Butrans® (buprenorphine) Transdermal System: Evaluation in the Pediatric Population

Joint Meeting of the Anesthetic and Analgesic Drug Products and the Drug Safety and Risk Management Advisory Committees

September 14, 2017

CC-1

Introduction

Craig Landau, MD
President and Chief Executive Officer
Purdue Pharma L.P.

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Key Commitments

- Purdue is not seeking a pediatric indication for Butrans
  - Data do not warrant an indication
- Purdue does not promote the use of opioids in children and will not promote the use of Butrans in children
- Purdue is committed to providing clinical data to inform appropriate opioid prescribing

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Pediatric Research Equity Act (PREA)

- In 2003, Congress enacted the Pediatric Research Equity Act (PREA), to require pediatric studies for certain drugs and establish a Pediatric Advisory Committee
- Prior to PREA, there was a paucity of data from pediatric patients and lack of information in drug labels
- "The purpose of the pediatric assessments under PREA is not to in any way broaden the use of the product, but to obtain data that will support the safe and effective use in pediatric patients that already use or could benefit from their use." [FDA Butrans Advisory Committee Briefing Document, 2017]

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Pediatric Research Equity Act (PREA) Requirement

- Butrans was approved by FDA in June 2010 with a postmarketing PREA requirement
- "Pharmacokinetic and safety study for the treatment of moderate to severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages 7-16."
  [FDA, 2010 Butrans Approval Letter]
- "The Agency had determined that for opioid analgesics, efficacy could be extrapolated from adults to pediatric patients as young as 2 years old because of similarity of the underlying disease process and the exposure response to buprenorphine in adults and pediatric patients."
  [FDA Butrans Advisory Committee Briefing Document, 2017]

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Agenda

Topic	Presenter
Introduction and Pediatric Study Context	Craig Landau, MD President and CEO Purdue Pharma L.P.
Regulatory History and Utilization of Opioids in Pediatric Patients	**Richard Fanelli, PhD** Head of Regulatory Affairs Purdue Pharma L.P.
Pediatric Clinical Trial	Stacy Baldridge, MSN, RN Pediatric Program Lead Purdue Pharma L.P.

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Regulatory History and Utilization of Opioids in Pediatric Patients

Richard Fanelli, PhD
Head of Regulatory Affairs
Purdue Pharma L.P.

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Product Description

- **Partial mu-opioid receptor agonist**
- **Schedule III, 7-day transdermal system available in 5, 7.5, 10, 15 and 20 mcg/hour**
- **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**
- **The Butrans U.S. Prescribing Information includes the Extended-Release/Long-Acting opioid boxed warning and a QTc prolongation warning**

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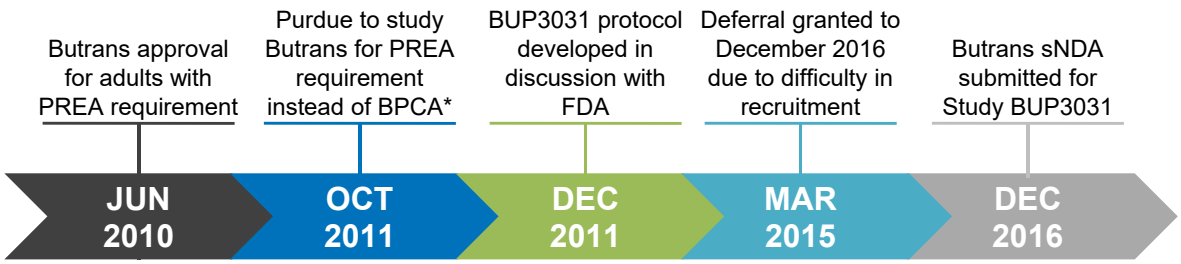
Regulatory History of PREA Commitment



*Best Pharmaceuticals for Children Act

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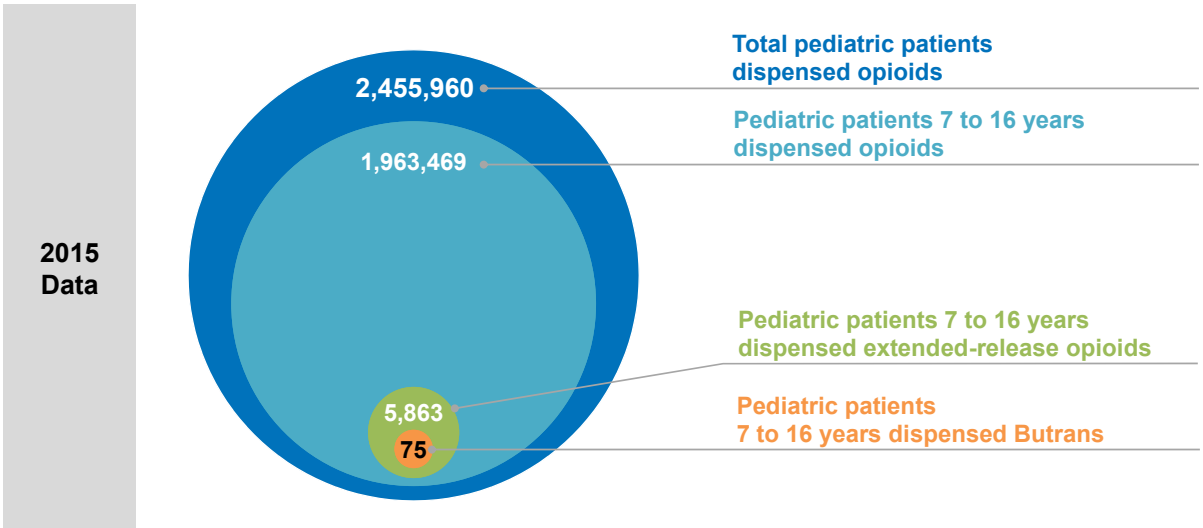
US Estimates of Pediatric Patients Ages 7 to 16 Years Dispensed Prescriptions for Opioids



Data Source: Symphony Health Solutions Integrated DataVerse (IDV) Years 2011-2015 (as reported in DHHS, FDA CDER, & OSE, 2016).

