec and QTcB was 458 msec. On day 11, 31-Jul-2015, the patient experienced an AE of prolonged QT (an increase in QTcB value > 50 msec as specified in the protocol), which was considered by the investigator to be mild in intensity and possibly related to the study drug. On the same day, the patient's QT was 440 msec, QTcB was 469 msec (ΔQTcB 60 msec) and QTcF 459 msec (ΔQTcF 41 msec). The study drug was permanently discontinued. On 03-Aug-2015, the event of somnolence resolved. On 10-Aug-2015, the patient was reported to have discontinued from the study due to the events of somnolence and prolonged QT. On the same day, the patient's QT was 395 msec, QTcB was 461.67 msec and QTcF was 438 msec. On 21-Aug-2015, it was reported that the event of prolonged QT resolved (QT was 389 msec, QTcB 425 msec and QTcF 413 msec).

Impression
This case was reviewed by the FDA cardiologist, who commented that the temporal relationship between drug administration and QTc prolongation followed by drug discontinuation with QTc resolution suggested that the prolonged QTcF was drug-related. However, the criteria for QTc prolongation for females (>470 msec) was not met by the measured QTcF intervals. This was a borderline case of QTc prolongation that did not meet the usual criteria for stopping a drug known to cause QTc prolongation, a QTc > 500 msec or an increase in QTc > 60 msec. Also the interpretation of the cause

of the QT prolongation is complicated by a possible salbutamol-mediated confounding effect.

The AE of somnolence was likely related to study drug but was not the cause of study drug discontinuation.

Patient Number: 9009004
Study: BUP3031
Discontinuation from Study Drug due to AE: worsening sinus tachycardia

This patient was a 10-year-old white female with a history of pain due to juvenile rheumatioid arthritis enrolled in study BUP3031. The patient's past medical was significant for: Crohns disease, iron deficiency anemia and sinus tachycardia. The patient was taking the following medications from screening to the start of study: ferrous sulfate, prednisone, esomeprazole, adalimumab, and Vicodin. The patient in addition to the previous listed medications was also taking the following medications during the treatment period: magnesium hydroxide, bisacodyl, docusate sodium, Vicodin, folic acid w/iron/minerals, vitamins and cyproheptadine hydrochloride.

On 20-Dec-2012, the patient began the screening period. On the same day, the patient's baseline average heart rate (HR) by ECG was 116 beats/min. On 07-Jan-2013, the patient began treatment with open-label BTDS 2.5, the patient's BTDS dose was up-titrated on 15-Jan-2013 to BTDS 5. On 15-Jan-2013, the patient experienced an AE of worsening sinus tachycardia which was considered by the investigator as mild in intensity and unlikely related to the study drug. On the same day, the patient's average HR by ECG was 130.67 beats/min (protocol criteria for tachycardia: HR> 130 bpm for patients aged 7 to 11 years). No treatment was reported for this event. On 18-Jan-2013, study drug was discontinued due to worsening sinus tachycardia with an average HR of 134 beats/min. On 18-Jan-2013, the patient's hemoglobin was 95 g/L (normal range: 115 to 150 g/L) and hematocrit was 0.31 (normal range: 0.33 to 0.43). On (b) (6) the patient was hospitalized and was diagnosed with worsening anemia, Crohns exacerbation and malnutrition.

Impression
This subject’s tachycardia was probably related to her overall medical condition. She had a history of anemia and malnutrition that may have resulted in tachycardia considering her heart rate was115 beats/minute at baseline prior to receiving BTDS.

Patient Number: 0024003
Study: BUP3031
Discontinuation from Study Drug due to AE: Fatigue/hypersomnolence

The patient summary can be found in Section 7.3.2 on nonfatal serious adverse events.

7.3.4 Significant Adverse Events

Discussed in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

QT prolongation
Buprenorphine is known to cause QTc prolongation. The Butrans label already includes a warning regarding QTc prolongation, "Do not exceed a dose of one 20 mcg/hour BUTRANS system due to the risk of QTc interval prolongation. In a clinical trial, BUTRANS 40 mcg/hour…resulted in prolongation of the QTc interval"

The label provides the following information on QTc prolongation from a thorough QT study (BUP1011) conducted in 2009:

> The effect of BUTRANS 10 mcg/hour and 2 x BUTRANS 20 mcg/hour on QTc interval was evaluated in a double-blind (BUTRANS vs. placebo), randomized, placebo and active-controlled (moxifloxacin 400 mg, open label), parallel-group, dose-escalating, single-dose study in 132 healthy male and female subjects aged 18 to 55 years…
>
> There was no clinically meaningful effect on mean QTc with a BUTRANS dose of 10 mcg/hour. A BUTRANS dose of 40 mcg/hour (given as two 20 mcg/hour BUTRANS Transdermal Systems) prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points.

A second thorough QT study (BUP1025) was conducted with higher doses of BTDS and naltrexone to support approval of an efficacy supplement to increase the maximum dose of BTDS from 20 mcg/hour to 40 mcg/hour in adults. This supplement was not approved due to lack of adequate evidence of a dose response with greater efficacy for Butrans 40 mcg/hour, relative to Butrans 20 mcg/hour. This was required for approval because an analgesic ceiling effect with buprenorphine is possible due to both opioid agonist and antagonist activity of buprenorphine. The BTDS doses studied in this thorough QT study were 10, 40 and 80 mcg/hour, and the naltrexone dose was 50 mg. As monotherapy, there was no QT effect at the 10 mcg dose. The 40 mcg dose showed a maximum mean ΔΔ QTcI of 9.1.ms (upper 90% CI: 11.2 ms). The 80 mcg dose showed a maximum mean ΔΔ QTcI of 11.2 ms (upper 90% CI: 13.9 ms). When combined with naltrexone, there was no significant QT prolongation effect for any BTDS dose.

The findings from this study were consistent with the previous findings where there was no significant QTc prolongation at the 10 mcg/hour dose, but a modest effect (~10 ms) at the 40 mcg/hour dose.

Given the potential of Butrans to prolong the QT interval, the Division required extensive ECG surveillance during the study. Electrocardiograms were performed using a

conventional 12-lead ECG, 3 ECGs per analysis, a minimum of 10 minutes apart. Patients were excluded from the study that had an average value of QT interval corrected using Bazett's formula (QTcB) and QT interval corrected using Fridericia's formula (QTcF) of 3 tracings > 460 msec or a single QTcB or QTcF value ≥ 480 msec. Patients were also excluded with QRS duration ≥ 110 msec (intraventricular conduction delay) or 1st degree atrioventricular (AV) block (P-R interval > 200 msec).

ECG monitoring was performed at screening, end of study weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24, with particular attention paid to QT interval measurements. Every time a patient's BTDS dose was up-titrated to BTDS 20, the patient had a conventional 12-lead ECG examination performed 2 to 3 days after the up- titration.

A prolongation of QTc interval was considered an adverse events (AEs or SAEs) in the following cases: Average QTc prolonged (≥ 460 msec; from 3 consecutive ECGs), QTcB prolonged (≥ 480 msec; on any single ECG), QTcF prolonged (≥ 480 msec), QTcB prolonged (increase in QTcB value ≥ 50 msec), and QTcF prolonged (increase in QTcF value ≥ 50 msec) from initial baseline value.

ECG Findings from Study BUP3031
Dr. Fred Senatore from the Division of Cardiovascular and Renal Products reviewed the QTc data and ECG adverse events from study BUP3031. He focused mostly on QTcF data since data collected from the Fridericia formulation (QTcF) is considered superior to that calculated from the Bazett formulation (QTcB) for predicting 30-day and 1-year mortality.

The following is a summary of the results reported by Dr. Senatore.

1. Mean Change in QTcF from Baseline
   The mean QTcF at baseline was 402 msec (Table 14). The overall mean ΔQTcF for the 24 weeks of study drug treatment was 4 msec. The maximum recorded mean ΔQTcF was 8 msec at week 4. Dr. Senatore concluded that all mean QTc measurements were within normal limits and the overall data did not suggest a safety signal regarding QTc interval prolongation.

Table 14: Mean QTc and Mean Change from Baseline QTc at Week 24

N	Time	Mean QTcB (SD) ms	Mean ΔQTcB (SD) ms	Mean QTcF (SD) ms	Mean ΔQTcF (SD) ms
41	Baseline	420 (20)	-----	402 (16)	----
40	Week 1	425 (20)	5 (13)	405 (17)	4 (10)
36	Week 2	423 (18)	3 (13)	406 (17)	5 (12)
32	Week 3	420 (20)	1 (17)	403 (18)	3 (13)
26	Week 4	425 (23)	7 (20)	408 (20)	8 (17)
22	Week 6	427 (15)	7 (15)	409 (16)	6 (11)
20	Week 8	425 (19)	6 (18)	409 (21)	6 (15)
16	Week 12	425 (17)	5 (12)	407 (16)	2 (11)
16	Week 16	420 (24)	0 (14)	407 (20)	2 (13)
16	Week 20	419 (25)	-1 (16)	403 (22)	-2 (14)
40	Week 24	425 (23)	4 (18)	407 (21)	5 (17)
41	Overall	425 (19)	4 (15)	406 (17)	4 (13)

Source: Table 14.3.6.1 CSR
Source: Cardiology Consult dated April 28, 2017 from Dr. Senatore

2. Mean Change in QTcF from Baseline at Maximum Dose (20 mcg/hr)
   The QTc data from baseline to week 24 for those subjects who were titrated to the maximum allowable dose of 20-mcg/hour is shown in Table 15. The mean QTcF at baseline was 398 msec. The overall mean ΔQTcF for the 24 weeks of study drug treatment was 7 msec. The maximum recorded mean ΔQTcF was 12 msec at week 4. The FDA cardiologist commented that the data in this subgroup was not significantly different from the overall population. All mean QTc measurements were within normal limits and did not suggest a safety signal regarding QTc interval prolongation.

