Development of Opioids in Pediatric Patients: Conclusions from FDA's September 15-16, 2016 Joint Meeting of the Anesthetic Analgesic and Drug Products Advisory Committee (AADPAC), Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC), and the Latest Agency Thinking on Studying Opioids in Children

Sharon Hertz, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
September 14, 2017
NDA 21306
Butrans Pediatric Supplement

Topics

- Pediatric drug development
- Pediatric analgesic development
- Pediatric analgesic study requirements
- Opioid analgesics and pediatric patients
- Advisory Committee meeting
- Moving forward

Pediatric Drug Development
General Principles

- Children should have access to products that have been appropriately evaluated
- Thoughtful drug development and inclusion of children in trials is critical to pediatric health

Current Pediatric Drug Legislation

- Best Pharmaceuticals for Children Act (BPCA) (2002)

- Pediatric Research Equity Act (PREA) (2003)

Best Pharmaceuticals for Children Act (BPCA)

- Provides for **voluntary** pediatric drug assessments via a Written Request (WR), including clinical and non-clinical studies
- Authorizes FDA to request studies for the drug moiety, for approved and unapproved pediatric indications including orphan indications
- Reflects a public health need for pediatric studies
- Provides a process for studying off-patent drugs
- Six months of marketing exclusivity granted if the terms of the WR are met

Pediatric Research Equity Act (PREA)

- Triggered by an application for a new indication, new dosage form, new dosing regimen, new route of administration or new active ingredient
- Authorizes FDA to **require** a pediatric assessment of certain drug/biologic products at the time the application is submitted.
- Provides criteria for FDA to waive or defer pediatric studies and requires a plan for deferred studies
- Establishes the Pediatric Review Committee (PeRC) to review pediatric plans & assessments and waiver & deferral requests

Pediatric Analgesic Drug Development

- Unmet needs in pediatric pain management
- Very few analgesics with pediatric indications or labeling, including opioids
- Most analgesic use in pediatric patients is off-label
- Although pediatric studies have been required by law since 2003, few analgesic studies have been completed
- Most infants and children are healthy and experience brief pain episodes, but some have severely painful conditions (i.e, epidermolysis bullosa, Osteogenesis imperfecta, cancer, metabolic/neurologic dis, sickle cell)

Analgesics with Pediatric Labeling or Indications

Acetaminophen, Aspirin, NSAIDs

- Oral APAP (≥2 y)
- IV APAP from birth
- ASA
- Ibuprofen (≥ 6 m)

NSAIDS for JIA indication

- Celecoxib
- Diflunisal
- EtodolacXL
- Indomethcin
- Ketorolac
- Mefenamic acid
- Meloxicam
- Naproxen
- Oxaprozin
- Tolmetin

Opioids

- **Fentanyl transdermal (≥2 y)**
- **Buprenorphine injection**
- **Fentanyl citrate injection**
- **Meperidine**
- **OxyContin (≥11 y)**

Combination Products

- **Codeine/APAP (≥ 3 y)**
- **Hydrocodone/APAP (≥2 y)**
- Pentazocine/APAP
- Dihydrocodeine/ASA/Caffeine
- Codeine/ASA/Butalbital/Caffeine
- Oxycodone/Ibuprofen
- Pentazocine/Naloxone
- Carisoprodol/ASA/Codeine
- Butalbital/APAP
- Butalbital/APAP/Caffeine

Analgesics Without Pediatric Labeling

NSAIDS

- Diclofenac
- Diclofenac potassium
- Diclofenac sodium/misoprostal
- Fenprofen
- Flurbiprofen
- Ketoprofen
- Nabumetone
- Piroxicam
- Sulindac

Combination Products

- Hydrocodone/ Ibuprofen
- Oxycodone/ Acetaminophen
- Oxycodone/ Aspirin
- Tramadol/ Acetaminophen

Single-Entity Opioids

- Fentanyl Oral Transmucosal
- Hydrocodone ER
- Hydromorphone IV/IR/ER
- Methadone
- Morphine sulfate IV/IR/ER
- Morphine/Naltrexone ER
- Oxycodone IR/ER
- Oxycodone/Naloxone ER
- Oxymorphone IV/IR/ER
- Tramadol IR/ER
- Tapentadol IR/ER
- Buprenorphine transdermal
- Butorphanol
- Levorphanol
- Nalbuphine
- Pentazocine

Study Requirements for Pediatric Analgesics

Pre 2010

- Pharmacokinetic, efficacy and safety studies for almost all analgesics, all age groups
- But industry could not enroll
  - Sponsors reluctant to conduct randomized, double-blind trials to assess efficacy
  - Ethical concerns of IRBs and investigators re use of placebo, allowing children to experience more than mild pain
  - Enrollment challenges: parents, study sites, investigators
  - Limited number of patients
  - Neonates: painful procedures, emotional impact on parents

FDA Scientific Workshop-2009

- **Are efficacy studies necessary? Can we extrapolate from adults?**
- FDA-sponsored Pediatric Analgesic Clinical Studies Scientific Workshop
  - Leading pediatric analgesic clinical trial design experts and pediatric clinical pain experts
  - Discussed which analgesic drug classes could have efficacy extrapolated from adults to children based on available scientific and medical support
    - What ages?
  - For analgesic drug classes where extrapolation is inappropriate, discussed alternative study designs

Importance of Extrapolation

- Children are a vulnerable population and require additional safeguards in studies (e.g., inability to consent or communicate symptoms as well as adults, developing organ systems)
- Extrapolating efficacy when possible is important because there are a limited number of pediatric patients available to enroll
  - Extrapolating efficacy allows studies to be smaller and enroll fewer patients

Legislation Allows for Extrapolation of Efficacy in Pediatric Patients

If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.