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Regulatory Summary

- As a result of the limited number of pediatric subjects available for study, the BUP3031 trial targeted a small number of patients
- Purdue is not requesting a pediatric indication
- Adding the pediatric patient experience for patients 12 to 16 years of age to the label will be informative to prescribers
- Purdue proposes describing the study results as an update to the Pediatric Use section
- Purdue has not promoted and will not promote Butrans for use in the pediatric population

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Agenda

Topic	Presenter
Introduction and Pediatric Study Context	**Craig Landau, MD** President and CEO Purdue Pharma L.P.
Regulatory History and Utilization of Opioids in Pediatric Patients	**Richard Fanelli, PhD** Head of Regulatory Affairs Purdue Pharma L.P.
Pediatric Clinical Trial	**Stacy Baldridge, MSN, RN** Pediatric Program Lead Purdue Pharma L.P.

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Pediatric Clinical Trial

Stacy Baldridge, MSN, RN
Pediatric Program Lead
Purdue Pharma L.P.

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BUP3031 Clinical Trial

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BUP3031 Protocol was Developed in Discussion with FDA

- **PREA requirement**
  - PK and safety study for the treatment of moderate to severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients 7 to 16 years of age
- **Primary objectives**
  - Characterize PK
  - Characterize safety
- **The study was completed prior to the September 2016 FDA Advisory Committee meeting that resulted in revised FDA recommendations for the study of opioids in pediatric patients**

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Key Inclusion Criteria

- **Aged 7 to 16 years with moderate to severe pain**
- **Anticipated to require continuous, around-the-clock, opioid treatment for at least 2 weeks**
- **Patients on opioids must have been taking:**
  - ≤40 mg/day morphine or equivalent if aged 7 to 11, or
  - ≤80 mg/day morphine or equivalent if aged 12 to 16
- **Incoming opioids were required to be tapered**
- **Patients with postoperative pain were included ≥48 hours after surgery**

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Key Exclusion Criteria

- Evidence of impaired renal or hepatic function
- History of seizures, increased intracranial pressure, sleep apnea, or paralytic ileus
- Cardiac conditions (structural disease, syncope, congestive heart failure, short/long QT syndromes, arrhythmias)
- Prolonged QTcB or QTcF or clinically significant findings on ECG /Holter
- Use of known, possible, or conditional QT prolonging medications
- History of substance abuse

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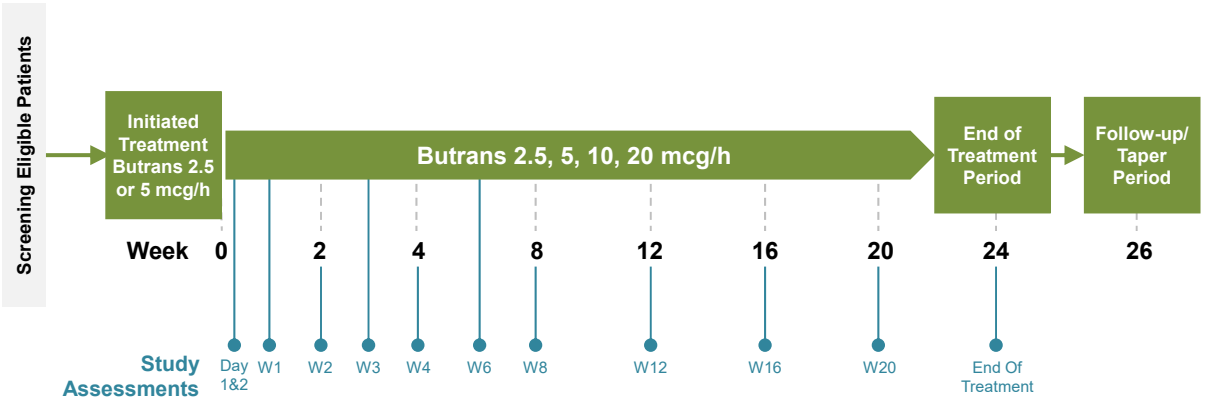
Open-Label Study Design with Flexible Dosing



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Open-Label Study Design with Flexible Dosing

- Patients were treated for up to 26 weeks
- 7 to 11 years: initiated treatment with Butrans 2.5 mcg/h
- 12 to 16 years: initiated treatment with Butrans 5 mcg/h
- Dose adjustments permitted based on tolerability, safety, pain intensity, and supplemental analgesic use
- Supplemental immediate release opioids or non-opioid medications were permitted

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Study Completer

A completer was defined as a patient who completed:

- 24 weeks of study drug dosing;

  Or

- At least 2 weeks of study drug dosing, had not met any of the discontinuation reasons and did not need additional treatment with an opioid medication at the minimum study drug dose;

  Or

- At least 2 weeks of treatment and was being tapered down from current Butrans dose in order to switch to another opioid analgesic and did not meet any of the discontinuation reasons

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Analgesic Trials in Pediatrics Are Challenging

- "Comparatively few children receive round-the-clock opioids for severe pain for time periods more than 4 weeks." [Berde et al, 2012]
- "Children are not treated with opioids very often and usually it's only for a limited period of time with close supervision by health care professionals." [CDER Conversation: Pediatric pain management option, 2015]
- Study design, lack of investigators, population challenges and the lack of potential study patients contribute to the difficulty of conducting such trials [Weisman, 2016]

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Recruitment Challenges – Investigators

- Few qualified sites
- Very few appropriate patients at each site
- Protocol-specific restrictions

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Recruitment Challenges – Patients

- **Few patients require opioids >2 weeks**
- **Protocol prohibited concomitant medications**
  - Including ondansetron, diphenhydramine, famotidine
- **Protocol dosing limits and required taper**