Table 15: Mean QTc and Mean Change from Baseline QTc at Week 24 in (Subjects titrated to maximum dose of 20 mcg/h)

N	Time	Mean QTcB (SD) ms	Mean ΔQTcB (SD) ms	Mean QTcF (SD) ms	Mean ΔQTcF (SD) ms
13	Baseline	413 (25)	----	398 (20)	----
13	Week 1	422 (23)	8 (11)	406 (20)	8 (9)
13	Week 2	418 (21)	5 (14)	404 (21)	7 (11)
12	Week 3	420 (23)	6 (14)	403 (21)	5 (14)
10	Week 4	425 (22)	11 (16)	409 (23)	12 (15)
8	Week 6	423 (18)	0 (14)	404 (22)	2 (11)
8	Week 8	431 (23)	8 (16)	411 (28)	9 (13)
7	Week 12	425 (19)	1 (14)	404 (22)	1 (13)
7	Week 16	421 (23)	-3 (15)	403 (25)	0 (13)
7	Week 20	415 (28)	-8 (17)	396 (28)	-6 (13)
12	Week 24	414 (19)	1 (18)	400 (22)	3 (19)
13	Overall	420 (20)	7 (13)	405 (20)	7 (11)

Source: Table 14.3.6.9 CSR
Source: Cardiology Consult (April 28, 2017) by Dr. Senatore

3. Range of Maximum QTcB and QTcF for each dose

The range of maximum QTcB and QTcF for each dose is shown in Table 16. At the dose of 2.5-mcg/hour, the range of maximum QTcF was 411-425 msec. At the dose of 5-mcg/hour, the range of maximum QTcF was 400-435 msec. At the dose of 10-mcg/hour, the range of maximum QTcF was 402-459 msec. At the dose of 20-mcg/hour, the range of maximum QTcF was 420-449 msec. The FDA cardiologist noted that the range of maximum QTcF overlapped between doses but there was an empirical trend towards a higher maximum QTcF range for the 20-mcg/hour dose compared to the 2.5-mcg/hour dose.

Note: The ΔQTcB and ΔQTcF values associated with the maximum QTcB and QTcF ranges shown in Table 3 were not the maximum ΔQTcB and ΔQTcF values which are shown in Table 17.

Table 16: Range of Maximum QTcB and QTcF per Dose with corresponding ΔQTcB and ΔQTcF

Dose (mcg/hour)	Maximum QTcB (ΔQTcB) msec	Maximum QTcF (ΔQTcF) msec
2.5	447 (11) ←→ 448 (8)	411 (9) ←→ 425 (19)
5.0	395 (46) ←→ 459 (26)	400 (47) ←→ 435 (22)
10.0	422 (35) ←→ 489 (48)	402 (13) ←→ 459 (41)
20.0	444 (35) ←→ 459 (27)	420 (13) ←→ 449 (29)

Source: Reviewer Derived Table 5. Note: the ΔQTcB and ΔQTcF values were those associated with the corresponding maximum QTcB and QTcF, respectively.
Source: Cardiology Consult (April 28, 2017) by Dr. Senatore

4. Range of Maximum ΔQTcB and ΔQTcF for each dose
   The range of maximum ΔQTcB and ΔQTcF values per dose is shown in Table 17. At the dose of 2.5-mcg/hour, the range of maximum ΔQTcF was 9-25 msec. At the dose of 5-mcg/hour, the range of maximum ΔQTcF was 22-47 msec. At the dose of 10- mcg/hour, the range of maximum ΔQTcF was 13-47 msec. At the dose of 20-mcg/hour, the range of maximum ΔQTcF was 13-33 msec. The FDA cardiologist concluded that the range of maximum ΔQTcF was dose independent.

Table 17: Range of Maximum ΔQTcB and ΔQTcF per Dose

Dose (mcg/hour)	Maximum ΔQTcB msec	Maximum ΔQTcF msec
2.5	8 ←→ 20	9 ←→ 25
5.0	22 ←→ 46	22 ←→ 47
10.0	7 ←→ 60	13 ←→ 47
20.0	5 ←→ 37	13 ←→ 33

Source: Reviewer Derived Table 5.
Source: Cardiology Consult (April 28, 2017) by Dr. Senatore

Dr. Senatore noted that QTc values exceeding 450 msec in males and 470 msec in females constitutes the diagnosis of prolonged QT but criteria for stopping a drug known to cause QTc prolongation are a QTc > 500 msec or an increase in QTc > 60 msec. The criteria for the diagnosis of QTc prolongation may have been met depending on gender but the criteria for stopping a drug known to prolong the QTc interval was not met.

Dr. Senatore also noted that a prior consultation by the DCRP on March 8, 2010 related to the safety data for NDA 21306 determined that there was a modest QT prolonging effect of BTDS at the highest therapeutic dose studied (20 mcg/hr). AEs and SAEs suggested that BTDS had minimal arrhythmogenic potential, if any, at the doses studied.

Subject Discontinuations Due to ECG Adverse Events
There were five subjects who had an ECG adverse event that led to study drug discontinuation. Two of the subjects were reported to have QT prolongation (subjects 0008003 and 0010011). The other subjects who discontinued had mild sinus tachycardia (subject 9009004), first degree atrio-ventricular block (subject 0010005), and QRS complex prolongation (subject 0010006). The narratives of all five patients were reviewed by the FDA cardiologist and a summary of each patient is provided in the section on discontinuations due to adverse events except for patient 0010005 with first degree heart block which is summarized in the section on SAEs. The temporal relationship between drug administration and QTc prolongation followed by drug discontinuation with QTc resolution suggested that the prolonged QTcF was drug-related in both cases. The temporal relationship also suggested that the QRS prolongation may have been drug-related. The discontinuations due to sinus tachycardia and first degree AV block did not appear to be drug related.

DCRP Conclusions
The following are the DCRP conclusions:

> The overall data did not suggest a safety signal regarding QTc interval prolongation. The data in the subgroup of subjects titrated to 20-mcg/hour was not significantly different from the overall ITT population and therefore did not suggest a safety signal regarding QTc interval prolongation.
>
> Those individual subjects who were titrated to BTDS 20-mcg/hour experienced various degrees of QTc prolongation and QTc shortening, with both time-dependent increases and decreases, while on 20-mcg/hour. QTc prolongation occurred at lower doses and QTc shortening occurred at higher doses. All of the QTcF intervals except one were within normal limits. The one subject having a QTcF interval exceed 450 msec (subject 0008003, 13 y/o M with QTcF 451 msec) at one time point was taking 10-mcg/hour BTDS. There were no QTCF intervals reaching the threshold of QTc prolongation at the dose of 20-mcg/hour. These data did not support a dose-dependent QTc prolongation effect at the doses studied and therefore lessened the likelihood that the observed QT prolongations were drug-related.
>
> In 3 of the 5 individual cases (see reviewer's note below) of study withdrawal due to ECG adverse events (i.e. Subject 0008003 with prolonged QTc on BTDS 10-mcg/hour; Subject 0010011 with prolonged QTc on 10-mcg/hour; and Subject 0010006 with QRS prolongation on 20 mcg/hour), the timing of the adverse event and its resolution relative to the start of drug and its discontinuation suggested the possibility of a drug-related effect at doses lower than that specified in the boxed warning…There were no arrhythmias or clinical sequelae associated with any of the ECG adverse events leading to withdrawal.
>
> *Reviewer's Note*: Dr. Senatore initially considered it possible that four subjects had adverse events related to study drug until additional information on Subject 0010005 with asymptomatic 1st degree AV block was provided by Purdue. After review of this additional information, it was considered unlikely that the AV block was due to study drug. I have revised the conclusions above to reflect this additional information.
>
> In conclusion, the overall data did not suggest a new safety signal, and the label already retains an adequate warning about QTc prolongation. The description of this study in section 8.4 of the label should include a description of the ECG-adverse events and the doses of BTDS when they occurred. However, we defer to DAAAP for overall risk/benefit assessment and labeling decisions.
>
> *Reviewer's Note*: In a telephone conference on September 8, 2017, the Division of Cardiovascular and Renal Products clarified that the recommendation for

including the description of the ECG adverse events in the label was only if the product received an indication for pediatrics. If there is no pediatric indication the current label provides an adequate warning about QT prolongation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A summary of treatment-emergent adverse events (TEAEs) considered to be related to study drug is provided in Table 18.