*21CFR §355c

PEDIATRICS®

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Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

Charles B. Berde, Gary A. Walco, Elliot J. Krane, K. J. S. Anand, Jacob V. Aranda, Kenneth D. Craig, Carlton D. Dampier, Julia C. Finkel, Martin Grabois, Celeste Johnston, John Lantos, Alyssa Lebel, Lynne G. Maxwell, Patrick McGrath, Timothy F. Oberlander, Laura E. Schanberg, Bonnie Stevens, Anna Taddio, Carl L. von Baeyer, Myron Yaster and William T. Zempsky

Pediatrics; originally published online January 16, 2012;
DOI: 10.1542/peds.2010-3591

Consensus

Since 2010

- Opioids, Nonsterioidal Anti-inflammatory Drugs (NSAIDS), Acetaminophen, and Local Anesthetics
  - Pharmacokinetics and safety all age groups
  - Extrapolate efficacy down to age 2 years
  - Efficacy studies only in patients less than age 2

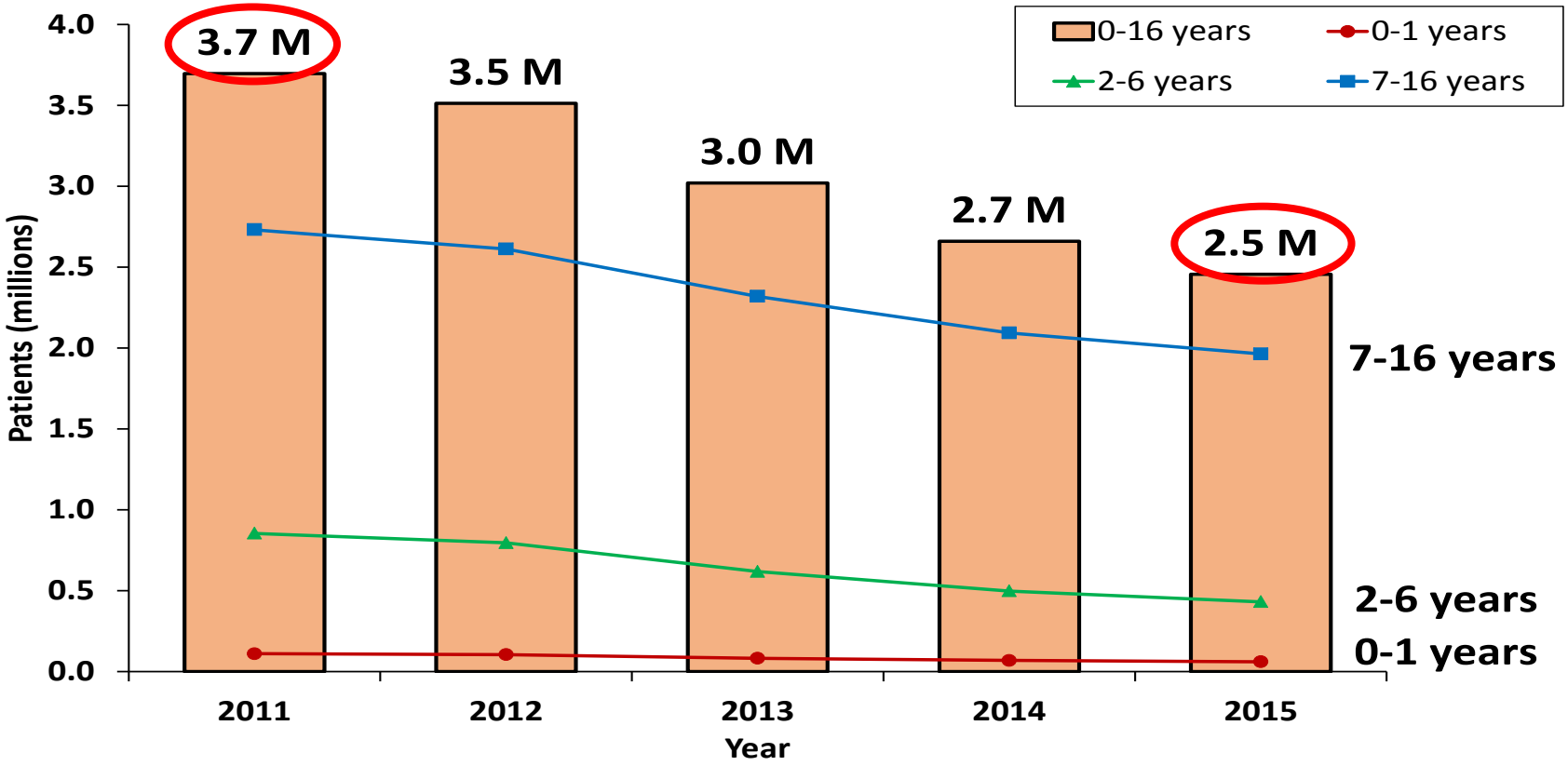
- All other drug classes
  - Pharmacokinetics, efficacy, and safety all age groups