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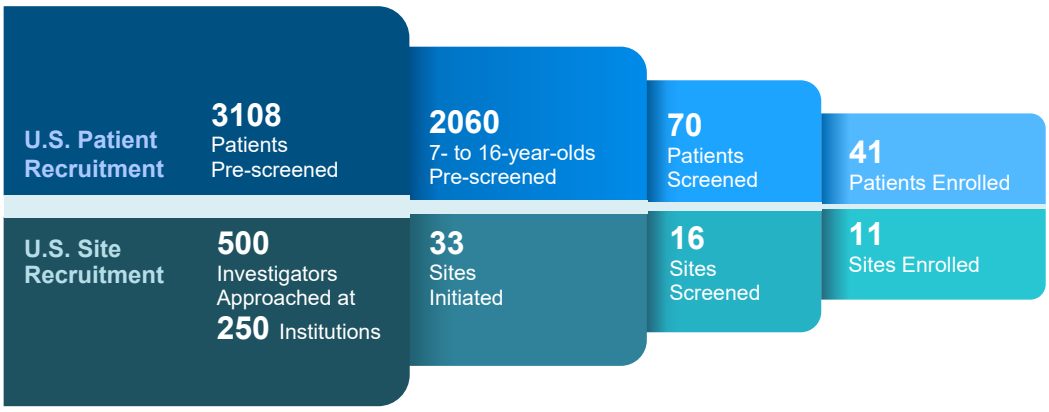
Recruitment Strategy and Challenges



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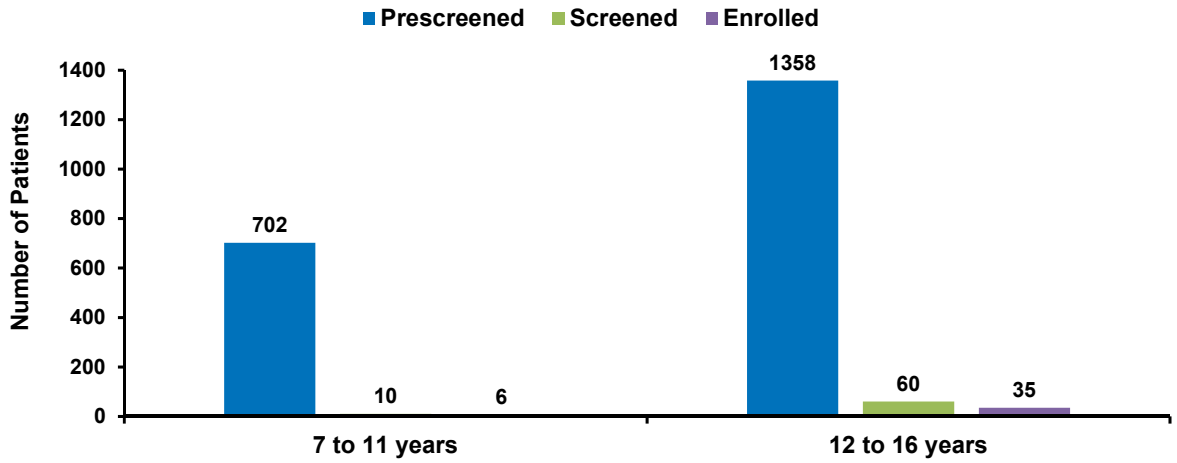
Patients Pre-screened, Screened and Enrolled were Predominantly 12 to 16 Years Old



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Patient Disposition by Age Group

Pre-screened
N=3108

Screened
N=70
7 to 11 years **n=10**
12 to 16 years **n=60**

Enrolled
N=41
7 to 11 years **n=6**
12 to 16 years **n=35**

Defined as Study Completer
N=23
7 to 11 years **n=2**
12 to 16 years **n=21**

Pre-screen Failures
N=3038

Top Reasons:	
Age requirement	31%
Duration of therapy	28%
Prohibited medications	20%

Screen Failures
N=29
7 to 11 years **n=4**
12 to 16 years **n=25**

Subject Choice	3
Failed Inclusion/ Exclusion	25
Adverse Event	1

Discontinued
N=18
7 to 11 years **n=4**
12 to 16 years **n=14**

Adverse Event	11
Subject Choice	3
Administrative	2
Lack of Effect	1
Diversion	1

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Demographics and Baseline Characteristics

	7 to 11 years N=6	12 to 16 years N=35	Total N=41
Age in years: Mean (SD)	10.3 (1.2)	14.6 (1.3)	14.0 (2.0)
Female, n (%)	3 (50)	23 (66)	26 (63)
Race, n (%)			
White	3 (50)	18 (51)	21 (51)
Black or African American	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)
Min, Max	22.2, 42.2	29.4, 111.5	22.2, 111.5
Prior opioid use	6 (100)	33 (94)	39 (95)

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Primary Pain Condition at Study Entry

Number of Patients	Primary Pain Condition
8	Back Pain
6	Migraine
5	Sickle Cell Anemia
8	Abdominal Pain (2), Crohn's Disease (2), Gun Shot Wound (2), Musculoskeletal Pain (2)
14	1 patient each Amniotic Band Syndrome, Arthralgia, Arthritis, Chest Wall Operation, Epstein-Barr Virus Antibody Positive, Hemipelvectomy, Hemoglobin C Disease, Juvenile Arthritis, Limb Crushing Injury, Osteonecrosis, General Body Pain, Pain In Extremity, Pelvic Pain, Systemic Sclerosis

