FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS (AADPAC) AND THE DRUG SAFETY AND RISK MANAGEMENT (DSaRM) ADVISORY COMMITTEES

Thursday, September 14, 2017

8:02 a.m. to 11:59 a.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:02 a.m.)

Call to Order

Introduction of Committee

DR. BATEMAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, or any other devices if you've not already done so. I would also like to identify the FDA press contact, Michael Felderbaum. If you're present, please stand.

My name is Brian Bateman. I'm the acting chairperson for today's meeting. I will now call the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. HERTZ: Good morning. Sharon Hertz, director for the Division of Anesthesia, Analgesic, and Addiction Products.

DR. STAFFA: Good morning. I'm Judy Staffa.

I'm the associate director for public health initiatives in the Office of Surveillance and Epidemiology in CDER at FDA.

DR. FLICK: Randall Flick, pediatric anesthesia, critical care, Mayo Clinic.

DR. PATRICK: Stephen Patrick, neonatology, Vanderbilt.

DR. SCHMID: Chris Schmid, biostatistics, Brown University.

DR. LITMAN: Good morning. Ron Litman. I'm a pediatric anesthesiologist at Children's Hospital of Philadelphia and the medical director of the Institute for Safe Medication Practice.

DR. DRACKER: Bob Dracker, member of the Pediatric Advisory Committee of the FDA, pediatrics, hematology, oncology, and blood banking.

DR. WARHOLAK: Terri Warholak, University of Arizona College of Pharmacy. My specialty is quality and safety.

DR. WADE: Kelly Wade, neonatologist for Children's Hospital of Philadelphia and member of

the Pediatric Advisory Committee for the FDA.

DR. EMALA: Charles Emala, professor of anesthesiology and vice-chair for research at Columbia University in New York.

LCDR BEGANSKY: Stephanie Begansky. I'm the DFO for today's meeting.

DR. BATEMAN: Brian Bateman. I'm associate professor of anesthesia at Brigham and Women's Hospital in Harvard Medical School.

DR. SHOBEN: Abby Shoben, biostatistics, the Ohio State University.

DR. HABEL: Laurel Habel, cancer epidemiologist, Kaiser Permanente Northern California.

DR. ZACHAROFF: Good morning. Kevin Zacharoff, expertise in anesthesiology, pain medicine, and pediatric anesthesiology at the Stony Brook School of Medicine.

DR. RUHA: Hi. I'm Michelle Ruha. I'm a medical toxicologist at the University of Arizona College of Medicine, Phoenix.

DR. MCCANN: Hi. I'm Mary Ellen McCann.

I'm associate professor of anesthesia at Harvard Medical School in Boston Children's Hospital.

DR. HIGGINS: Jennifer Higgins, the AADPAC consumer representative.

MS. ROBOTTI: Hi. Suzanne Robotti. I am the consumer rep on drug safety and risk management and the executive director of MedShadow and DES Action.

MS. PORTIS: I'm Natalie Compagni Portis. I'm the patient representative this morning.

DR. GREENE: Good morning. I'm Bill Greene. I'm chief pharmaceutical officer and member of the Department of Pharmaceutical Sciences at St. Jude Children's Research Hospital.

DR. HAVENS: Peter Havens, pediatric infectious diseases at the Medical College of Wisconsin and Children's Hospital Wisconsin in Milwaukee and a member of the Pediatric Advisory Committee of the FDA.

DR. SCARAZZINI: Good morning. Linda Scarazzini, head of pharmacovigilance and patient safety at AbbVie and the industry rep for drug

safety and risk management.

DR. BATEMAN: We have Dr. Cunningham calling in by phone. Dr. Cunningham, can you introduce yourself?

(No response.)

DR. BATEMAN: We'll come back.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are

anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

I'll now pass it to Lieutenant Commander Stephanie Begansky, who will read the conflicts of interest statement.

Conflict of Interest Statement

LCDR BEGANSKY: Thank you.

The Food and Drug Administration is convening today's joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of

interest laws and regulations.

The following information on the status of these committees' compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses, minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of supplemental new drug application 021306 for Butrans, buprenorphine transdermal system, submitted by Purdue Pharma, evaluating Butrans in pediatric patients, ages 7 through 16 years, for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees will be asked to discuss the findings of the clinical study of Butrans conducted in pediatric patients and whether

they support additional labeling.