- Chronic pain or ER analgesics
  - Waive studies in patients less than 7 years due to small numbers

Use of Opioids in Pediatric Patients

Pediatric Utilization: Patient-Level Data

National estimates of total pediatric patients (0-16 years*) who received dispensed prescriptions for opioid analgesics** from U.S. outpatient retail pharmacies



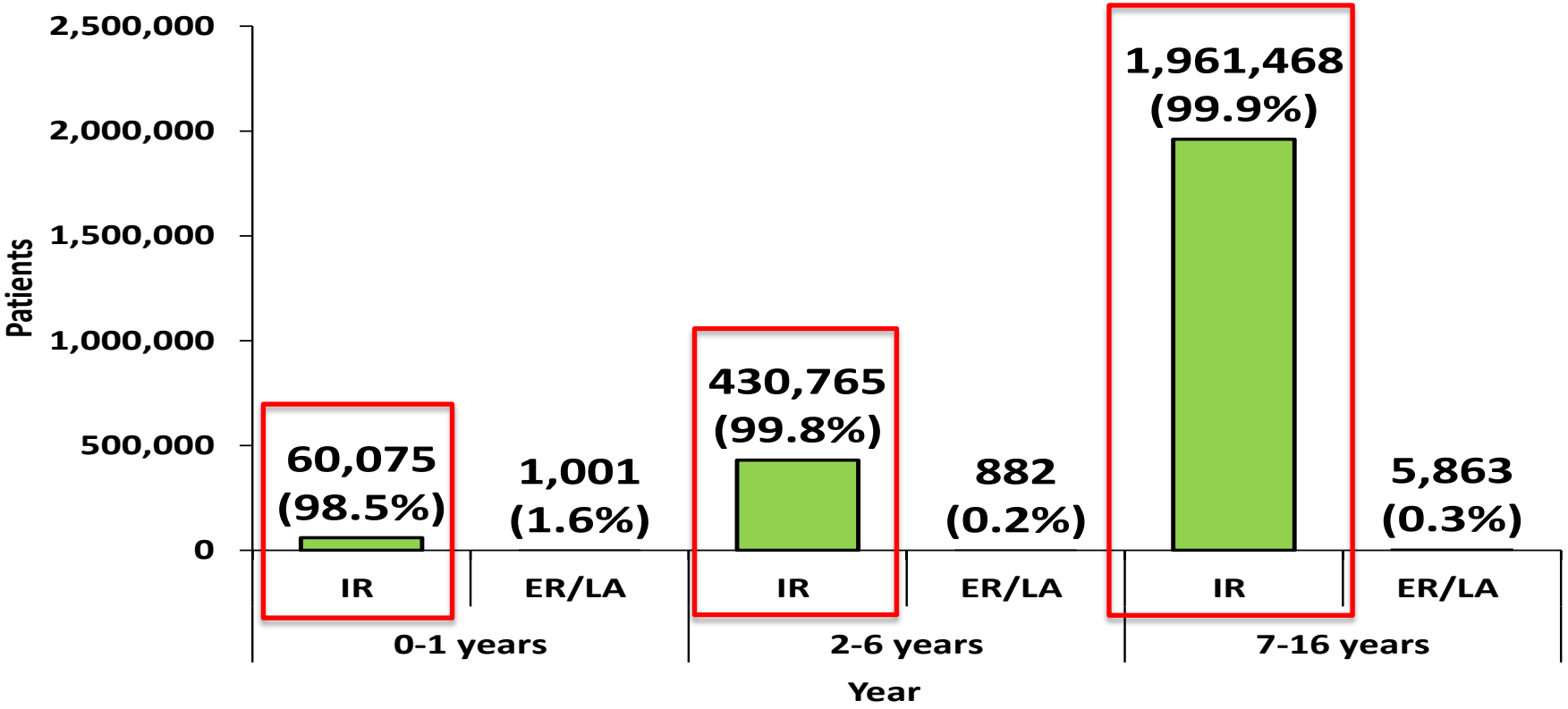
Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2011-2015. Data extracted August 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric Patients: IR and ER/LA Opioid Analgesics

National estimates of pediatric patients by patient age* who received prescriptions dispensed for IR or ER/LA opioid analgesics** from U.S. outpatient retail pharmacies in 2015



Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Year 2015. Data extracted August 2016.
**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*
***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric Utilization:
Top Dispensed Opioid Analgesics

National estimates of pediatric patients by patient age* who received prescriptions dispensed for the top IR or ER/LA opioid analgesics** from U.S. outpatient retail pharmacies in 2015