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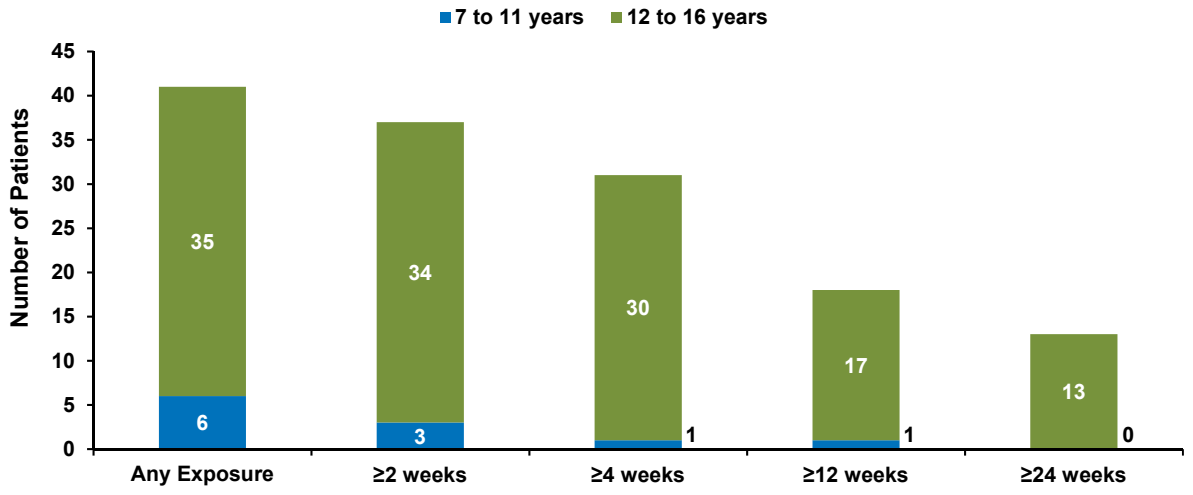
Butrans Exposure



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Butrans Exposure by Dose Strength

	Butrans Dose			
	2.5 mcg/h	5 mcg/h	10 mcg/h	20 mcg/h
Any exposure				
Age 7 to 11 years	6	5	1	0
Age 12 to 16 years	15	35	24	13
At least 2 weeks exposure				
Age 7 to 11 years	1	2	0	0
Age 12 to 16 years	6	19	18	10
At least 4 weeks exposure				
Age 7 to 11 years	1	1	0	0
Age 12 to 16 years	1	9	10	6

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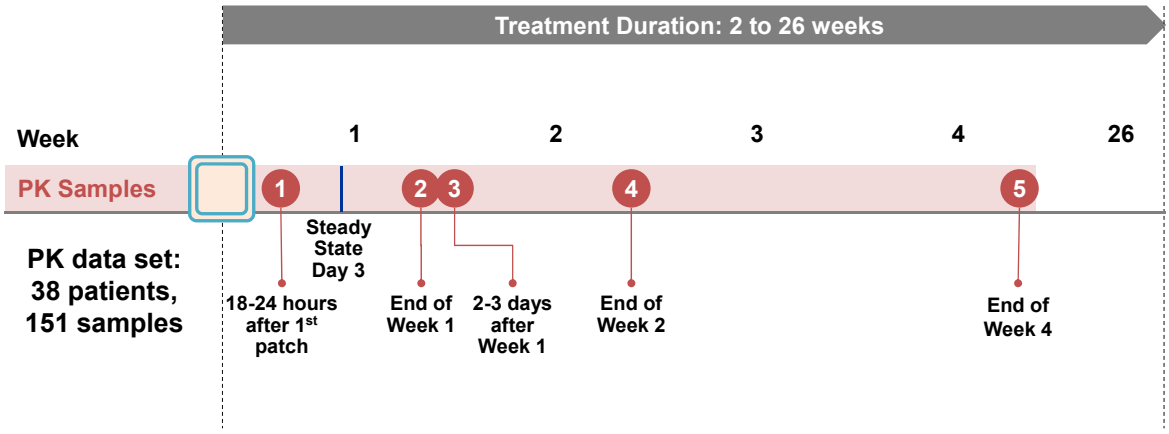
BUP3031 Pharmacokinetics

CC-31

PK Sampling



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Pediatric Population Pharmacokinetics Modeling

- Consistent with FDA 2014 guidance
- Leveraged population PK from adults
- Covariate modeling: clearance and volume parameters scaled allometrically to pediatric body weight
- The pediatric population PK of buprenorphine from Butrans in patients 7 to 16 years of age was described by a 2-compartment model with sequential zero- and first-order absorption from patch

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Pediatric Population Pharmacokinetics Modeling (cont.)

- Simulations were performed to identify pediatric dose expected to achieve target exposure in adults
- Pediatric ideal body weight was found to be the most important factor influencing buprenorphine PK following administration of Butrans

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Initial Pediatric Dose to Target Adult Exposure

Predicted Buprenorphine AUCss (ng.hr/mL) in Pediatric Patients to Target Adult Butrans 5 mcg/h exposure (17 ng.hr/mL)

Age (Years)	Ideal Body Weight (kg)	Dose (mcg/h)	AUCss, ng.hr/mL (Range)
7-11	34.4	2.5	14 (9.1-22.6)
12-16	56.6	5	19.8 (12.5-31.1)
Target adult Butrans exposure			
>18	70	5	17

Note: Results are presented as Median (95% prediction interval)

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Clinical Pharmacology Conclusions

- For children 12 to 16 years of age who are at least 50 kg, the PK data suggest that no dose modification is needed from adult dosing
- For children 12 to 16 years of age who are less than 50 kg, the PK data suggest that half of the adult dose should be used

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BUP3031 Safety

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Safety – A Primary Study Objective

- **Safety assessments included**
  - Adverse events
  - Vital signs, including hemoglobin-oxygen saturation
  - Clinical laboratory tests
  - Somnolence (University of Michigan Sedation Scale)
  - Conventional 12-lead ECGs
  - 24-hour digital 12-lead ECGs (Holter monitor)

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Overall Adverse Event Summary (Safety Population)*

	7 to 11 years N=6 n (%)	12 to 16 years N=35 n (%)
Any AE	6 (100)	26 (74)
Mild	0	12 (34)
Moderate	4 (67)	9 (26)
Severe	2 (33)	5 (14)
Related AE**	5 (83)	16 (46)
AE leading to treatment discontinuation	3 (50)	8 (23)
Serious AE	4 (67)	4 (11)
Deaths	0	0