This is a particular matters meeting during which specific matters related to Purdue's supplemental NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Linda Scarazzini is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Scarazzini's role at this meeting is to represent industry in general and not any particular company. Dr. Scarazzini is employed by AbbVie.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. BATEMAN: So we will now proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

FDA Opening Remarks - Sharon Hertz

DR. HERTZ: Good morning, Dr. Bateman, members of the Anesthesia and Analgesic Drugs Advisory Committee, members of the Drug Safety and Risk Management Advisory committee, and invited AC members as well as invited guests. Thank you for joining us today.

This morning, we'll be discussing a supplemental application from Purdue Pharma, describing a study in pediatric patients with the product Butrans, which is a transdermal system or patch containing buprenorphine.

It's an extended-release formulation, and as you may know, buprenorphine is a partial agonist. In adults, it's indicated 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 Butrans's initial approval in 2010, a postmarketing requirement was issued according to the Pediatric Research Equity Act or PREA, and this describes a set of requirements for pediatric studies.

For the long-acting and extended-release class of opioid analgesics, the pediatric study requirement consists of a safety and PK pharmacokinetic study in patients 7 to 17 years. Following presentations by the applicant and FDA, we will ask you to discuss any concerns you have

regarding the data from the evaluation of Butrans in children and whether the data from the study is appropriate for inclusion in the pediatric section of the labeling.

The applicant has not requested an indication based on the limited data available. In cases where pediatric studies do not lead to an indication, it's common to put language into the drug label that states efficacy and safety have not been demonstrated as well as any particular safety concerns that may have been uncovered during the study.

As described in the opioid action plan released last February, a year ago February, FDA feels strongly that all applications related to the use of opioids in pediatric patients are presented before an advisory committee in order to gain input from our committee members as well as the public for the application.

Children experience pain in a number of settings, and the imperative to relieve their suffering is no less great than for adults. Most

of the analgesic products that are currently used to manage pain in children today, both opioid and non-opioid, do not have pediatric efficacy, safety, or dosing instructions because they have not been studied in children.

The serious public health problem associated with the misuse and abuse of prescription opioid analgesics and the problems of addiction, overdose, and death must always be kept in mind when discussing opioid analgesics. However, it's critically important to address the medical needs of children, which includes providing clinicians age-appropriate information about the safety, efficacy, and pharmacokinetics of the products they use.

Today, you're going to hear presentations from the applicant as they describe their program, then you'll hear presentations from FDA, including some summaries of where we've been up until now more recently with pediatric opioid analgesic development.

We're asking for your expertise, your

experience, your best insights in order to help us make a reasonable and responsible decision regarding this application. Your advice and recommendations are always essential in assisting us with addressing this complex and critical public health concern.

We're grateful that you have agreed to join us for this important discussion and look forward to an interesting and productive discussion. Thank you.

DR. BATEMAN: We'll now move on to the sponsor's presentation. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationship they may have with the

applicant, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests, and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We'll now proceed with Purdue Pharma's presentations.

Sponsor Presentation - Craig Landau

DR. LANDAU: Mr. Chairman, members of the combined committees, representatives from the agency, and all others, good morning. My name is Craig Landau. I'm the president and CEO of Purdue. I want to thank everyone involved for the opportunity to be here and to speak about Butrans, and specifically the study designed to meet the PREA requirements, and our combined goal to develop

high-quality data to guide the safe use of these products in all patients, including pediatric patients.

I know a number of you out in the audience. I'm an anesthesiologist and pain practitioner myself. I practiced in a variety of settings. I've treated many patients in a civilian setting, in both academia and private practice, and also for 15 years with the United States Army Medical Corps.

In parallel to most of that, I have spent 20 years in the pharmaceutical industry, most of which has been in R&D, for the first 15 years in fact in R&D. And I've developed or helped to develop a number of analgesic medications that are available today on the U.S. and other markets, one of which is Butrans, so it's near and dear to my heart.

Specifically, I was the lead clinician for Butrans in its development here up to and including the approval in the United States. So it's in this context and with this experience, and given the last two and a half months of my career as

president of the U.S. Purdue organization, that I want to be here personally to assure the combined committees and the agencies of three important commitments that we're making as a company.