	0-1 years		2-6 years		7-16 years	
Product	**Patients**	**%**	**Patients**	**%**	**Patients**	**%**
IR Opioid Analgesics	**60,075**	***100.0%***	**430,765**	***100.0%***	**1,961,468**	***100.0%***
Hydrocodone-Acetaminophen	27,967	*46.6%*	181,566	*42.1%*	934,918	*47.7%*
Codeine-Acetaminophen	19,821	*33.0%*	197,495	*45.8%*	721,016	*36.8%*
ER/LA Opioid Analgesics	**1,001**	***100.0%***	**882**	***100.0%***	**5,863**	***100.0%***
Oxycodone ER	19	*1.9%*	21	*2.4%*	1,765	*30.1%*
Fentanyl transdermal	294	*29.4%*	599	*67.9%*	1,628	*27.8%*
Morphine	23	*2.3%*	48	*5.4%*	1,537	*26.2%*
Methadone	645	*64.4%*	208	*23.6%*	613	*10.5%*

Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Year 2015. Data extracted August 2016.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

***Data included opioid analgesics with oral, transdermal, and nasal formulations.*

Pediatric* Patient Utilization Data

- Butrans Use
  - Patients 11 years and younger→ too low for reliable national estimates
  - Patients 12-16 years → less than 100 patients annually from 2012-2016
- Belbuca*Use
- (buprenorphine buccal film) Patients 11 years and younger→ no use
  - Patients 12-16 years → too low for reliable national estimates

Source: Symphony Health Solutions' Integrated Dataverse® (IDV). Years 2012-2016. Data extracted July 2017.
*Belbuca approved October 2015.

Note: The patient estimates are nationally projected data based on a sample of approximately 90% of all U.S. retail prescriptions. Statistical accuracy increases as the projected number increases, national estimates of 10 patients or less were too low to be reliable

Opioid Utilization

- Opioid analgesics were prescribed and dispensed to pediatric patients of all ages
- In 2015, ~2.5 million pediatric patients (4% of total 66.5 million patients of any age) were dispensed opioid analgesics
- Total outpatient pediatric opioid analgesic utilization declined since 2011
- There is minimal use of Butrans in the pediatric population

OxyContin

- Purpose of study was to describe the PK and safety of OxyContin in pediatric patients requiring treatment with an extended-release opioid analgesic
- Pediatric indication approved August 2015
  - Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent
- **Approval did not create novel uses for OxyContin in pediatric patients-but provided data in patients who require this treatment**

- http://www.fda.gov/Drugs/NewsEvents/ucm456973.htm

OxyContin

----------INDICATIONS AND USAGE----------

OXYCONTIN is an opioid agonist indicated 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 in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

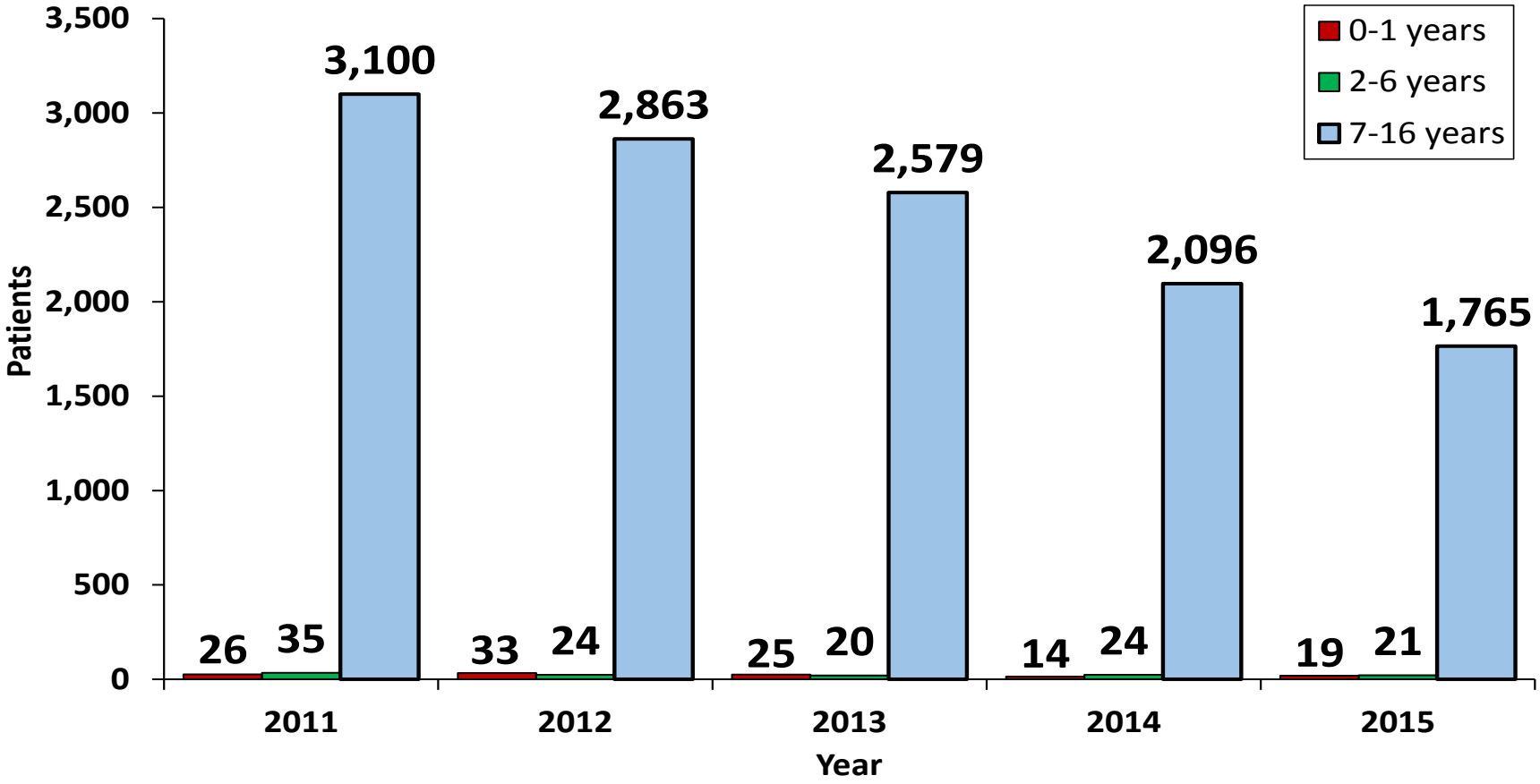
- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