* For this presentation, adverse events are defined as any event reported by the investigator from the time of initiation of dosing through 7 days after drug discontinuation
** A related event is any adverse event considered by the investigator to be caused by the study drug

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Most Frequently Reported AEs (≥10% of Patients)

	7 to 11 years N=6 n (%)	12 to 16 years N=35 n (%)	Total N=41 n (%)
Any AE	6 (100)	26 (74)	32 (78)
Nausea	1 (17)	7 (20)	8 (20)
Application site pruritus	0	7 (20)	7 (17)
Somnolence	1 (17)	5 (14)	6 (15)
Headache	1 (17)	5 (14)	6 (15)
Application site irritation	1 (17)	4 (11)	5 (12)
Sickle cell anemia with crisis	0	4 (11)	4 (10)
Vomiting	1 (17)	3 (9)	4 (10)

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Application Site Related Adverse Events

- **11 patients experienced application site related adverse events**
  - Most events were mild
- **Application site pruritus and application site irritation were the most common**
- **One patient withdrew from the study due to a single event of application site irritation**

CC-41

Serious Adverse Events

Safety – Serious Adverse Events (SAEs)

- **Eight patients (4 in each age group) reported SAEs**
- **The majority of events were attributed to the patients' underlying medical condition**
  - One SAE (first degree AV block) was reported by the investigator as unlikely to be related to study drug
  - The remaining SAEs were reported by the investigator as not related to the study drug

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Serious Adverse Events in Patients 7 to 11 Years

Age/Sex	Verbatim Term	Severity	Relationship to Study Drug*	Study Drug Action Taken/ Other Action Taken
11-year-old male	Appendicitis	Severe	Not related	None/ Treatment given
10-year-old female	Worsening anemia	Moderate	Not related	None/ Treatment given
	Crohn's exacerbation	Moderate	Not related	None/ Treatment given
	Malnutrition	Moderate	Not related	None/ Treatment given
11-year-old female	Hypersomnolence	Moderate	Not related	Stopped permanently/ Withdrawn from study
11-year-old female	First degree AV block	Moderate	Unlikely	Stopped permanently/ Withdrawn from study

*A related event is any adverse event considered by the investigator to be caused by the study drug

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Serious Adverse Events in Patients 12 to 16 years

Age/Sex	Verbatim Term	Severity	Relationship to Study Drug*	Study Drug Action Taken/ Other Action Taken
13-year-old male	Vaso-Occlusive Crisis (3 events)	Moderate (1) Severe (2)	Not related	None/ Treatment given
	Vaso-Occlusive Sickle Cell Pain Crisis	Severe	Not related	Dose increased/ Treatment given
16-year-old female	Vaso-Occlusive Crisis	Moderate	Not related	None/ Treatment given
	Vaso-Occlusive Crisis	Moderate	Not related	Stopped permanently/ Treatment given
16-year-old female	Suspected worsening of chronic osteomyelitis	Mild	Not related	None/ Treatment given
13-year-old male	Exacerbation of migraine pain	Severe	Not related	Stopped permanently/ Treatment given

*A related event is any adverse event considered by the investigator to be caused by the study drug

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Adverse Events Leading to Study Discontinuation

- 5 protocol-mandated discontinuations due to ECG findings (1 SAE)
- 3 serious adverse events: exacerbation of migraine pain, vaso-occlusive crisis, and hypersomnolence
- 3 non-serious adverse events: increased migraine pain, worsening pain due to neuroma, and irritation at patch site

CC-46

ECG, Vital Sign, and Laboratory Findings

Electrophysiology – Monitoring

- **A thorough QT study of Butrans in adults showed that supratherapeutic doses of 40 mcg/h resulted in prolongation of the QT interval**
- **In BUP3031, patients with cardiac abnormalities or those receiving medicines that had known or possible association with QTc prolongation were excluded**
- **ECG monitoring was performed throughout the study**
- **Protocol criteria for cardiac parameters and discontinuation requirements were conservative**

CC-48

Electrophysiology – Protocol Mandated Discontinuations

Age Sex Weight	Protocol ECG Parameter Exceeded	Baseline Prior to Treatment	ECG Finding	Butrans Dose (mcg/h)	Treatment Day
13 years male 38 kg	QTcB >480 ms	QTcB = 441 ms QTcF = 403 ms	QTc prolongation: QTcB = 489 ms QTcF = 451 ms	10	28
16 years female 57 kg	QTcB ≥50 ms increase from baseline	QTcB = 409 ms QTcF = 418 ms	QTc prolongation: QTcB = 469 ms QTcF = 459 ms	10	11
15 years female 112 kg	QRS duration >90 ms	QRS = 86 ms	QRS prolongation: 95 ms	20	55
11 years female 35 kg	PR >180 ms	PR = 144 ms	1st degree AV block (SAE): PR interval = 196 ms	5	8
10 years female 22 kg	HR >130 bpm	HR = 116 bpm	Sinus tachycardia: HR = 131 bpm	5	9

CC-49

Vital Signs – No Clinically Significant Changes

- No clinically significant changes in blood pressure or pulse
- No patients with treatment-emergent clinically significant respiratory depression
- No treatment-emergent clinically significant SpO2 events

CC-50

Laboratory Assessments

- **Majority stayed within the normal range for hematologic and blood chemistry values during study**
- **3 patients had laboratory toxicity grades ≥3* after baseline:**
  - 8-year-old male: low lymphocytes, neutrophils, and white blood cells (Ewing's Sarcoma and chemotherapy)
  - 13-year-old male: low hemoglobin (sickle cell anemia)
  - 12-year-old female: single elevated ALT (213 [5-30]) and AST (192 [0-36]) that returned to normal while on study drug