First and foremost, as Dr. Hertz mentioned in her opening remarks, we're not seeking an indication for Butrans in pediatric patients. Second, we have not and we do not promote opioids for their use in children. And regardless of the outcome of this committee and this meeting today, we don't plan to promote the use of Butrans in pediatric patients.

Our only goal is to develop high-quality data, in this case to meet PREA requirements, to guide the safe and appropriate use of our products in all patients, adults and in pediatrics, and it's with pediatrics in mind that we're here to discuss really PREA requirements.

So for those of you who are less familiar than others, in 2003, as Dr. Hertz mentioned, Congress enacted PREA, the Pediatric Research Equity Act, and it was really intended to address a

very widely-accepted gap in pediatric data in product monographs here in the United States.

Most drugs are approved, or studied and approved, for use in adults. But we understand, most of us, especially those with kids, clinicians, while they act like adults at times, kids are not small adults physiologically, pharmacokinetically, and even in response.

So they demand that data be generated to guide their safe and effective use if a physician, a treating physician, determines that the benefit of using a medicine outweighs the risk of using that medicine in an individual patient.

So it's with this in mind that the government, in this case the agency, requires sponsors with a new drug application to conduct certain studies. How does this apply to Butrans?

In 2010, after a number of years in development, Butrans was approved here in the United States by FDA, and it came with a mandatory requirement through PREA to conduct a safety and pharmacokinetic study in subjects ages 7 to 16.

On the efficacy side, as you will hear in a presentation from the agency, it was determined at that time that efficacy could be extrapolated from the pivotal studies conducted in the adult population.

Now, we ran and designed study BUP3031 -- we're going to discuss it today -- and it was designed in concert with the comments from the agency, both the analgesic division, but also the Pediatric Review Committee. Those comments were incorporated. We ran the study. It sought to enroll 40 some-odd subjects, which at the time was the standards, I'd say, for these types of studies.

Now thankfully, there are relatively few pediatric patients with pain severe enough to require treatment with opioids around the clock, but these patients definitely do exist and they need to be cared for. They need to be treated. They need to be treated appropriately.

So it's for these few pediatric patients who have exhausted all other treatment mechanisms or treatment means, and from whom their treating

physicians believe the benefits of a certain medicine, including an opioid but not limited to opioids, outweighs the risks, that we need to generate high-quality data to guide their safe use, and that was the purpose of the BUP3031 study.

After my introduction, which I'm about to wrap up, you're going to hear from two other people from our company, first from Dr. Richard Fanelli, who heads up our regulatory affairs group. He's going to talk in a little bit more detail about the regulatory history, the program itself, the pediatric program, and specifically about the utilization of opioids in kids.

Stacy Baldridge, who's a pediatric nurse and pediatric critical care nurse, also leads our pediatric research programs in house, is going to come up and actually talk about the design, conduct, and results from the study.

So we have a full morning and a tight time frame. We appreciate the time, looking forward to the discussion, and thanks again, Mr. Chairman and committee. Thank you.

Sponsor Presentation - Richard Fanelli

DR. FANELLI: Good morning. As Craig said, I'm Richard Fanelli, the head of regulatory affairs at Purdue. This morning I will give a brief description of the regulatory background for our pediatric program with Butrans, and then discuss the utilization of opioids in pediatric patients.

Butrans transdermal system contains buprenorphine, a partial mu opiate receptor agonist. Butrans is a Schedule III opiate analgesic, and the patch delivers buprenorphine over 7 days at dosage strengths from 5 to 20 micrograms per hour.

Butrans is approved for the management of pain severe enough to require daily, around-the-clock long-term treatment for which alternative treatments are inadequate. The Butrans full prescribing information, as with other extended-release long-acting opioids, includes warnings about addiction, abuse, and misuse, respiratory depression, accidental exposure, neonatal opiate withdrawal syndrome, and the risk of concomitant

use with benzodiazepines and other CNS depressants.

The Butrans label also includes warnings not to exceed a dose of 20 micrograms per hour due to the risk of QTc interval prolongation that was observed in a study of healthy adults at a dose of 40 micrograms per hour, twice the maximum approved dose. These characteristics and warnings have implications for the design of and enrollment in a pediatric trial, as you will hear about shortly.

The Butrans patch was approved by the FDA in June of 2010. This transdermal buprenorphine formulation has been approved in marketing in over 40 countries worldwide. With the approval in the U.S., a postmarketing program under PREA was required to study pediatric patients aged 7 to 16.