OxyContin Post-Marketing Requirements

- Novel PMRs were put in place to further understand the impact of pediatric indication for OxyContin
- The Sponsor is required to assess the safety and use of Oxycontin in pediatric patients in two postmarketing studies:
  - Study 1:
    - Assess risks of respiratory depression, overdose, misuse, accidental exposure and med errors in opioid tolerant patients aged 11-17 and children younger than approved age range or do not meet criteria for opioid tolerance
    - Analysis of postmarket adverse events described above on all pediatric ages
  - Study 2:
    - National drug utilization study to characterize use of OxyContin in pediatrics
    - Data from study will provide denominator for study 1 to assess risk

Pediatric Patient-Level Data: Oxycodone ER

National estimates of pediatric patients by patient age* who received prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies



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**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).*

FDA's September 15-16, 2016 Joint Meeting of the Anesthetic Analgesic and Drug Products Advisory Committee (AADPAC), Drug Safety and Risk Management Advisory Committee (DSaRM), and Pediatric Advisory Committee (PAC)

Continued Challenges

- Sponsors have trouble enrolling pediatric patients into trials

  Reluctance of investigators, study sites and IRBs
  - Too few patients, especially youngest patients and chronic pain
  - Parental concerns
  - Ethical and logistical concerns-neonates (blood sampling, use of placebo and unnecessary pain, emotional impact on parents)
- Cannot complete trials in a reasonable period of time: Oxycontin-4 years
- Public misunderstanding regarding the use and approval of opioids in pediatric patients

FDA's September 15-16, 2016 Joint Meeting of the AADPAC/DSaRM/PAC

- Part of the Commissioner's Opioid Action Plan
- Obtain advice on the development of opioid analgesics in the pediatric population
- Three committees
  - Anesthetic and Analgesic Drug Products, Drug Safety and Risk Management, and Pediatric Advisory Committees
- FDA and outside speakers
- http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm

Highlights

- General
  - **Data is needed to inform labeling and use of opioids in pediatric patients**
  - There are pediatric patients who require opioid analgesics for a variety of conditions
  - Untreated or poorly treated pain in children can have lasting, profound, and irreversible effects, sensitizing to greater risk of chronic pain in the future
  - Need to consider risk/benefit to patients when prescribing opioids
  - Pediatric patients are vulnerable to drug use and addiction due to ongoing brain development. Proper prescribing, patient selection, education is crucial
  - Approvals of opioids in pediatric patients will be accompanied by post marketing requirements to assess the safety of these products in children

Highlights

- **Which pediatric patients are currently treated with opioid analgesics?**
  - Chronic pain conditions or pain requiring treatment for two or more weeks:
    - Cancer, end of life care, post op pain after extensive surgeries such as orthopedic procedures on spine, cardiothoracic procedures, critical illness, mechanical ventilation, complex regional pain syndrome, burns
  - Acute pain conditions, short-term use
    - post op pain, injury, trauma, burns/dressing changes, sickle cell pain crises (intermittent use)
- Very important to select an appropriate pediatric patient population who requires treatment with an opioid to enroll in studies
    - for ERLA opioids, patients require treatment for at least 2 weeks

Challenges Remain

- Enrollment, few patients, parental concerns, investigator concerns, study sites
- Studies in patients < 2 years old, especially < 6 month olds
- Completing studies in timely manner
- Measurement of pain, particularly in youngest patients

Moving Forward

- There are major information gaps regarding the use opioid analgesics in pediatric patients that must be filled
- There is no evidence that appropriate labeling of opioids children increases use in this population
- Clinical trials are needed to improve how opioid analgesics are prescribed to children with acute and chronic pain
- Strongly recommend that sponsors discuss their pediatric study plans with the Agency early in product development
- Open to discussing innovative approaches
- Applications for pediatric labeling for opioids will be taken to advisory committee

Useful References

Pediatric AC Information:

- http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm

- Analgesic Guidance for Industry:

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm384691.pdf

- Clinical Pharmacology and Pediatric Studies Draft Guidance for Industry

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm425885.pdf

- "Pediatric analgesic clinical trial designs, measures, and extrapolation: report of an FDA scientific workshop," Berde, Walco, Krane, et. al.

https://www.ncbi.nlm.nih.gov/pubmed/22250028

Thank you


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Clinical Review of Study 3031 and Discussion