Table 18: Incidence of TEAEs Possibly Related to Study Drug

	Age Group		
MedDRA System Organ Class Preferred Term	7 to 11 years (N = 6) n (%)	12 to 16 years (N = 35) n (%)	Total (N = 41) n (%)
Any Related Adverse Event	5 (83)	16 (46)	21 (51)
Blood and Lymphatic System Disorders	1 (17)	0	1 (2)
Neutropenia	1 (17)	0	1 (2)
Cardiac Disorders	2 (33)	0	2 (5)
Atrioventricular Block First Degree	1 (17)	0	1 (2)
Sinus Tachycardia	1 (17)	0	1 (2)
Eye Disorders	0	1 (3)	1 (2)
Vision Blurred	0	1 (3)	1 (2)
Gastrointestinal Disorders	2 (33)	6 (17)	8 (20)
Nausea	1 (17)	6 (17)	7 (17)
Constipation	1 (17)	1 (3)	2 (5)
Vomiting	1 (17)	1 (3)	2 (5)
General Disorders and Administration Site Conditions	1 (17)	10 (29)	11 (27)
Application Site Pruritus	0	7 (20)	7 (17)
Application Site Irritation	1 (17)	4 (11)	5 (12)
Application Site Erosion	0	1 (3)	1 (2)
Application Site Pain	0	1 (3)	1 (2)
Fatigue	0	1 (3)	1 (2)
Infections And Infestations	1 (17)	0	1 (2)
Clostridium Difficile Colitis	1 (17)	0	1 (2)
Investigations	0	3 (9)	3 (7)
Electrocardiogram QT Prolonged	0	2 (6)	2 (5)
Electrocardiogram QRS Complex Prolonged	0	1 (3)	1 (2)
Hepatic Enzyme Increased	0	1 (3)	1 (2)
Metabolism and Nutrition Disorders	0	1 (3)	1 (2)
Decreased Appetite	0	1 (3)	1 (2)
Musculoskeletal and Connective Tissue Disorders	0	3 (9)	3 (7)
Back Pain	0	2 (6)	2 (5)
Pain In Extremity	0	1 (3)	1 (2)
Nervous System Disorders	2 (33)	10 (29)	12 (29)
Somnolence	1 (17)	5 (14)	6 (15)
Dizziness	1 (17)	2 (6)	3 (7)
Headache	0	3 (9)	3 (7)
Paraesthesia	0	2 (6)	2 (5)
Migraine	0	1 (3)	1 (2)
Sedation	1 (17)	0	1 (2)
Psychiatric Disorders	0	3 (9)	3 (7)
Agitation	0	1 (3)	1 (2)
Anxiety	0	1 (3)	1 (2)
Initial Insomnia	0	1 (3)	1 (2)
Insomnia	0	1 (3)	1 (2)
Tearfulness	0	1 (3)	1 (2)

Renal and Urinary Disorders	0	1 (3)	1 (2)
Bilirubinuria	0	1 (3)	1 (2)
Proteinuria	0	1 (3)	1 (2)
Respiratory, Thoracic And Mediastinal Disorders	1 (17)	0	1 (2)
Epistaxis	1 (17)	0	1 (2)
Skin And Subcutaneous Tissue Disorders	0	2 (6)	2 (5)
Dermatitis Contact	0	1 (3)	1 (2)
Pruritus	0	1 (3)	1 (2)
Vascular Disorders	0	1 (3)	1 (2)
Hot Flush	0	1 (3)	1 (2)

Abbreviations: N = number of patients in the population; n = number of patients with event.
Cross Reference: Table 14.3.1.3
Related to study drug = unlikely, possibly, probably or definitely related categories of the adverse event CRF. If a patient had more than 1 occurrence of the same system organ class/preferred term, the worst relationship was summarized and counted only once. If a relationship was missing for an adverse event, it was assumed to be related to study drug.
Notes: MedDRA Version 15.0 was used to code adverse events.
Percentages are based on N.
Source: CSR 3031. Table 27, p.120

The most frequently reported adverse events that are considered likely to be related to study drug include: application site conditions (includes pruritus, irritation, erosion and pain) 11 patients (27%), nausea 7 patients (17%), somnolence 6 patients (15%), dizziness 3 patients (7%), headache 3 patients (7%), constipation 2 patients (5%), and vomiting 2 patients (5%). These adverse events are not unexpected with the use of opioids and administration of transdermal patches.

Somnolence

Somnolence frequently occurs with opioids and was assessed in this study using the University of Michigan Sedation Scale (UMSS) at screening, 30 minutes before and 1 hour after the initial BTDS application on day 1, and once daily in the morning, 30 to 60 minutes after the patient awakened for the first 4 days of treatment with BTDS, and for the first 4 days following an up-titration. The UMSS consists of a numeric rating scale of 0 corresponding to “Awake and alert,” to a rating scale of 4 “Unarousable”.

Somnolence was reported as a treatment-emergent adverse event, occurring in 6 patients (15%). There was one SAE of hypersomnia in Subject # 0024003 described in the section on SAEs. This SAE may have been exacerbated by the BTDS but did not appear to be due to it given a history of hypersomnia in this patient prior to starting BTDS and after discontinuing study drug. Three patients were reported to have dose reductions due to adverse events of either somnolence (2) or sedation (1). A total of six patients (15%) had a somnolence score of greater than or equal to 3. The reported somnolence is not unexpected with the use of an opioid.

7.4.2 Laboratory Findings

Hematology and chemistry laboratory tests were obtained at screening and end of weeks 2, 4, 6, 8, 12, 16, 20 and 24/early termination.

Chemistry

Blood chemistry values that shifted from normal to high and normal to low from baseline to end of study are summarized in Table 19 and Table 20. For the younger age group there were very few shifts from normal to high or normal to low. In the older age group, the most common shift from normal to high was for phosphorous in 10 of 25 patients and the most common shifts from normal to low was for bicarbonate/CO2 in 4 of 21 patients (19%) and creatinine in 4 of 23 patients (17%). The mean changes in the blood chemistry values were also reviewed. Overall the clinical significance of the changes in mean values and shifts in chemistry was difficult to interpret without a control group for comparison but in general there did not appear to be any clinically significant changes related to study drug.

Table 19 : Shifts from Normal to High From Baseline to End of Study for Blood Chemistry Values

	Age Groups	
	7 to 11 Years (N = 6)	12 to 16 Years (N = 35)
Laboratory Parameter	n/NN (%)	n/NN (%)
Aspartate Transferase (SGOT) (U/L)	0/4 (0)	1/28 (4)
Alanine Transferase (SGPT) (U/L)	0/4 (0)	2/29 (7)
Blood urea nitrogen (mmol/L)	0/4 (0)	1/29 (3)
Calcium (mmol/L)	0/4 (0)	1/32 (3)
Chloride (mmol/L)	1/4 (25)	2/29 (7)
Blood glucose (mmol/L)	1/4 (25)	2/22 (9)
Lactic dehydrogenase (U/L)	0/3 (0)	1/28 (4)
Magnesium (mmol/L)	1/4 (25)	1/31 (3)
Phosphorous/inorganic phosphate (mmol/L)	0/3 (0)	10/25 (40)
Sodium (mmol/L)	0/3 (0)	1/31 (3)
Uric acid (µmol/L)	0/4 (0)	3/27 (11)
Bilirubin Direct (µmol/L)	0/4 (0)	2/30 (7)

Abbreviations: µmol/L = micromoles per Liter; mmol/L = millimoles per Liters; N = number of patients in population groups; n = number of patients with data; NN = number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; U/L = units per Liter.

Source: Table 35 CSR BUP3031

Table 20: Shifts from Normal to Low From Baseline to End of Study for Blood Chemistry Values

	Age Groups	
	7 to 11 Years (N = 6)	12 to 16 Years (N = 35)
Laboratory Parameter	n/NN (%)	n/NN (%)
Blood urea nitrogen (mmol/L)	0/4 (0)	1/29 (3)
Chloride (mmol/L)	1/4 (25)	0/29 (0)
Bicarbonate/carbon dioxide (mmol/L)	0/3 (0)	4/21 (19)
Creatinine (µmol/L)	0/2 (0)	4/23 (17)
Blood glucose (mmol/L)	0/4 (0)	1/22 (5)
Total Bilirubin (umol/L)	0/4 (0)	3/30 (10)
Total protein (g/L)	0/2 (0)	2/31 (6)

Abbreviations: g/L = grams per Liter; µmol/L = micromoles per Liter; mmol/L = millimoles per Liter; N = number of patients in population groups; n = number of patients with data; NN = number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study.

Source: Table 36 CSR BUP3031

Liver Function Tests

A detailed review of liver function tests was conducted since cases of hepatitis and hepatic failure have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence. The shifts in AST, ALT, and total bilirubin using different cut-off values (i.e., AST, ALT ≤1 x ULN, >1 to ≤3 x ULN, >3 to ≤5 x ULN, >5 to ≤10 x ULN, >10 to ≤20 x ULN, and > 20 x ULN; total bilirubin ≤1 x ULN, >1 to ≤2.5 x ULN, >2.5 x ULN) were analyzed.

AST and ALT

Shifts from baseline to highest value during the study for ALT are shown in Table 21 and shifts for AST are shown in Table 22. For the overall population, over 70% of patients had AST and ALT values that remained ≤ 1 ULN during the entire study. For the 7 to 11 year age group, the highest ALT value during exposure to BTDS was > 1 to ≤ 3 × ULN for 1 patient (25%) and no patient had an AST value >1 × ULN. In the older age group, the highest ALT and AST values during BTDS exposure were > 5 to ≤ 10 × ULN in one patient (Patient 0010001) and returned to normal while on study drug. The summary for this Patient 0010001 is provided later in this section.