* Toxicity grading is based on the National Cancer Institute Common Toxicity Criteria, Version 2

CC-51

Safety Summary

- **No new safety issues specific to pediatric patients**
- **The reported adverse events for the 12- to 16-year age group were consistent with the known safety profile of Butrans observed in adult clinical trials and post marketing experience**
- **Insufficient data to draw conclusions in the 7- to 11-year age group**

CC-52

Study Conclusions

- **Pharmacokinetics**
  - For children 12 to 16 years of age who are at least 50 kg, the PK data suggest that no dose modification is needed from adult dosing
  - For children 12 to 16 years of age who are less than 50 kg, the PK data suggest that half of the adult dose should be used
- **Safety**
  - No new safety issues identified

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Available to Answer Questions

Topic	Presenter
Questions Moderator	**Stacy Baldridge, MSN, RN** Pediatric Program Lead
Purdue Respondents	**Richard Fanelli, PhD** Head of Regulatory Affairs **Ram Kapil, PhD** Clinical Pharmacology Lead **Marc Cataldo, PharmD** Medical Affairs Lead **Paul Coplan, ScD, MBA, FISPE** Epidemiology Lead
External Respondent	**Ramesh Iyer, MD** Attending Electrophysiologist, Children's Hospital of Philadelphia Professor of Clinical Pediatrics Perelman School of Medicine at the University of Pennsylvania

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Backup Slides Shown

CC-55

PK in Patients with Cardiac AEs

NONMEM ID	Weight (kg)	Age (year)	First Dose mcg/hr	Last Dose mcg/hr	CL/F_i (L/hr)	Observed Cmax (pg/mL)	AUCss LD* (ng*hr/mL)	AUCss 5* (ng*hr/mL)	Cardiac Adverse Events
14	38.2	13	5.0	10.0	276	126	36.3	18.1	QTprolong>480
31	22.2	10	2.5	5.0	108	118	46.3	46.3	sinus tachycardia
33	34.7	11	2.5	5.0	159	259	31.4	31.4	AV block
34	111.5	15	5.0	20.0	311	136	64.3	16.1	QRS prolongation
38	56.5	16	5.0	10.0	215	462	46.4	23.2	QT prolong QTcB increase>50 from base

- **PK in adults at 40 mcg/hr**
- **Cmax = 931 pg/mL**
- **AUCss = 116.5 ng.hr/mL**

AUCss = predicted AUCss (ng*hr/mL) for BUP3031 patients using individual post-hoc CL/F estimates.
*AUCss LD = AUCss using Last Dose mcg/hr
*AUCss 5 = AUCss using BTDS 5 mcg/hr

CP-13

Predicted Steady-State AUCss (ng*hr/mL) for Pediatric Patients in Study 3031

Target Adult Butrans 5 mcg/h exposure (17 ng.hr/mL)

NONMEM ID	Weight (kg)	Age (year)	First Dose mcg/hr	Last Dose mcg/hr	CL/F_1 (L/hr)	AUCss LD* (ng*hr/mL)	AUCss 5* (ng*hr/mL)
7	25.2	8	2.5	2.5	135	18.5	37.0
31	22.2	10	2.5	5	108	46.3	46.3
10	31.3	11	2.5	5	203	24.6	24.6
33	34.7	11	2.5	5	159	31.4	31.4
41	42.2	11	2.5	5	201	24.8	24.8
12	62.7	12	5	10	165	60.5	30.2
21	54.9	12	5	10	276	36.2	18.1
32	70.3	12	5	10	188	53.1	26.5
14	38.2	13	5	10	276	36.3	18.1
18	71.4	13	5	10	309	32.4	16.2
37	104.7	13	5	20	265	75.4	18.8
39	46.8	13	5	5	194	25.8	25.8
40	29.4	13	5	20	198	101	25.2
1	44.4	14	5	5	265	18.9	18.9
3	58.2	14	5	2.5	183	13.7	27.3
6	53	14	5	2.5	248	10.1	20.2
20	63	14	5	5	232	21.5	21.5
25	59.9	14	5	5	257	19.4	19.4
26	75.3	14	5	5	238	21	21
30	60.3	14	5	5	252	19.8	19.8
2	60.8	15	5	20	321	62.3	15.6
8	60	15	5	2.5	220	11.4	22.7
11	89.7	15	5	20	263	76.2	19
22	82.6	15	5	5	278	18	18
23	77.6	15	5	20	298	67.1	16.8
27	54.9	15	5	10	254	39.3	19.7
28	76.2	15	5	5	311	16.1	16.1
29	55.8	15	5	10	345	29	14.5
34	111.5	15	5	20	311	64.3	16.1
5	46.5	16	5	2.5	250	10	20
13	95.2	16	5	20	314	63.8	15.9
15	65.5	16	5	5	336	14.9	14.9
16	53.5	16	5	20	253	79.2	19.8
19	53.5	16	5	10	278	36	18
24	56.2	16	5	10	376	26.6	13.3
35	56.9	16	5	10	321	31.1	15.6
36	96.4	16	5	20	310	64.5	16.1
38	56.5	16	5	10	215	46.4	23.2

AUCss = predicted AUCss (ng*hr/mL) for BUP3031 patients using individual post-hoc CL/F estimates. *AUCss 5 = AUCss using BTDS 5 mcg/hr. *AUCss LD = AUCss using BTDS Last Dose mcg/hr.