PREA was initially considering more extensive studies to satisfy written requests from FDA under the Best Pharmaceuticals for Children Act to study pediatric patients to treat acute pain, chronic pain, and neonatal abstinence syndrome.

We subsequently determined that given the challenges of these pediatric research for these

conditions, these studies were not feasible, and we would only conduct a pediatric study to satisfy the PREA requirement.

In December of 2010, a revised protocol, BUP3031, was submitted following discussions with guidance from FDA. Due to the difficulties in recruitment, Purdue requested and FDA granted a deferral to complete the study.

In December of 2016, the final study report from this pediatric trial was submitted as part of a supplemental new drug application, which included revised labeling, to include the information from this trial in the pediatric portion of the special population section of the Butrans label. With this submission, Purdue met its postmarketing commitment under PREA.

Currently, there is limited use with extended-release opioid analgesics in children and very limited use of Butrans in this population.

As reviewed by today's committees, in addition to the Pediatric Advisory Committee during a meeting in September of 2016 to discuss clinical

trials of opioid analgesics in pediatric patients, and again included in your briefing materials for this meeting, FDA's drug utilization review of these data demonstrate in the year 2015, approximately 2 and a half million pediatric patients were dispensed prescriptions for opiate medications. Of these, 2 million were aged 7 to 16, a range included in our Butrans pediatric clinical trial.

The number of dispensed extended-release opioids in this group was less than 0.3 percent of this total, about 6,000 prescriptions, with 75 of these for the Butrans patch in 2015.

As a result of the limited number of pediatric subjects available for study, our pediatric open-label study, BUP3031, only targeted and enrolled a small number of patients. Because of this, we are not requesting a pediatric indication.

Instead, we are proposing to add the pediatric patient experience from this trial, for the 12 to 16 age group, to the label to inform

prescribers, as an update to section 8.4 of the Butrans full prescribing information, of the pediatric use portion of the use in special populations, as described in FDA's 2013 draft guidance for the inclusion of pediatric information in labeling.

Purdue has not promoted and will not promote Butrans for use in the pediatric population, regardless of today's discussion.

Stacy Baldridge will now discuss the design, details, and results of the Butrans pediatric clinical program, which provides information to prescribers regarding the pharmacokinetics and safety of Butrans in pediatric patients with chronic pain.

Sponsor Presentation - Stacy Baldridge

MS. BALDRIDGE: Thank you, Dr. Fanelli. Good morning. My name is Stacy Baldridge. I'm a pediatric nurse by training and the pediatric program lead at Purdue Pharma. I want to thank the FDA and the combined advisory committees for the opportunity to work with you towards the common

goal of providing important data to healthcare professionals who care for pediatric patients with pain.

I have worked on the Butrans pediatric trial for 5 years, supporting our sites and our investigators. The trial was an open-label multi-center study of the safety and pharmacokinetics of Butrans in children from 7 to 16 years of age who require continuous opioid analgesia for moderate to severe pain. Moving forward, I will refer to the study as BUP3031.

The BUP3031 protocol was developed in discussion with the FDA and incorporated FDA recommendations. The protocol was designed to meet the Pediatric Research Equity Act, PREA, requirement, defined as 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 to 16 years. The primary objectives of the study were to characterize both pharmacokinetics and safety.

Efficacy for opioid analgesics can be fully extrapolated from adults to pediatric patients as young as 2 years because of similarity of underlying disease process and the exposure response to buprenorphine in adults and pediatric patients.

The study was designed and completed prior to the 2016 FDA Pediatric Advisory Committee meeting that resulted in revised FDA recommendations for the study of opioids in pediatric patients. The inclusion and exclusion criteria were designed to identify patients for whom Butrans would be a useful treatment option.

Key inclusion criteria for the BUP3031 protocol included patients aged 7 to 16 years with moderate to severe pain anticipated to require around-the-clock opioid treatment for at least 2 weeks.

There was an upper limit for incoming opioid dose as the doses of Butrans in the study may not have provided adequate analgesia for patients requiring high doses of daily opioids. Patients 7

to 11 years were required to be on less than 40 milligrams per day of morphine or equivalent, and for patients 12 to 16 years, the maximum daily dose was 80 milligrams per day of morphine or equivalent. In addition, higher doses of incoming opioids were required to be tapered down due to the potential for Butrans to precipitate withdrawal in patients already receiving opioids.