Table 21: Categorization of Highest ALT value During Exposure to BTDS Compared to Baseline Value

		Number (%) of Patients with Shifts in ALT Value					
		Baseline ALT Value					
Age Group	Highest ALT Value	<=1 x ULN	>1 to <=3 x ULN	>3 to <=5 x ULN	>5 to <=10 x ULN	>10 to <=20 x ULN	>20x ULN
7 to 11 years (N=4)	<=1x ULN	3 (75)	0	0	0	0	0
	>1 to <=3x ULN	1 (25)	0	0	0	0	0
	>3 to <=5x ULN	0	0	0	0	0	0
	>5 to <=10x ULN	0	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	4 (100)	0	0	0	0	0
12 to 16 years (N=32)	<=1x ULN	21 (72)	2 (67)	0	0	0	0
	>1 to <=3x ULN	6 (21)	1 (33)	0	0	0	0
	>3 to <=5x ULN	1 (3)	0	0	0	0	0
	>5 to <=10x ULN	1 (3)	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	29 (100)	3 (100)	0	0	0	0
Total (N=36)	<=1x ULN	24 (73)	2 (67)	0	0	0	0
	>1 to <=3x ULN	7 (21)	1 (33)	0	0	0	0
	>3 to <=5x ULN	1 (3)	0	0	0	0	0
	>5 to <=10x ULN	1 (3)	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	33 (100)	3 (100)	0	0	0	0

Cross Reference: Appendix 16.2.8.2
Note: N = Number of patients with a baseline value and at least 1 post-baseline value. Percentages are based on the total number of patients in each column as the denominator.
Baseline is defined as the last scheduled or unscheduled (repeat) laboratory test value obtained prior to the first dose of study drug.
Scheduled and unscheduled assessments obtained during treatment with study drug and up to 7 days after the last dose of study drug were considered in these evaluations.
SAS program: T14-03-04-06-01-ALT-BTDS.sas, 02JUN2016 11:00

Source: Applicant's Table 14.3.4.5.1 CSR BUP3031

Table 22: Categorization of Highest AST Value During Exposure to BTDS Compared to Baseline Value

		Number (%) of Patients with Shifts in AST Value					
		Baseline AST Value					
Age Group	Highest AST Value	<=1 x ULN	>1 to <=3 x ULN	>3 to <=5 x ULN	>5 to <=10 x ULN	>10 to <=20 x ULN	>20x ULN
7 to 11 years (N=4)	<=1x ULN	4 (100)	0	0	0	0	0
	>1 to <=3x ULN	0	0	0	0	0	0
	>3 to <=5x ULN	0	0	0	0	0	0
	>5 to <=10x ULN	0	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	4 (100)	0	0	0	0	0
12 to 16 years (N=32)	<=1x ULN	20 (71)	2 (50)	0	0	0	0
	>1 to <=3x ULN	7 (25)	2 (50)	0	0	0	0
	>3 to <=5x ULN	0	0	0	0	0	0
	>5 to <=10x ULN	1 (4)	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	28 (100)	4 (100)	0	0	0	0
Total (N=36)	<=1x ULN	24 (75)	2 (50)	0	0	0	0
	>1 to <=3x ULN	7 (22)	2 (50)	0	0	0	0
	>3 to <=5x ULN	0	0	0	0	0	0
	>5 to <=10x ULN	1 (3)	0	0	0	0	0
	>10 to <=20x ULN	0	0	0	0	0	0
	>20x ULN	0	0	0	0	0	0
	Total	32 (100)	4 (100)	0	0	0	0

Cross Reference: Appendix 16.2.8.2
Note: N = Number of patients with a baseline value and at least 1 post-baseline value. Percentages are based on the total number of patients in each column as the denominator.
Baseline is defined as the last scheduled or unscheduled (repeat) laboratory test value obtained prior to the first dose of study drug.
Scheduled and unscheduled assessments obtained during treatment with study drug and up to 7 days after the last dose of study drug were considered in these evaluations.

Source: Applicant's Table 14.3.4.5.2 CSR BUP3031

Table 23 summarizes the highest total bilirubin value during exposure to BTDS compared to baseline value. For the 7 to 11 year age group bilirubin values remained at ≤ 1 × ULN in all four patients during the entire study. For the 12 to 16 year age group 30 patients had bilirubin values ≤ 1 × ULN at baseline and one of these patients (3%) had a shift in bilirubin values from ≤ 1 × ULN at baseline to > 1 to ≤ 2.5 × ULN during the study. This patient's bilirubin returned within the normal range by the end of the study. Two patients that started with bilirubin > 1 to ≤ 2.5 x ULN and the values for these patients remained in the same range throughout the study.

Table 23: Categorization of Highest Total Bilirubin Value During Exposure to BTDS Compared to Baseline Value

		Number (%) of Patients with Shifts in Total Bilirubin Value		
		Baseline Total Bilirubin Value		
Age Group	Highest Total Bilirubin Value	<=1x ULN	>1 to <=2.5x ULN	>2.5x ULN
7 to 11 years (N=4)	<=1x ULN	4 (100)	0	0
	>1 to <=2.5x ULN	0	0	0
	>2.5x ULN	0	0	0
	Total	4 (100)	0	0
12 to 16 years (N=32)	<=1x ULN	29 (97)	0	0
	>1 to <=2.5x ULN	1 (3)	2 (100)	0
	>2.5x ULN	0	0	0
	Total	30 (100)	2 (100)	0
Total (N=36)	<=1x ULN	33 (97)	0	0
	>1 to <=2.5x ULN	1 (3)	2 (100)	0
	>2.5x ULN	0	0	0
	Total	34 (100)	2 (100)	0

Cross Reference: Appendix 16.2.8.2
Note: N = Number of patients with a baseline value and at least 1 post-baseline value. Percentages are based on the total number of patients in each column as the denominator.
Baseline is defined as the last scheduled or unscheduled (repeat) laboratory test value obtained prior to the first dose of study drug.
Scheduled and unscheduled assessments obtained during treatment with study drug and up to 7 days after the last dose of study drug were considered in these evaluations.

Source: Applicant's Table 14.3.4.5.3 CSR BUP3031

Hematology

A summary of hematologic values that shifted from normal at baseline to high at end of study and from normal at baseline to low at the end of the study is provided in Table 24 and Table 25. For the younger age group, at most only one patient shifted from normal to high or normal to low for some of the hematologic categories. Interpretation of the findings is limited since only six subjects were in this age group. The most frequent shifts from normal to high for the older age group were 6 of 28 patients (21%) for eosinophils and 5 of 26 patients (19%) for lymphocytes. The most prevalent shifts from normal to low in the older age group were for monocytes 7 of 24 patients (29%) and for neutrophils 8 of 30 patients (27%). The mean changes from baseline for hematology parameters were reviewed. Overall the clinical significance of the changes in mean values and shifts in hematology parameters was difficult to interpret without a control group for comparison but in general there did not appear to be any clinically significant changes related to study drug.

Table 24: Shifts from Normal to High From Baseline to End of Study for Hematologic Values

	Age Groups	
	7 to 11 Years (N = 6)	12 to 16 Years (N = 35)
Laboratory Parameter	n/NN (%)	n/NN (%)
Bands (fraction)	1/3 (33)	0/32 (0)
Bands absolute (10^6/L)	1/3 (33)	0/32 (0)
Eosinophils (fraction)	1/3 (33)	6/28 (21)
Eosinophils absolute (10^6/L)	0/3 (0)	3/30 (10)
Lymphocytes (fraction)	1/3 (33)	5/26 (19)
Lymphocytes absolute (10^6/L)	0/3 (0)	1/28 (4)
Neutrophils absolute (10^6/L)	0/3 (0)	1/29 (3)
White blood cells (10^9/L)	0/3 (0)	1/29 (3)

Abbreviations: N = number of patients in population groups; n = number of patients with data; NN = number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study.
Cross-reference: Table 14.3.4.2.1
Notes: Units reflected as SI units. Percentages are based on NN.

Source: Applicant's Table 33 CSR BUP3031

Table 25: Shifts from Normal to Low From Baseline to End of Study for Hematologic Values

	Age Groups	
	7 to 11 Years (N = 6)	12 to 16 Years (N = 35)
Laboratory Parameter	n/NN (%)	n/NN (%)
Hematocrit (fraction)	0/2 (0)	1/22 (5)
Hemoglobin (g/L)	0/2 (0)	1/20 (5)
Lymphocytes (fraction)	1/3 (33)	0/26 (0)
Lymphocytes absolute (10^6/L)	1/3 (33)	0/28 (0)
Monocytes (fraction)	0/4 (0)	2/27 (7)
Monocytes absolute (10^6/L)	1/3 (33)	7/24 (29)
Neutrophils (fraction)	0/1 (0)	8/30 (27)
Neutrophils absolute (10^6/L)	1/3 (33)	4/29 (14)
Platelet (10^9/L)	1/3 (33)	0/31 (0)
White blood cells (10^9/L)	1/3 (33)	5/29 (17)

Abbreviations: g/L = grams per Liter; N = number of patients in population groups; n = number of patients with data; NN = number of patients with normal laboratory test results at baseline and laboratory test results available at the end of study.
Cross-reference: Table 14.3.4.2.1
Note: Units reflected as SI units. Percentages are based on NN.