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

September 14, 2017

Butrans

Presentation Overview

- Pediatric Research Equity Act (PREA) Requirement from Approval Letter
- Brief Protocol Summary
- Results of Study 3031
- Discussion

PREA REQUIREMENT FROM APPROVAL LETTER AND SUBSEQUENT ADVICE

June 30, 2010 Approval Letter

PREA Requirement

- …a 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 through 16
  - The study was deferred
- The pediatric study requirement for ages birth through six years was waived

FDA Advice

- 40 completers with at least 6-months of exposure needed to assess safety
- The four-week treatment duration is acceptable for the pharmacokinetic aspect of the study
- These recommendations have evolved since the approval of Butrans
  - We now request a database of 125 patients for the 12 to 17 year age group and 50 patients for the 7 to 11 year age group

STUDY DESIGN

Study 3031

- **Objective:** Characterize the safety and PK of Butrans in patients 7 to 16 years old who require continuous around-the-clock opioid analgesia for moderate to severe pain
- **Design:** Open-label, multicenter, multiple dose study with treatment for a minimum of 2 weeks and up to 24weeks. The study was not designed to demonstrate efficacy and no formal hypothesis testing was performed
- **Butrans Doses**: 2.5, 5, 10, and 20 mcg/h were studied

Study 3031

Inclusion Criteria

- Male and female patients aged 7 to 16 years, inclusive
- 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 judgement
- Patients with post-operative pain were allowed if at least 48 hours after surgery
- Patients may have been opioid-naïve or opioid-experienced
  - taking ≤80 mg/day morphine or equivalent if aged 12 to 16 years, or ≤40 mg/day morphine if aged 7 to 11 years
- Stable vital signs, including hemoglobin-oxygen saturation ($SpO_2 \geq 92\%$), and normal respiratory rate

Study 3031

Dose Initiation

- Patients in the 7 to 11 year age group initiated treatment with Butrans 2.5 mcg/hour and patients in the 12 to 16 year age group initiated treatment with Butrans 5 mcg/hour
- Patients who were opioid-naïve or receiving ≤ 10 mg/day oral morphine or equivalent were required to be inpatients at the initiation of treatment and remain hospitalized for the first 48 hours of treatment
- Short-acting rescue opioids were permitted

Dose Titration

- Upward or downward titration of the Butrans dose was allowed
- Patients were allowed to use supplemental short-acting opioid or non-opioid medications

RESULTS

Study 3031

Dates conducted: July 23, 2012 to April 12, 2016

Baseline Characteristics: A total of 41 patients were treated

Age of Patients			
Category	**Age Group**		**Total N=41 n (%)**
	7 to 11 years N=6	**12 to 16 years N=35**	
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

Study 3031

Exposure			
Cumulative Number of Days on BTDS	**Age Group**		**Total N=41 n (%)**
	7 to 11 yrs N=6, n (%)	**12 to 16 yrs 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)
≥ 4 weeks	1 (17)	30 (86)	31 (76)
≥ 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)

- Exposure to Butrans 20 mcg/hour: limited to older age group
  - 13 subjects ≥1 dose, 10 subjects ≥2 weeks and 6 subjects ≥4 weeks

Study 3031

Reasons for Pain at Study Entry	
Primary pain condition	Number of subjects
Low Back Pain	8
Migraine Headaches	6
Sickle Cell Disease	6
Surgical Procedure	4
Abdominal pain	3
Crohns Disease	2
Musculoskeletal pain (CRPS)	1
Epstein Barr antibody positive	1
Chronic foot pain (neuroma/osteomyelitis)	1
Amniotic band syndrome (chronic osteomyelitis/right club foot)	1
Pelvic pain	1
Knee arthritis	1
Diffuse scleroderma	1
Joint pain	1
Juvenile rheumatoid arthritis	1
Generalized rheumatologic pain	1
Avascular necrosis of both hips (Sickle Cell)	1
GSW lower extremity	1

Safety for Study 3031

- There were no deaths
- 8 patients experienced treatment-emergent serious adverse events (SAEs)
  - Butrans was not considered to be the cause of any of the SAEs except for possibly exacerbating the SAE of hypersomnolence
- The most frequently reported treatment-emergent adverse events were consistent with the known opioid and transdermal patch adverse event profile and included: local application site reactions, nausea, somnolence, dizziness, headache, constipation and vomiting

SUMMARY

Summary

- Given the small database size, there are not sufficient data to fully describe the safety profile and therefore, we recommend that Butrans not receive an indication in pediatric patients for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.
- Data from this study supports adding information about Butrans to the pediatric section of the labeling, without adding an indication for use in this population.
  - The new information will include a brief description of Study 3031
- Future studies of opioids in children must recruit suitable patients with clearly documented reasons for the use of opioid analgesics.

Pediatric Pharmacokinetic Assessment of Butrans in Study 3031

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CDER, FDA

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
September 14, 2017

Outline

- Considerations for pediatric extrapolation
- FDA's assessment of the Applicant's analyses
  - Study BUP3031

Considerations for Pediatric Extrapolation

Is it reasonable to assume that children when compared to adults have a similar: (1) disease progression and (2) response to intervention

Yes to both

Is it reasonable to assume similar exposure-response in pediatric and adults?

Yes

Is the drug (or active metabolite) concentration measurable and predictive of clinical response?