Patients with post-operative pain meeting the study eligibility requirements were allowed to be enrolled 48 hours after the surgical procedure. Exclusion criteria were designed to avoid exposing patients who may not tolerate Butrans.

Key exclusion criteria included evidence of impaired renal or hepatic function, various medical history restrictions, specifically a restriction of cardiac conditions and prolonged QTc interval, use of QT-prolonging medicines such as ondansetron, a commonly used antiemetic, and patients with a history of substance abuse were excluded.

The trial was designed to align with medical practice for the care of pediatric patients with

pain. This open-label clinical trial was designed to offer treatment for up to 26 weeks with Butrans with dose titrations permitted. Patients initiated treatment with 2.5 or 5 micrograms per hour of Butrans based on age, and they could be titrated flexibly using doses of 5, 10, or 20 micrograms per hour.

Dose decreases could occur at any time during the study. Dose increases could occur only after a minimum of 72 hours of treatment at a current dose level to ensure patients reach steady state. Clinic visits and study assessments were conducted throughout the study as shown.

The open-label clinical trial was designed to offer up to 26 weeks of treatment with Butrans. Initial dosing was based on patient age, with patients in the 7- to 11-year age group, initiating treatment with a 2.5-microgram per-hour patch, and patients in the 12- to 16-year age group, initiating treatment with 5 micrograms per hour.

Dose adjustments were allowed based on tolerability, safety, pain intensity, and the use

of supplemental analgesics. Supplemental analgesia with immediate-release opioids and non-opioids was permitted throughout the study.

As defined in the protocol, patients could be considered study completers if they completed the full 24 weeks of study drug dosing or at least 2 weeks of treatment and had not met any of the discontinuation reasons, and did not need additional treatment with an opioid at the minimum study drug dose; or had completed at least 2 weeks of treatment and were being tapered down from their current Butrans dose in order to switch to another opioid analgesic for tapering purposes and did not meet any of the discontinuation reasons in the protocol.

The difficulties conducting analgesic trials in children have been described by experts in the field. Few pediatric patients receive around-the-clock opioids for extended periods of time. Study design, lack of investigators, and a lack of potential study participants further compound those difficulties.

We encounter challenges in recruiting both investigators and patients for the study. There are few investigators and sites with the necessary experience and resources to conduct studies of opioids in pediatric patients. We approached investigators with appropriate pediatric specialties and experience prescribing opioids.

Few sites approached had sufficient numbers of potentially qualifying patients. Additional protocol-specific restrictions such as prohibited medications, cardiac monitoring, and the need for multiple blood samples for pharmacokinetic analysis also limited investigators' ability to participate.

The identification of potential patients was also limited by several factors, including the protocol requirement for at least 2 weeks of treatment since few pediatric patients require treatment with opioids for more than 2 weeks. Protocol prohibited concomitant medications with the potential to prolong the QT interval, such as ondansetron, diphenhydramine, and famotidine, further restricted the potential patient

population. That restriction significantly limited the enrollment of patients with cancer as those medications are commonly used in this population. Finally, the protocol limits for incoming opioid dose and the required taper imposed further limitations on eligible patients.

The selection of investigators and institutions with the appropriate patient population and resources to conduct the study proved challenging over the five years we conducted the trial. Purdue approached 500 investigators at 250 institutions in the United States, and of those, only 33 sites were initiated on the study. Of those 33 sites, 16 screened patients and 11 sites enrolled or dosed at least one patient on the study.

Similar challenges were encountered in identifying appropriate patients for enrollment on the study. Pre-screening was conducted to encourage active recruitment of appropriate patients and to provide information on patients who did not qualify for the study.

Pre-screening information was collected from any child with pain whom an investigator considered for study enrollment based on their clinical judgment. This initial consideration further prompted a more detailed review of the patient's medical chart and medical history by that study team to determine if the patient might be an appropriate candidate to formally approach for the trial.

For example, sites reviewed inpatient census, clinical schedules, and potentially OR schedules for patients who would be anticipated to require 2 weeks of therapy with opioids.

Over 3,000 patients were pre-screened. Of those, approximately 2,000 were in the appropriate age group for the protocol, 7 to 16 years. Seventy patients were screened for the trial and 41 patients were enrolled. Overall, only 1.3 percent of pre-screened patients were enrolled. For the younger age group, that percentage was even lower.