Source: Applicant's Table 34 CSR BUP3031

Seven patients were reported to have significant laboratory events due to abnormal chemistry or CBC values (Table 26). Summaries for these patients are provided below.

Table 26: Patients with Significant Laboratory Events

Patient	Age/ Gender/Race	ALT and/or AST > 3 × ULN and/or Bilirubin > 1.5 × ULN	Any laboratory value ≥ NCI grade 3 after screening	Any NCI grade increase of 2 grades after screening
0071A-0015002	14/F/B	--	--	blood glucose
0071A-0015004	15/M/W	alanine transferase (SGPT)	--	alanine transferase (SGPT)
1843A-0027004	8/M/W	--	lymphocytes absolute; neutrophils absolute; white blood cells	neutrophils absolute; white blood cells
2125A-0024001	16/F/B	total bilirubin	--	--
2493A-0009006	12/M/W	--	--	neutrophils absolute
2527A-0010001	12/F/W	alanine transferase (SGPT); aspartate transferase (SGOT)	alanine transferase (SGPT); aspartate transferase (SGOT)	alanine transferase (SGPT); aspartate transferase (SGOT)
2763A-0028001	13/M/B	total bilirubin	hemoglobin	--

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI = National Cancer Institute; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamate pyruvate transaminase; U/L = units per Liter; ULN = upper limit of normal.
Gender: F = female; M = male. Race: W = White, B = Black or African American.

Source: CSR BUP3031. p.138

Summaries of patients with significant LFTs or CBC Abnormalities

Patient Number: 0010001
Study: BUP3031
Lab Abnormality: alanine transferase (SGPT) and aspartate transferase (SGOT) elevated

This was a 12-year-old, 70 kg, girl with a history of generalized rheumatologic pain enrolled in study BUP3031. Her relevant past medical history included asthma, attention deficit disorder, and kyphosis. She was taking the following medications from screening to the start of study drug: ibuprofen, paracetamol, gabapentin, tramadol, and methylphenidate hydrochloride. The patient was also taking bismuth subsalicylate during the treatment period.

On 24-Oct-2012, the patient began the screening period. On 08-Nov-2012, she began treatment with BTDS 5, the dose was up-titrated on 15-Nov-2012 to BTDS 10 and on 06-Dec-2012, and the last BTDS 10 patch was removed. AEs reported by the patient during this study were intermittent nausea, intermittent vomiting, anxiety, tearfulness, and constipation. Relevant clinical laboratory test results are presented in the table below.

Patient BUP3031-2527A-0010001: Clinical Laboratory Test Results

Analysis Visit	Lab Date	Alanine Transferase (SGPT) (U/L) Ref: 5-30 [Toxicity Grade]	Aspartate Transferase (SGOT) (U/L) Ref: 0-36 [Toxicity Grade]	Alkaline Phosphatase (U/L) Ref: 0-299 [Toxicity Grade]	Total Bilirubin (umol/L) Ref: 3-21 [Toxicity Grade]
Screening	2012-10-24T09:20	18 N [0]	19 N [0]	162 N [0]	5 N [0]
End of Week 2	2012-11-21T09:50	213 H [3]	192 H [3]	182 N [0]	14 N [0]
Unplanned Visit	2012-12-03T08:50	28 N [0]	28 N [0]	149 N [0]	7 N [0]
EOT/Early DC	2012-12-06T09:50	23 N [0]	30 N [0]	157 N [0]	7 N [0]

DC = discontinuation; EOT = end of treatment; H = value > upper limit of normal range; N = normal; Ref = reference range; umol/L = micromoles per liter; U/L = units per liter.

Impression
This patient had a transient increase in LFTs (ALT 7 x ULN, AST 5 x ULN, bilirubin and alkaline phosphatase WNL) 13 days after starting BTDS. LFTs returned to normal by the time of the next laboratory test 13 days later while the patient remained on the same dose of study drug. It is unclear whether BTDS contributed to this transient increase in AST and ALT but it is important to note that values returned to baseline while on study drug.

Patient Number: 0024001
Study: BUP3031
Lab Abnormality: total bilirubin increased

Patient 0024001 was a 16 year old African American female with a history of pain due to sickle cell disease enrolled in study BUP3031. The patient's relevant past medical history included: pneumococcal sepsis, snoring, cholecystectomy, acute chest

syndrome, headaches, asthma, vitamin D deficiency, avascular necrosis of the hip, and GERD. The patient was taking the following medications from screening to the start of study drug: oxycodone, ibuprofen, folic acid, phenoxymethylpenicillin potassium, nasal fluticasone propionate, acetaminophen/codeine, respiratory inhalation salbutamol, topiramate, intramuscular medroxyprogesterone acetate, morphine sulfate, hydroxycarbamide, and famotidine.

On 25-Aug-2014, the patient began the screening period. On 25-Sep-2014, the patient began treatment with open-label BTDS 5. The patient stopped the study drug on 10-Mar-2015 and completed the study on 20-Mar-2015. AEs reported by the patient during this study were worsening headache, leg pain due to vase-occlusive crisis and shoulder pain. Relevant clinical laboratory test results are presented below.

Patient BUP3031-2125A-0024001; Clinical Laboratory Test Results

Analysis Visit	Lab Date	Alanine Transferase (U/L) Ref: 5-30	Aspartate Transferase (U/L) Ref: 0-31	Alkaline Phosphatase (U/L) Ref: 0-186	Total Bilirubin (umol/L) Ref: 3-21
Screening	2014-09-10T10:30	22 N	46 H	91 N	36 H
End of Week 2	2014-10-07T10:45	21 N	43 H	88 N	38 H
End of Week 4	2014-10-21T11:30	28 N	46 H	82 N	32 H
Week 6	2014-11-04T11:53	15 N	39 H	85 N	29 H
Week 8	2014-11-18T14:00	37 H	51 H	82 N	38 H
Week 12	2014-12-16T12:15	14 N	34 H	81 N	43 H
Week 16	2015-01-13T13:10	14 N	35 H	78 N	27 H
Week 20	2015-02-11T08:30	13 N	29 N	80 N	32 H
EOT/Early DC	2015-03-12T13:45	16 N	37 H	74 N	29 H

H = value > upper limit of normal range; N = normal; Ref = reference range; U/L = units per liter; umol/L = micromoles per liter.

Impression
This patient had an elevated bilirubin greater than 1.5 x the ULN at screening and during the study. There was no significant change in LFTs while the patient was on treatment with BTDS.

Patient Number: 0015004
Study: BUP3031
Lab Abnormality: alanine transferase (SGPT) elevated

Patient 0015004 was a 15-year-old, 61 kg white male with musculoskeletal pain enrolled in study BUP3031. The patient's relevant medical history included: nausea, low vitamin D, mood disorder, complex regional pain syndrome and muscle spasms. The patient was taking the following medications from screening to the start of study drug: tramadol, diclofenac, baclofen, and cholecalciferol.

On 18-Apr-2014, the patient began the screening period. On 01-May-2014, the patient began treatment with open-label BTDS 5, which was up-titrated on 08-May-2014 to BTDS 10, and up-titrated on 23-May-2014 to BTDS 20. On 13-Jun-2014, the patient was discontinued from the study due to lack of therapeutic effect.

Adverse events reported by this patient during the study were pulled muscle in chest area, anxiety attack, severe cough, and nose bleed. Relevant clinical laboratory test results are summarized in the table below.

Analysis Visit	Lab Date	Alanine Transferase (SGPT) (U/L) Ref: 5-30	Alkaline Phosphatase (U/L) Ref: 0-389	Aspartate Transferase (SGOT) (U/L) Ref: 0-38	Total Bilirubin (umol/L) Ref: 3-21
Screening	2014-04-18T13:00	24 N	108 N	16N	5N
End of Week 2	2014-05-16T14:52	82 H	117 N	46H	7N
End of treatment	2014-05-30T12:30	96 H	119 N	30N	5N

Patient BUP3031-0071A-0015004; Clinical Laboratory Test Results
H = value > upper limit of normal range; N = normal; Ref = reference range; U/L = units per liter; umol/L = micromoles per liter.

Impression
This patient with normal LFTs at screening had an increase in ALT > 3 x ULN. Alkaline phosphatase and total bilirubin remained normal. No follow-up labs were provided after study drug was discontinued but although ALT remained elevated, AST had returned to normal while still on study drug at the time of the last lab draw.

Patient Number: 0028001
Study: BUP3031
Lab Abnormality: hemoglobin decreased and total bilirubin elevated

This was a 13-year-old African American male who had decreased hemoglobin and elevated bilirubin which was likely related to his history of sickle cell disease and episodes of sickle cell crisis. He was enrolled in study BUP3031 with chronic low back pain. His relevant past medical history included: sickle cell disease, sickle cell pain crisis, sickle cell retinopathy, depression, and microalbuminuria. The patient was taking the following medications from screening to the start of study drug: folic acid, macrogol, nasal fluticasone, Vicodin, ondansetron, morphine, hydroxycarbamide, ibuprofen, respiratory (inhalation) salbutamol, IV ceftriaxone, loratadine, ketorolac, and lidocaine. During the treatment period in addition to the previous medications the patient was taking: tramadol, hydroxyzine, heparin sodium, Vicodin, and azithromycin.