Yes

Full-extrapolation:
Efficacy can be extrapolated from adequate and well controlled studies in adults to pediatric population

Considerations for Pediatric Extrapolation

Dose Selection

- Additional pharmacokinetic studies may be needed to support the selection of a "target" pediatric dose/dosing regimen which results in *exposure range or distribution comparable to adults*
- Modeling & Simulation can serve as a powerful tool to aid in the identification of the "target" pediatric dose/dosing regimen

Safety

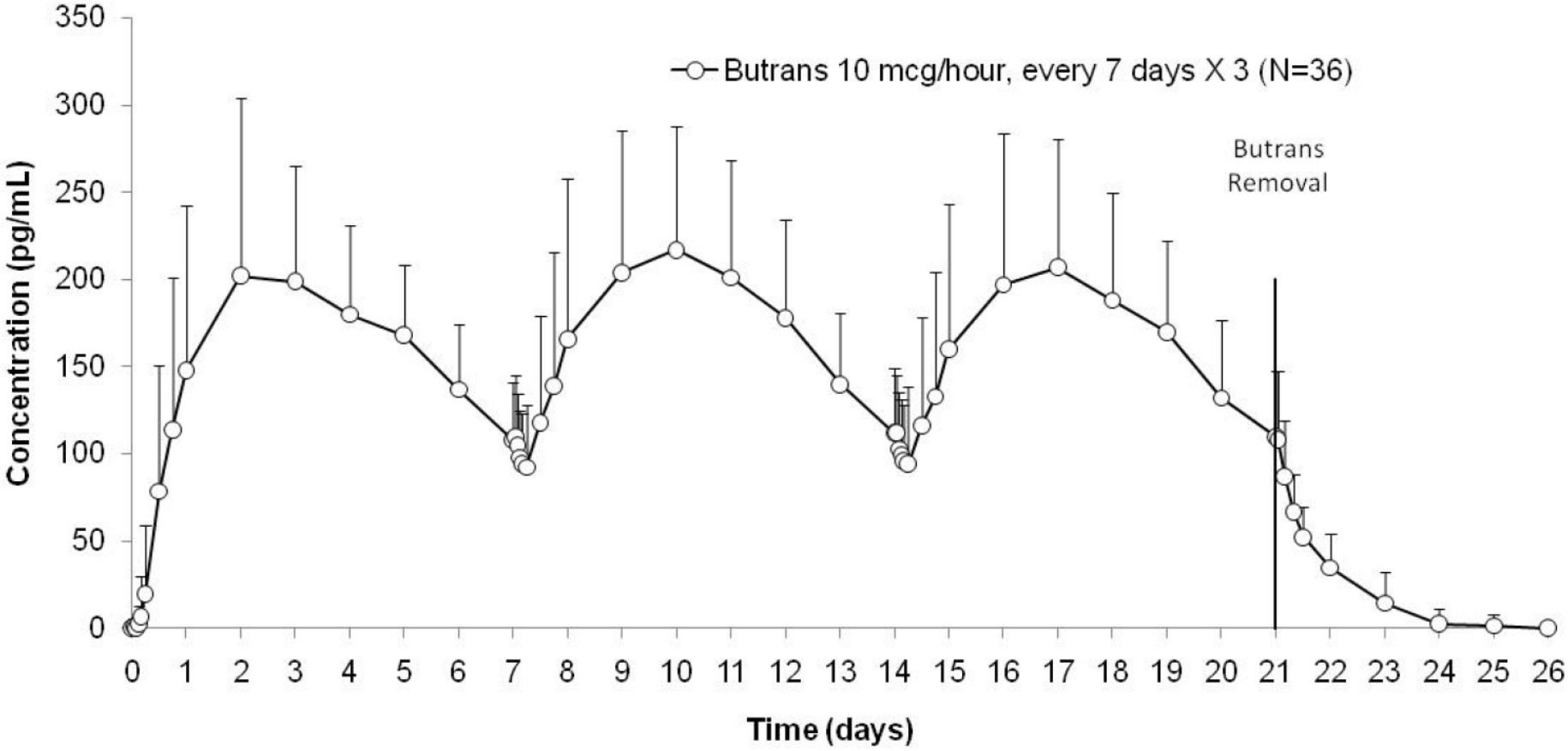
- *Cannot* be extrapolated
- Safety data needs to evaluated at all proposed doses to be used in pediatric patients

Butrans - Regulatory History

- Buprenorphine transdermal system (Butrans) was approved in adults at doses ranging between 5-20 mcg/hr

- Clinical pharmacology:
  - Absolute bioavailability ~15%
  - Dose proportional PK in the dose range of 5-20 mcg/hr
  - Buprenorphine undergoes hepatic metabolism via CYP3A4 pathway, which is mature by age of 7 years
  - Steady-state exposure levels achieved in 2-3 days

Butrans - Adult Pharmacokinetics



Butrans – Pediatric Supplement

- PMR 1655-1: Final study report BUP3031
  - Open label, multicenter study of safety, PK and efficacy of Butrans in children from 7-16 years of age, inclusive, who require continuous opioid analgesia for moderate to severe pain.
  - Treatment duration: up to 24 weeks
  - Dose initiation:

    2.5 mcg/hr (7-11 years); 5 mcg/hr (12-16 years)
  - Dose titration:
    - Up: based on tolerability and inadequate pain control, titrated to next higher dose at least 72 hours after treatment
    - Down: tolerability and AEs

Pediatric PK Database

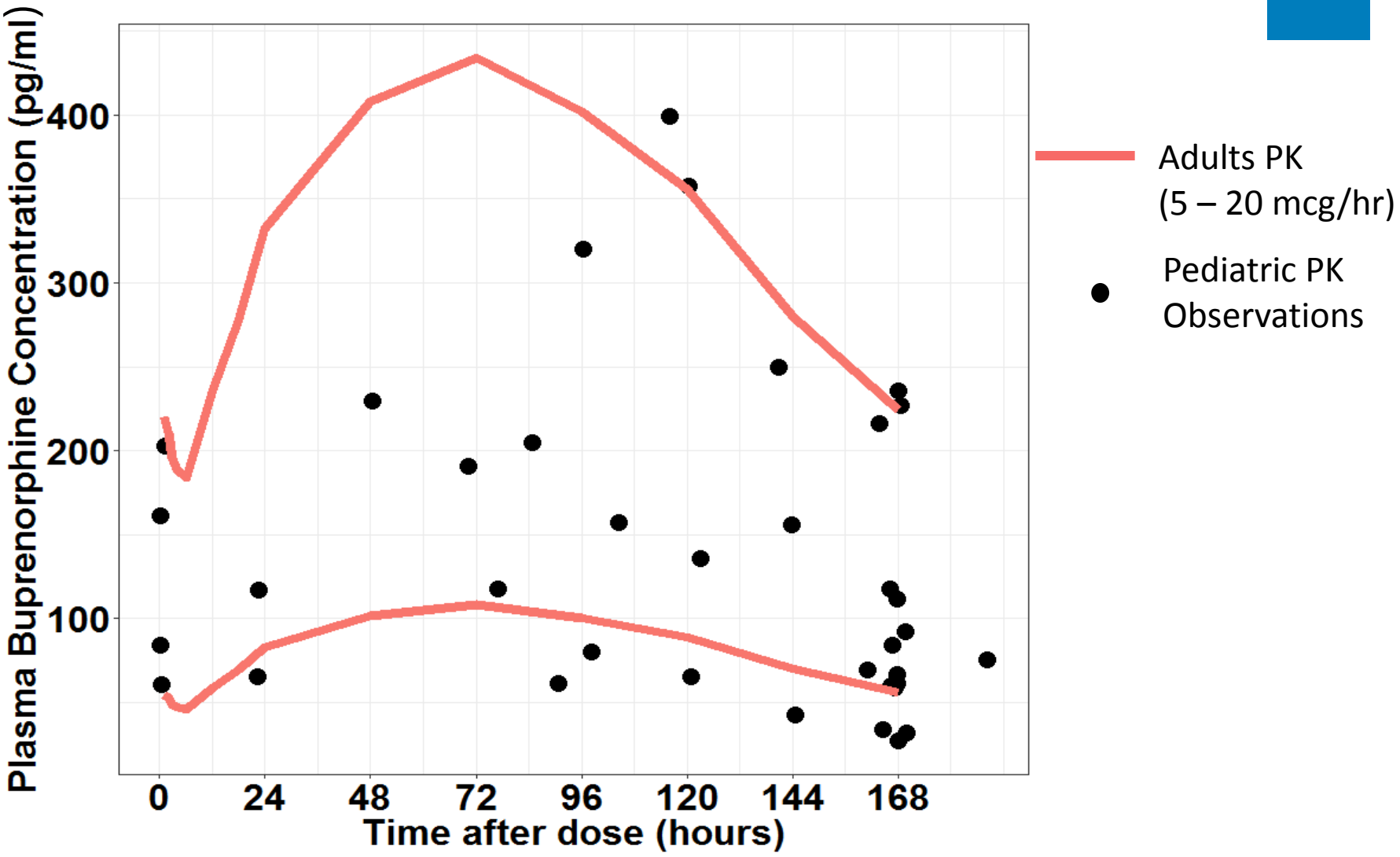
- Sparse PK blood samples collected:
  - 18-24 hours after first application of Butrans
  - end of week 1
  - 2-3 days after end of weeks 1, 2, and 3 or at discontinuation, if it happened prior to the last scheduled draw

Analysis dataset:

- N=41 received treatments: **6** (7-11 years); 35 (12-16 years)
- Final dataset 38 patients (14M/24F), total of 151 plasma concentrations

Final Titrated Dose (mcg/hr)	2.5 (7-11)	5 (7-11)	2.5 (12-16)	5 (12-16)	10 (12-16)	20 (12-16)
Count	2	4	4	11	11	9

Pediatric Buprenorphine PK Observations



Pediatric PK Assessment

- Overall, a population PK model was able to characterize the pediatric PK data.
  - This model can be used to perform simulations to identify the “target” pediatric Butrans dose, which results in exposure range or distribution comparable to that observed in adults.
  - Furthermore, body-weight based dosing recommendations can be derived to match the pediatric exposures to adults.
- However, due to the small safety database, we do not propose specific pediatric dosing recommendations for Butrans.

Thank you