Patients pre-screened, screened, and enrolled were predominantly in the 12- to 16-year

age group. In the 7- to 11-year age group, 1.4 percent of patients pre-screened were screened and even fewer were enrolled. In the 12- to 16-year age group, 4.4 percent of pre-screened patients were screened, but even fewer enrolled.

Patients were selected for pre-screening by an investigator based on the patients' medical history, level of pain, and opioid analgesic requirements through chart review or review of clinic schedules. Again, over 3,000 patients were pre-screened for this study with approximately 2,000 in the appropriate age range for the protocol.

Patients were excluded at pre-screening primarily due to the age requirement, the anticipated duration of treatment of 2 weeks, and those protocol-restricted concomitant medications such as ondansetron, diphenhydramine, and famotidine, among others.

Seventy patients were screened for the study, which means that informed consent was obtained and study-specific screening procedures

were conducted. It's important to note that there were 29 screen failures for reasons such as abnormal CG findings, abnormal laboratory findings, and other medical exclusions. Of the 41 patients enrolled, 23 patients met the protocol definition of study completer with treatment durations ranging from 2 to 26 weeks.

There were 18 discontinuations with treatment durations of up to 23 weeks. Eleven of those 18 patients discontinued due to an adverse event. I will present those later in detail.

We enrolled a population reflective of pediatric patients with pain requiring at least 2 weeks of treatment with an around-the-clock opioid. There were 6 patients enrolled in the 7- to 11-year age group and 35 patients in the 12- to 16-year age group.

African-American patients were well represented and reflective of the occurrence of sickle cell disease in this population. On average, the weight of patients 7 to 11 years was approximately half that of patients aged 12 to 16

years, consistent with expectations in the pediatric population. All but 2 of these patients were using opioids prior to being enrolled in the study. Reasons for moderate to severe pain at study entry were varied.

The study protocol included patients with moderate to severe pain requiring or anticipated to require continuous around-the-clock opioid treatment for at least 2 weeks. The most commonly investigated reported sources of pain were back pain, migraine, and pain related to sickle cell anemia.

Back pain was the most common primary pain etiology and was often related to a complex underlying health condition occurring in patients with Crohn's and irritable bowel syndrome, kidney stones, sickle cell disease, and lupus or Sjogren's.

Thirty-nine of 41 patients were receiving opioids to treat their pain prior to study enrollment. Many patients require treatment with Butrans for an extended period of time.

Thirty-seven patients had at least 2 weeks of treatment. Of those, 18 patients had 12 weeks of exposure to Butrans, which aligns with the FDA definition of chronic therapy. Thirteen patients completed the full study treatment of 24 weeks. The mean number of days on Butrans was higher in the older age group, 12 to 16 years, at 101 days, compared with the younger age group at 26 days.

Butrans dose adjustments were permitted throughout the study. Exposure to the highest dose in the trial, 20 micrograms per hour, occurred only in the older age group with 13 patients exposed to at least 1 dose of 20 micrograms per hour. Ten patients were exposed to at least two weeks of the 20-microgram per-hour dose, and 6 patients were exposed to that dose for at least 4 weeks.

The characterization of pharmacokinetics of Butrans in children was a primary objective of the trial consistent with the PREA requirement. The study provides an adequate description of the pediatric PK data. Population pharmacokinetic analyses were performed using sparse samples

obtained at 5 time points during the first 4 weeks of treatment as steady state is reached during the first patch application by day 3, so all subsequent samples are at steady state.

The majority of patients had all 5 samples obtained. The pharmacokinetic data set of 38 patients, including 151 samples, provided a basis for modeling to characterize the population pharmacokinetics of transdermal buprenorphine in pediatric patients.

Population pharmacokinetics were performed consistent with FDA guidance. We leveraged population pharmacokinetics from adults in the planning and analysis of the pediatric population. A covariate modeling approach was applied with 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 two-compartment model with sequential zero and first-order absorption, which provided an adequate description of the pediatric

PK data.

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

We determined the starting doses to target the exposure seen in adults. We observed that a Butrans dose of 2.5 micrograms per hour in a 7- to 11-year-old patient and 5 micrograms per hour in a 12- to 16-year-old patient yielded buprenorphine plasma concentrations matching the targeted exposure in adults, dosed with 5 micrograms per hour of Butrans.