On 17-Sep-2014, the patient began the screening period. On 25-Sep-2014, the patient began treatment with BTDS 5 and the dose was up-titrated on 30-Sep-2014 to BTDS 10. On (b) (6) the patient developed vasa-occlusive sickle cell pain crisis, and was hospitalized. (b) (6) the patient's BTDS dose was up-titrated to BTDS 20 due to the event. On (b) (6) the event of vasa-occlusive sickle cell pain crisis resolved and the patient was discharged from hospital. On (b) (6) the patient developed another episode of vasa-occlusive crisis. (b) (6) the patient presented at the emergency department with complaints of chest pain and lower back pain. On 20-Feb-2015, the patient developed a third episode of vasa-occlusive crisis. On (b) (6) the patient was hospitalized. The patient was treated with Vicodin, IVP ketorolac, IVP morphine, ibuprofen, and hydroxycarbamide. On (b) (6) the event of vasa-occlusive crisis resolved and the patient was discharged from the hospital.

On 10-Mar-2015, down-titration of the patient's BTDS dose began. On 20-Mar-2015, the patient developed vaso-occlusive crisis and on the same day completed the down-titration of the study drug. On 24-Mar-2015, the patient completed the study. On 25-March-2015, the event of vaso-occluslve crisis resolved.

Relevant LFTs and hemoglobin results are presented in the tables below. It is noted that on September 18, prior to receiving study drug his bilirubin was elevated and his hematocrit decreased.

Patient BUP3031-2763A-0028001;,Clinical Laboratory Test Results

Analysis Visit	Lab Date	Total Bilirubin (umol/L) Ref: 3-21 [Toxicity Grade]	Alkaline Phosphatase (U/L) Ref: 0-389 [Toxicity Grade]	Aspartate Transferase (U/L) Ref:0-38 [Toxicity Grade]	Alanine Transferase (U/L) Ref: 5-30 [Toxicity Grade]
Screening	18-Sep-2014	31 H [1]	135 N [0]	49 H [1]	22 N [0]
End of Week 2	09-Oct-2014	26 H [1]	155 N [0]	48 H [1]	20 N [0]
End of Week 4	21-Oct-2014	34 H [2]	163 N [0]	50 H [1]	24 N [0]
Week 6	05-Nov-2014	43 H [2]	175 N [0]	65 H [1]	22 N [0]
Week 8	21-Nov-2014	29 H [1]	142 N [0]	47 H [1]	19 N [0]
Week 12	18-Dec-2014	38 H [2]	177 N [0]	74 H [1]	27 N [0]
Week 16	13-Jan-2015	32 H [2]	145 N [0]	59 H [1]	17 N [0]
Week 20	10-Feb-2015	24 H [1]	162 N [0]	39 H [1]	18 N [0]
EOT / Early DC	10-Mar-2015	24 H [1]	126 N [0]	50 H [1]	29 N [0]

D/C = discontinuation; EOT = end of treatment; H = value > upper limit of normal range; N= normal; umol/L = micromoles per liter; U/L = units per liter.

Patient BUP3031-2763A-0028001;Clinical Laboratory Test Results

Lab test date	Hematocrit (fraction) (Ref: 0.37-0.51)	Hemoglobin (g/L) (Ref: 123-170) [Toxicity grade]
18-Sep-2014	0.20 L	69 L [3]
09-Oct-2014	0.24 L	79 L [3]
21-Oct-2014	0.23 L	79 L [3]
05-Nov-2014	0.24 L	83 L [2]
21-Nov-2014	-	65 L [3]
18-Dec-2014	0.25 L	84 L [2]
13-Jan-2015	0.24 L	83 L [2]
10-Feb-2015	0.25 L	82 L [2]
10-Mar-2015	0.23 L	78 L [3]

g/L = grams per liter; L = value < lower limit of normal range; Ref = reference range

Impression
This patient's increased bilirubin and anemia are probably related to his sickle cell disease and unlikely due to study drug since both the abnormal bilirubin and hemoglobin were present prior to starting BTDS.

Patient Number: 0015002
Study: BUP3031
Lab Abnormality: blood glucose decreased

This was a 14-year old girl with a history of pain due to sickle cell hemoglobin C disease. At baseline her blood glucose was normal at 3.3 mmol/L (normal 3.3 to 5.6 mmol/L) and remained within the normal range at weeks 2, 4 and 6. At week 8 her glucose was 2.9 mmol/L but returned to the normal range at weeks 12, 16, 20 and end of treatment. Given the decreased glucose was an isolated event with previous and subsequent blood glucoses in the normal range, this event was not related to study drug.

Patient Number: 0009006
Study: BUP3031
Lab Abnormality: Neutrophils absolute decreased

This was a 12 year old 55 kg boy with a history of chronic low back pain enrolled in study BUP3031. His past medical history included: kidney stones, attention deficit hyperactivity disorder, abdominal pain, gastroesophageal reflux disease, gross hematuria, and irritable bowel syndrome. Prestudy opioids included: Vicodin (7.5/325 mg, BID).
The patient was taking the following medications from screening to the start of study: bupropion hydrochloride, nasal fluticasone propionate, montelukast sodium, citric acid, esomeprazole, melatonin, Vicodin, and macrogol. The patient was taking the following medications during the treatment period in addition to the previous listed medications: ibuprofen, azithromycin, lenoltec with codeine, hyoscyamine sulfate, phenazopyridine hydrochloride, hydrochlorothiazide, other drugs for functional bowel disorders, potassium citrate, lactulose, and magnesium citrate.

On 26-Mar-2014, the patient began the screening period. On 07-Apr-2014, the patient began treatment with open-label BTDS 5. The patient's BTDS dose was increased to BTDS 10 on 14-Apr-2014 and further up-titrated to BTDS 20 on 29-Aug-2014. The patient's BTDS dose was down-titrated to BTDS 10 on 23-Sep-2014, and down-titrated to BTDS 5 on 30-Sep-2014. On 06-0ct-2014, the patient removed the last BTDS 5 patch and completed the study on the same day. AEs reported for the patient during this study included upper respiratory infection and bladder spasm.

Relevant clinical laboratory tests are shown in the table below.

Patient BUP3031-2493A-0009006; Clinical Laboratory Test Results

Analysis Visit	Lab Date	Neutrophils Absolute (10^6/L) Ref: 1800-8000 [Toxicity Grade]
Screening	2014-03-26T11:15	2150, N [0]
End of Week 2	2014-04-21T09:10	3670, N [0]
End of Week 4	2014-05-05T11:30	2940, N [0]
Week 6	2014-05-19T09:40	1880, N [1]
Week 8	2014-06-03T09:43	1380, L [2]
Week 12	2014-07-01T14:44	3380, N [0]
Week 16	2014-07-28T14:10	3440, N [0]
Week 20	2014-08-25T15:20	2390, N [0]
EOT/Early DC	2014-09-22T14:30	1530, L [1]

DC = discontinuation; EOT = end of treatment; N=Normal, L=Test < Lower Limit of normal range or liter; Ref = reference range.

Impression
The reason for this patient's neutropenia is unclear but since the neutrophil count fluctuated while on BTDS it does not appear to be related to study drug. It is noted that at all times the absolute neutrophil count was above 1000 x 10^6/L.

Patient Number: 00027004
Study: BUP3031
Lab Abnormality: Decrease lymphocytes (grade 3), decreased neutrophils (Grade 4) and decreased white blood cells (Grade 4)

This was an 8 year old boy with a history of left partial hemipelvectomy for Ewing's sarcoma and history of chemo induced neutropenia. The patient was receiving chemotherapy with etoposide, ifosfamide and mesna during the study. The decrease in white blood cells was due to his chemotherapy and not from BTDS.

7.4.3 Vital Signs

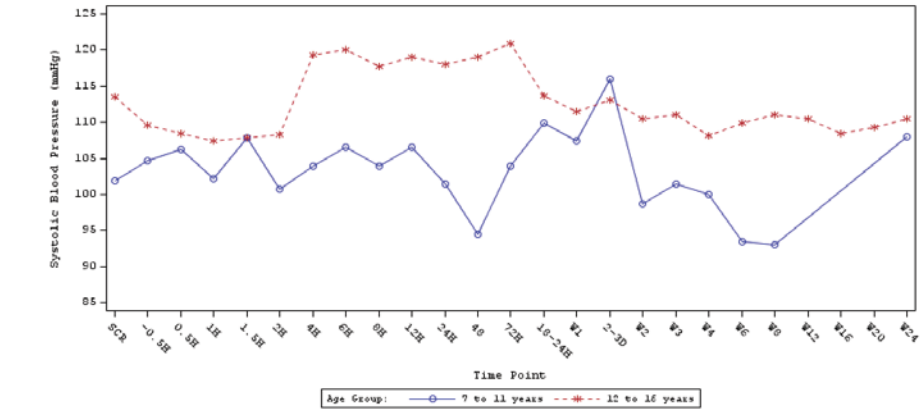
Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) and SpO_2 were recorded at: screening, before and after initial BTDS application, and before and after any up-titration. Vital signs (not SpO_2) were recorded at all scheduled and unscheduled visits.

Serial assessments of vital signs and SpO_2 were obtained at the following times:

- Vital signs and SpO_2 were recorded 30 minutes before and 30, 60, 90, and 120 minutes after (1) the initial BTDS application (for all patients) and (2) any BTDS up-titration performed at the clinical site.
- For inpatients only, vital signs and SpO_2 were also recorded at 4, 6, 8, 12, 24, 48, and 72 hours after (1) the initial BTDS application and (2) after any BTDS up titration.