CP-25

Predicted Steady-State AUCss (ng*hr/mL) Summary for Pediatric Patients (12-16 Years) in Study BUP3031

	AUCss 5* (ng*hr/mL)
N	33
Mean	19.5
SD	4.0
Coefficient of variation (%)	20.7
Minimum	13.3
Median	18.9
Maximum	30.2
GeoMean	19.5

17 ng.hr/mL
(Target Adult Butrans 5 mcg/h exposure)

AUCss = predicted AUCss (ng*hr/mL) for BUP3031 patients using individual post-hoc CL/F estimates.
*AUCss 5 = AUCss using BTDS 5 mcg/hr

CP-24

Purdue Analysis: Adverse Events of Interest

Narrow

- ECG QT interval abnormal
- ECG QT prolonged
- long QT syndrome
- long QT syndrome congenital
- torsade de pointes
- ventricular tachycardia

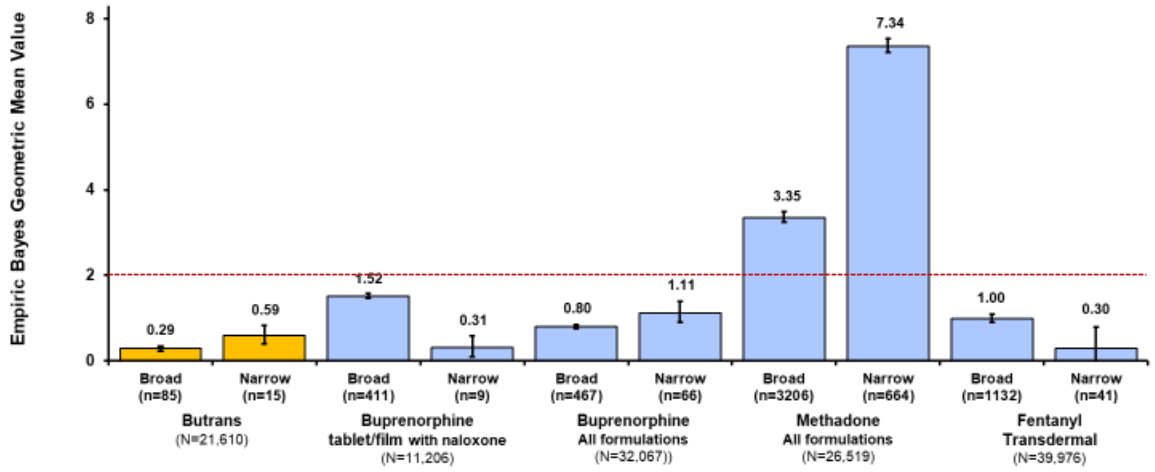
Broad

- All narrow scope terms
- cardiac arrest
- cardiac death
- cardiac fibrillation
- cardio-respiratory arrest
- electrocardiogram repolarization abnormality
- electrocardiogram U-wave abnormality
- loss of consciousness
- sudden cardiac death
- sudden death
- syncope
- ventricular arrhythmia
- ventricular fibrillation
- ventricular flutter
- ventricular tachyarrhythmia

BA-93

Postmarketing Cardiac Arrhythmic Adverse Event Reports Relative to All AEs in FDA Adverse Event Reporting System

1969 to 2015



Source: Sessler et al. Postgraduate Medicine 2017
90% CI shown. A lower confidence interval value of ≥ 2 indicates a disproportionate number of cardiac arrythmia events
Total FAERS AE report cases = 8,270,285

BA-90

Analysis of Torsade de Pointes and QT-prolongation AEs in WHO Global Safety Report Database [VigiBase]

IC_{025}= Lower limit of the 95% informational component credibility interval
A value ≥0 (yellow higlight) indicates a disproportionate number of adverse event reports

Opioid Grouping	BUPRENORPHINE								METHADONE	
	All Formulations		All Transdermal		Butrans patch 5-20 mcg/hour		Transtec® patch 35-70 mcg/hour		All formulations	
Cases with opioid mention	N= 16,266		N= 5095		N= 2118		N= 1638		N= 20,167	
	Count[1]	IC_{025}	Count	IC_{025}	Count	IC_{025}	Count	IC_{025}	Count	IC_{025}
Cases with Cardiac	386	-0.04	77	-0.88	20	-1.9	26	-1.07	2913	2.66
Arrhythmia event[3]										
-SMQ TdP/QT [narrow][4]	20	-1.63	5	-2.72	1	-5.68	1	-5.34	538	3.36
ECG QT interval abnormal	1	-2.93	0	-10.25	0	-10.1	0	-10.08	8	2.07
ECG QT prolonged	10	-1.9	5	-1.73	0	-12.54	1	-4.46	379	3.86
Long QT syndrome	2	-1.57	0	-10.54	0	-10.24	0	-10.19	14	2.51
Long QT syndrome congenital	0	-10.03	0	-10	0	-9.99	0	-9.99	0	-10.04
Torsade de pointes	7	-1.29	1	-4.66	1	-3.73	0	-11.27	260	4.62
Ventricular tachycardia	5	-3.17	0	-13.51	1	-4.63	0	-12.11	100	1.95

Total cases in VigiBase database from 1978 to Jun 2014 = 9,350,995 Analyses conducted by Uppsala Monitoring Center, Sweden

BA-95

Adult Thorough QTc Studies

Study	Dose	Difference of LS Means	90% CI	Maximum Mean QTc Increase	90% CI
BUP1011 (n=44)	BTDS 40	5.91 msec	(3.4, 8.4)	9.22 msec	(5.2, 13.3)
BUP1025 (n=58 to 63)	BTDS 40	6.64 msec	(4.4, 8.9)	9.16 msec	(6.5, 11.8)
	BTDS 80	9.50 msec	(7.2, 11.8)	11.46 msec	(8.8, 14.1)

Current FPI based on BUP1011:

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.
(Reference: FPI Section 12.2 Pharmacodynamics – Effects on Cardiac Electrophysiology)

SA-131

Pediatric QTc data (Bup3031)

	QTcB (Bazett's)	
	7-11 years (N=6)	**12-16 years (N=35)**
	mean change (msec)	**mean change** (msec)
mean (SD)	-4.16 (13.595)	5.82 (14.976)
median	-3.25	5.66
min, max	-21.7, 12.1	-30.0, 54.3
90%CI	(-15.34, 7.03)	(1.54, 10.10)
BTDS exposure	2.5- 10 mcg/hr	5- 20 mcg/hr