Review of the vital signs revealed no evidence of significant changes in mean systolic blood pressure (Figure 3), diastolic blood pressure (Figure 4) or heart rate (Figure 5). There were variations throughout the study more noticeable in the 7 to 11 year age group due to the small number of subjects.

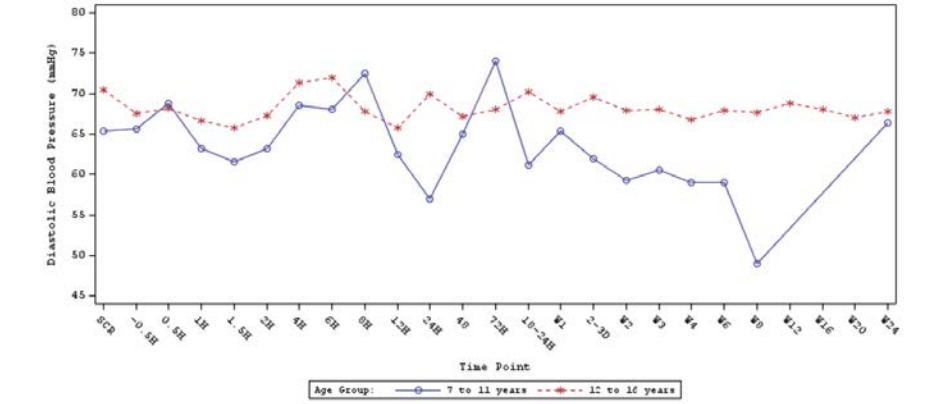
Figure 3: Mean Systolic Blood Pressure over Time



Note: SCR=Screening; -0.5H=Start of BTDS, Predose (30 min prior); 0.5H=Start of BTDS, 0.5 Hour Postdose; 1H=Start of BTDS, 1 Hour Postdose; 1.5H=Start of BTDS, 1.5 Hours Postdose; 2H=Start of BTDS, 2 Hours Postdose; 4H=Start of BTDS, 4 Hours Postdose; 6H=Start of BTDS, 6 Hours Postdose; 8H=Start of BTDS, 8 Hours Postdose; 12H=Start of BTDS, 12 Hours Postdose; 24H=Start of BTDS, 24 Hours Postdose; 48H=Start of BTDS, 48 Hours Postdose; 72H=Start of BTDS, 72 Hours Postdose; 18-24H=18-24 Hours After Start of BTDS; W1=End of Week 1; 2-3D=2-3 Days After End of Week 1; W2=End of Week 2; W3=End of Week 3; W4=End of Week 4; W6=Week 6; W8=Week 8; W12=Week 12; W16=Week 16; W20=Week 20; W24=Week 24/EOT/Early DC.
SAS program: F14_03_05_02_VS.sas, 09JUN2016 22:41

Source: CSR, p. 1370

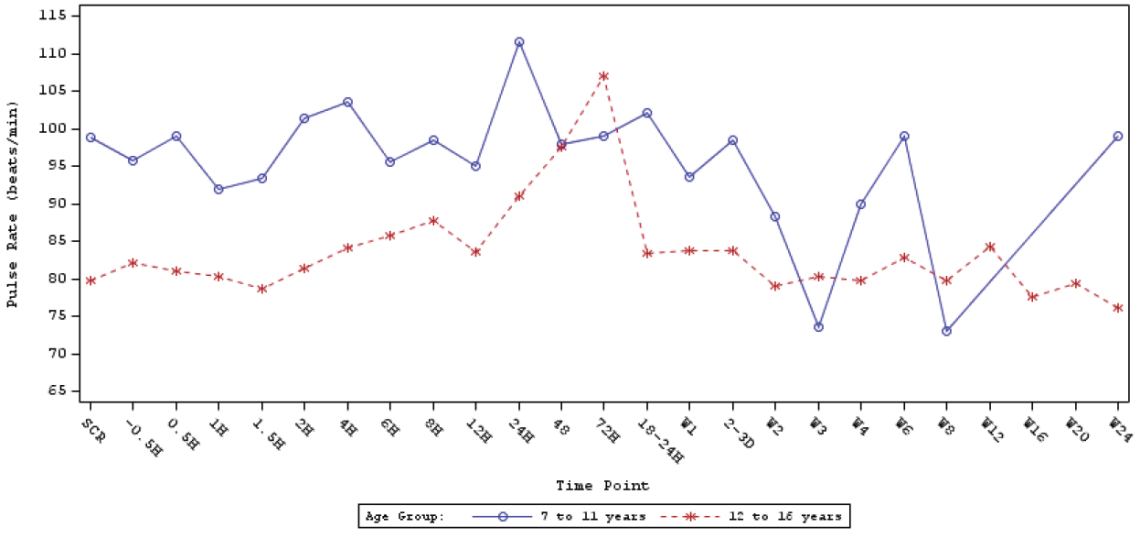
Figure 4: Mean Diastolic Blood Pressure over Time



Note: SCR=Screening; -0.5H=Start of BTDS, Predose (30 min prior); 0.5H=Start of BTDS, 0.5 Hour Postdose; 1H=Start of BTDS, 1 Hour Postdose; 1.5H=Start of BTDS, 1.5 Hours Postdose; 2H=Start of BTDS, 2 Hours Postdose; 4H=Start of BTDS, 4 Hours Postdose; 6H=Start of BTDS, 6 Hours Postdose; 8H=Start of BTDS, 8 Hours Postdose; 12H=Start of BTDS, 12 Hours Postdose; 24H=Start of BTDS, 24 Hours Postdose; 48H=Start of BTDS, 48 Hours Postdose; 72H=Start of BTDS, 72 Hours Postdose; 18-24H=18-24 Hours After Start of BTDS; W1=End of Week 1; 2-3D=2-3 Days After End of Week 1; W2=End of Week 2; W3=End of Week 3; W4=End of Week 4; W6=Week 6; W8=Week 8; W12=Week 12; W16=Week 16; W20=Week 20; W24=Week 24/EOT/Early DC.
SAS program: F14_03_05_02_VS.sas, 09JUN2016 22:41

Source: CSR, p. 1371

Figure 5: Mean Pulse Rate over Time



Note: SCR=Screening; -0.5H=Start of BTDS, Predose (30 min prior); 0.5H=Start of BTDS, 0.5 Hour Postdose; 1H=Start of BTDS, 1 Hour Postdose; 1.5H=Start of BTDS, 1.5 Hours Postdose; 2H=Start of BTDS, 2 Hours Postdose; 4H=Start of BTDS, 4 Hours Postdose; 6H=Start of BTDS, 6 Hours Postdose; 8H=Start of BTDS, 8 Hours Postdose; 12H=Start of BTDS, 12 Hours Postdose; 24H=Start of BTDS, 24 Hours Postdose; 48H=Start of BTDS, 48 Hours Postdose; 72H=Start of BTDS, 72 Hours Postdose; 18-24H=18-24 Hours After Start of BTDS; W1=End of Week 1; 2-3D=2-3 Days After End of Week 1; W2=End of Week 2; W3=End of Week 3; W4=End of Week 4; W6=Week 6; W8=Week 8; W12=Week 12; W16=Week 16; W20=Week 20; W24=Week 24/EOT/Early DC.

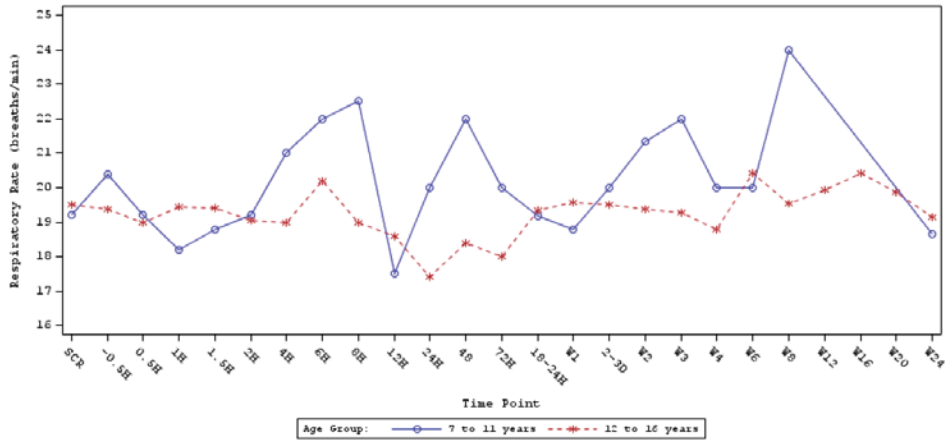
Source: CSR, p. 1373

Clinically significant respiratory rate, and SpO_2 were defined as follows:

- Respiratory rate of ≤ 10 breaths per minute for patients aged 12 to 16 years, ≤ 12 breaths per minute for patients aged 7 to 11 years
- Pulse oximetry SpO_2 ≤ 90% for patients without cyanotic heart disease.

There were no patients with clinically significant respiratory depression during the study. Figure 6Figure 7 presents the mean respiratory rate during the study and Figure 7 the mean pulse oximetry during the study.