Reference: Bup3031 CSR Table 14.3.6.1

SA-133

Adult QTc Data (Adult Chronic Pain Studies, FDA Submission)

	Double-blind period							
	Placebo		BTDS 5		BTDS 10		BTDS 20	
	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change	Mean baseline value	Mean change
	N=496	NN= 476	N=448	NN=415	N=210	NN=203	N=639	NN=594
QTcB (msec)	411.6	1.1	414.4	1.3	410.7	0.4	413.9	3.2
QTcF (msec)	403.2	-1.0	404.4	1.0	402.9	1.6	404.1	3.8

(References: Appendix 11, Tables 6.1.1 and 6.1.2)
N=Number of subjects with a baseline
NN=number of subjects with a baseline and postbaseline value
Note: The baseline value is the value at screening. The mean changes were calculated based on the number of subjects who had ECGs at both baseline and the end of the open-label run-in or double-blind period.

SA-135

Body Weight Based Dosing Recommendation to Match Pediatric Exposure to Adults

Table 5: Predicted Buprenorphine AUCss (ng*hr/mL) in Pediatric Patients to Match Adult BTDS 10 exposure (34.1 ng*hr/mL) or Following BTDS 2.5, 5, 7.5, 10, 15, or 20 mcg/hr

Age (year)	IBW (kg)	Optimal Dose* (mcg/hr)	AUCss 2.5 (ng*hr/mL)	AUCss 5 (ng*hr/mL)	AUCss 7.5 (ng*hr/mL)	AUCss 10 (ng*hr/mL)	AUCss 15 (ng*hr/mL)	AUCss 20 (ng*hr/mL)
7	24.2	4.56	18.7	37.4	56.1	74.7	112	149
		(2.90,7.20)	(11.8,29.4)	(23.7,58.7)	(35.5,88.1)	(47.3,117)	(71.0,176)	(94.7,235)
8	28.4	5.14	16.6	33.2	49.8	66.4	99.6	133
		(3.27,8.11)	(10.5,26.1)	(21.0,52.2)	(31.5,78.2)	(42.0,104)	(63.1,156)	(84.1,209)
9	34.2	5.90	14.4	28.9	43.3	57.8	86.6	116
		(3.76,9.32)	(9.14,22.7)	(18.3,45.4)	(27.4,68.1)	(36.6,90.7)	(54.9,136)	(73.1,181)
10	40.5	6.70	12.7	25.4	38.2	50.9	76.3	102
		(4.27,10.6)	(8.05,20.0)	(16.1,40.0)	(24.2,59.9)	(32.2,79.9)	(48.3,120)	(64.4,160)
11	45.6	7.32	11.6	23.3	34.9	46.6	69.9	93.2
		(4.66,11.6)	(7.38,18.3)	(14.8,36.6)	(22.1,54.9)	(29.5,73.2)	(44.3,110)	(59.0,146)
12	50.5	7.91	10.8	21.6	32.3	43.1	64.7	86.2
		(5.03,12.5)	(6.83,16.9)	(13.7,33.9)	(20.5,50.8)	(27.3,67.7)	(41.0,102)	(54.6,135)
13	56.7	8.63	9.88	19.8	29.6	39.5	59.3	79.1
		(5.49,13.6)	(6.26,15.5)	(12.5,31.1)	(18.8,46.6)	(25.0,62.1)	(37.5,93.2)	(50.1,124)
14	57.2	8.68	9.82	19.6	29.5	39.3	58.9	78.5
		(5.53,13.7)	(6.22,15.4)	(12.4,30.8)	(18.7,46.3)	(24.9,61.7)	(37.3,92.5)	(49.7,123)
15	60.6	9.07	9.40	18.8	28.2	37.6	56.4	75.2
		(5.77,14.3)	(5.95,14.8)	(11.9,29.5)	(17.9,44.3)	(23.8,59.1)	(35.7,88.6)	(47.6,118)
16	61.5	9.17	9.30	18.6	27.9	37.2	55.8	74.4
		(5.84,14.5)	(5.89,14.6)	(11.8,29.2)	(17.7,43.8)	(23.6,58.4)	(35.3,87.6)	(47.1,117)
7-11	34.4	5.94	14.4	28.7	43.1	57.4	86.2	115
		(3.78,9.37)	(9.09,22.6)	(18.2,45.1)	(27.3,67.7)	(36.4,90.2)	(54.6,135)	(72.8,180)
12-16	56.6	8.61	9.90	19.8	29.7	39.6	59.4	79.2
		(5.48,13.6)	(6.27,15.5)	(12.5,31.1)	(18.8,46.6)	(25.1,62.2)	(37.6,93.3)	(50.1,124)

Results are presented as Median (95% prediction interval)

CP-3

Summary of Supplemental Pain Medication by Preferred Term (Safety Population)

	Age Group		
Preferred Term	7 to 11 years (N = 6) n (%)	12 to 16 years (N = 35) n (%)	Total (N = 41) n (%)
Any Concomitant Analgesic Supplemental Medication	6 (100)	34 (97)	40 (98)
Opioid	6 (100)	31 (89)	37 (90)
Vicodin	1 (17)	12 (34)	13 (32)
Tramadol	2 (33)	7 (20)	9 (22)
Oxycodone	2 (33)	4 (11)	6 (15)
Panadeine Co	1 (17)	4 (11)	5 (12)
Oxycocet	0	5 (14)	5 (12)
Morphine	0	4 (11)	4 (10)
Hydromorphone	0	3 (9)	3 (7)
Fentanyl	1 (17)	1 (3)	2 (5)
Hydromorphone Hydrochloride	1 (17)	2 (6)	3 (7)
Morphine Sulfate	0	2 (6)	2 (5)
Tramadol Hydrochloride	0	2 (6)	2 (5)
Lenoltec With Codeine No 1	0	1 (3)	1 (2)
Oxycodone Hydrochloride	0	1 (3)	1 (2)

EF-4