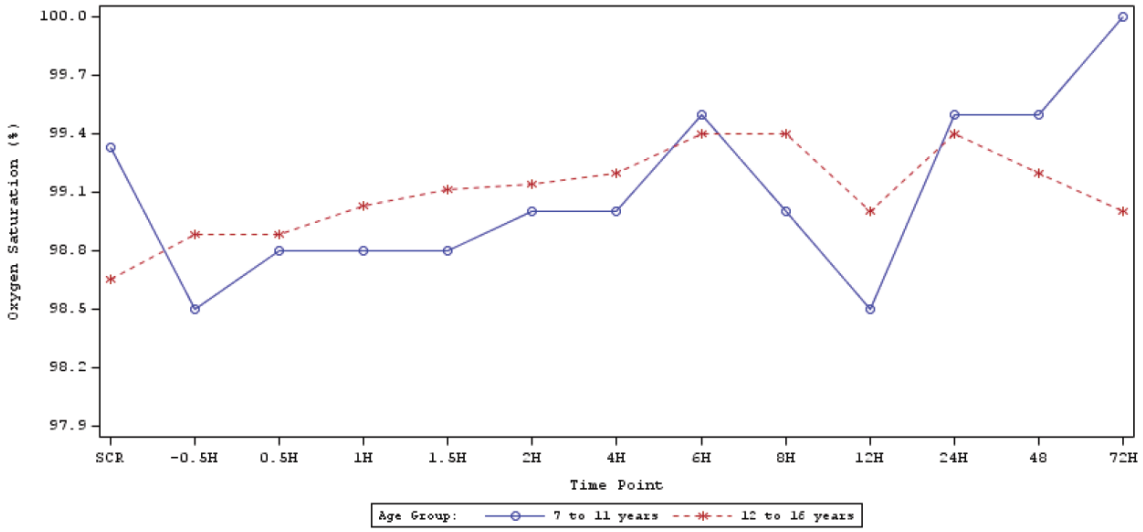
Figure 6: Mean Respiratory Rate over Time



Note: SCR=Screening; -0.5H=Start of BTDS, Predose (30 min prior); 0.5H=Start of BTDS, 0.5 Hour Postdose; 1H=Start of BTDS, 1 Hour Postdose; 1.5H=Start of BTDS, 1.5 Hours Postdose; 2H=Start of BTDS, 2 Hours Postdose; 4H=Start of BTDS, 4 Hours Postdose; 6H=Start of BTDS, 6 Hours Postdose; 8H=Start of BTDS, 8 Hours Postdose; 12H=Start of BTDS, 12 Hours Postdose; 24H=Start of BTDS, 24 Hours Postdose; 48H=Start of BTDS, 48 Hours Postdose; 72H=Start of BTDS, 72 Hours Postdose; 18-24H=18-24 Hours After Start of BTDS; W1=End of Week 1; 2-3D=2-3 Days After End of Week 1; W2=End of Week 2; W3=End of Week 3; W4=End of Week 4; W6=Week 6; W8=Week 8; W12=Week 12; W16=Week 16; W20=Week 20; W24=Week 24/EOT/Early DC.

Source: CSR, p. 1372

Figure 7: Mean Pulse Oximetry over Time



Note: SCR=Screening; -0.5H=Start of BTDS, Predose (30 min prior); 0.5H=Start of BTDS, 0.5 Hour Postdose; 1H=Start of BTDS, 1 Hour Postdose; 1.5H=Start of BTDS, 1.5 Hours Postdose; 2H=Start of BTDS, 2 Hours Postdose; 4H=Start of BTDS, 4 Hours Postdose; 6H=Start of BTDS, 6 Hours Postdose; 8H=Start of BTDS, 8 Hours Postdose; 12H=Start of BTDS, 12 Hours Postdose; 24H=Start of BTDS, 24 Hours Postdose; 48H=Start of BTDS, 48 Hours Postdose; 72H=Start of BTDS, 72 Hours Postdose; 18-24H=18-24 Hours After Start of BTDS; W1=End of Week 1; 2-3D=2-3 Days After End of Week 1; W2=End of Week 2; W3=End of Week 3; W4=End of Week 4; W6=Week 6; W8=Week 8; W12=Week 12; W16=Week 16; W20=Week 20; W24=Week 24/EOT/Early DC.

Source: CSR, p. 1376

7.4.4 Electrocardiograms (ECGs)

Refer to Section 7.3.5 discussion of QT prolongation

7.4.5 Special Safety Studies/Clinical Trials

None

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

No analyses were performed.

7.5.2 Time Dependency for Adverse Events

No analyses were performed

7.5.3 Drug-Demographic Interactions

No analyses were performed.

7.5.4 Drug-Disease Interactions

No analyses were performed.

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.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies done

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Butrans is an opioid with a known risk for overdose and drug abuse. In Study 3103 no abuse of study drug by patients was reported but the numbers are too small to draw any definitive conclusions. There was one incident of drug diversion described below.

Patient Summary of Drug Diversion
Patient Number: 0009014
Study: BUP3031
Event: Suspected or Confirmed Diversion

A 15-year-old boy with a history of abdominal pain was enrolled in Study 3031. Prestudy medications included hydrocodone/acetaminophen and oxycodone/acetaminophen. The patient started treatment with BTDS 5 and nine days later during a follow-up visit to the study site, the investigator discovered that the BTDS 10 patch was missing. The patient denied opening and removing the patch. The patient's mother informed the investigator that they had recently moved houses and had several people moving in and out. The investigator assessed that the missing drug was due to drug diversion and it was reported that the drug was stolen. The patient was discontinued from the study due the suspected drug diversion.
Impression
Based on the history provided, the missing drug was attributed to the drug being stolen. It is impossible to know for certain whether the patient was involved in taking the drug. However, the exact circumstances surrounding the missing drug do not change the underlying concern about the potential for opioids to be misused and diverted. Diversion of opioids is not an unexpected event with opioids and this one report does not change the overall benefit-risk assessment.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Purdue conducted a safety analysis of postmarketing pediatric adverse event reports for BuprenorphineTransdermal System captured in Purdue Pharma's International Pharmacovigilance Adverse Event System (IPAES) Database, Argus Safety. Purdue estimated that the cumulative global patient exposure since the time of first approval (July 2003 in Denmark) through December 2015, estimated on the basis that one patch is used for 7 days, was (b) (4) patient months. Purdue identified a total of 54 pediatric cases (10 serious and 44 non-serious) involving 131 adverse events (18 serious & 113 non-serious) through 05 December 2016. Eighteen of the cases (33%) were from the United States and 12 cases (22%) were from the UK. There were 24 cases in the age group 13 to < 18 years; 23 cases in the age group 1 to <13 years; 6 cases in the age group 1 month to < 1year and; 1 case in a neonate (<1 month).

The most frequently reported adverse events for the 54 cases in descending order were: application site pruritus 8; application site erythema 6; accidental exposure to

product by child 5; off label use 5; vomiting 5; somnolence 4; drug ineffective 3; nausea 3 and; product adhesion issue 3.

There were ten serious adverse event reports that contained a total of 18 adverse events: coma 1; drug abuse 1; overdose 1; hallucination 1; headache 1; drug abuse 1; bradypnea 1; vomiting 1; seizure 1; accidental exposure to product by child 1 excessive eye blinking 1; 1acial spasm 1; depressed level of consciousness 1; somnolence 1; accidental exposure to product by child 2; aneurysm arteriovenous 1 and; fetal exposure during pregnancy 1.

There were two case reports resulting in fatal outcomes: a newborn with congenital anomaly exposed to buprenorphine and morphine, and a child that ate Butrans and died. A newborn with a fatal congenital anomaly was exposed in utero to buprenorphine, morphine sulfate, clonidine, gabapentin, and paracetamol/codeine. The baby was born with arteriovenous aneurysm to a 39-year old female who was taking medications for chronic back pain. The baby was delivered at term by caesarean and died a few days later. The other case involved a male child who, reportedly, ate Butrans and died. However, Purdue noted that, upon follow up, the reporter stated that the previous information was relayed to her by a third party, a lawyer, and that she was not sure of the person's name or date of incident.

The review of pediatric postmarketing adverse event reports by Purdue did not identify any new unexpected safety concerns. There were a few reports of drug overdose and abuse but this is not unexpected with an opioid.

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

The following preliminary labeling changes could be considered for Section 8.4:

> 8.4 Pediatric Use
> The safety and efficacy of Butrans in pediatric patients have not been established.
>
> Butrans has been evaluated in an open-label clinical trial of 41 pediatric patients, ages 7 to 16 years, with moderate to severe chronic pain. The study was designed to assess safety and pharmacokinetics; limited efficacy data were collected.

There is inadequate safety experience from study BUP3031 (n = 6 in the age range of 6-11 years and n = 35 in the age range of 7-12 years) to support a pediatric indication and pediatric dosing information. The most frequently observed adverse reactions in the clinical trial included local application site conditions, nausea, somnolence, dizziness, headache, constipation, and vomiting. Overall the safety profile for Butrans in pediatric patients was generally consistent with adults but the number of patients and exposure were limited.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting is scheduled for September 14, 2017 to discuss the following topics:

1. Concerns regarding the use of Butrans in pediatric patients
2. Whether there is adequate data to support adding information about the pediatric study to the labeling of Butrans

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/s/

ROBERT A LEVIN
09/11/2017

ROBERT B SHIBUYA
09/12/2017