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

Evaluation of safety identified no new safety issues in pediatric patients not already

established as part of the Butrans safety profile for adult patients. The second primary objective of the study was to characterize safety. Safety assessments included adverse events, vital signs, oxygen saturation, laboratory tests, somnolence, and cardiac monitoring.

Adverse events were similar to those observed in the adult clinical trials. Overall, 32 patients experienced adverse events throughout the study, with 26 patients in the older age group experiencing adverse events. Of those 32 events, 12 were mild, 13 were moderate, and 7 were severe.

Twenty-one of those patients had adverse events that were classified by the investigator as related to study treatment. Eleven patients had events leading to discontinuation of treatment and 8 patients experienced serious adverse events. There were no deaths.

The most frequently reported adverse events were mostly those consistent with events commonly associated with the use of opioid analgesics or with a transdermal route of administration. The

most frequently reported adverse events included nausea, application site pruritus and irritation, somnolence, headache, and vomiting. Events of sickle cell anemia with crisis occurred in patients with underlying sickle cell disease. As with adults, some pediatric patients experienced application site reactions and a few of those patients had multiple events.

Eleven patients experienced application site-related adverse events and most of those were classified as mild. No events were classified as severe. The most common events were application site pruritis and irritation. Only one patient withdrew to the study due to a single event of application site irritation.

Now, turning to serious adverse events, 8 patients, including 4 in each age group, reported serious adverse events. One of those events, first degree AV block, was reported by the investigator as unlikely to be related to study drug. The remaining serious adverse events were reported by the investigators as not related to study drug, but

rather could be attributed to the patient's underlying condition.

The serious adverse events occurring in the 7- to 11-year age group included one patient with appendicitis, one patient with a Crohn's exacerbation, worsening anemia, and malnutrition, one patient with hypersomnolence, and one patient with first degree AV block. Two of these 4 events resulted in study discontinuation.

The serious adverse events occurring in the 12- to 16-year age group included 2 patients with multiple events of vaso-occlusive crisis, both patients with underlying sickle cell disease, one patient with a worsening of their osteomyelitis, and one patient with an exacerbation of migraine pain. Two of those patients discontinued study treatment following the serious adverse event. Seven additional patients discontinued treatment due to a non-serious adverse event.

In total, including both serious and non-serious adverse events, 11 patients discontinued the study due to those events. Five of those

patients had ECG findings that led to protocol-mandated study discontinuation, of which one event was considered serious. One of the patients who discontinued due to an ECG finding also had a prior adverse event of somnolence associated with that discontinuation.

The patients with protocol-mandated discontinuation due to ECG findings will be presented in detail separately. Again, 3 patients with serious adverse events discontinued treatment. Those events were shown earlier. These events were exacerbation of migraine pain, vaso-occlusive crisis, and hypersomnolence. In 3 patients, non-serious events of increased migraine pain, worsening pain due to neuroma, and skin irritation at the patch site led to study discontinuation.

There were protocol-specified thresholds for ECG, vital sign, and laboratory findings that led to further evaluation. Intensive electrocardiogram monitoring was performed throughout the study, with particular attention paid to QT interval measurements.

A thorough QT study of Butrans in adults showed that supertherapeutic doses of 40 micrograms per hour of Butrans resulted in prolongation of the QT interval. Patients with cardiac abnormalities or those receiving medicines that had known or possible association with QTc prolongation were excluded from the trial. ECG monitoring was performed throughout the study.

The protocol criteria for cardiac parameters and discontinuation requirements were conservative. Five patients had protocol-mandated discontinuation due to ECG findings, including 2 patients with QT prolongation, one patient with a prolonged QRS, one patient with first degree AV block, and one patient with sinus tachycardia. None of these findings was associated with clinical symptoms.

The serious adverse event of first degree AV block resolved while the patient was receiving Butrans. The event of sinus tachycardia occurred in a patient with a known history of sinus tachycardia, which persisted following discontinuation of treatment. Each of these cases

were reviewed by our pediatric cardiology consultant, Dr. Ramesh Iyer. Dr. Iyer is with us today and can answer questions related to these patients.

There were no clinically significant changes in blood pressure or pulse from baseline to the end of study. There were no patients with treatment-emergent clinically significant respiratory depression in either age group by age parameters. There were no clinically significant pulse oximetry changes.

The majority of patients stayed within the normal range for hematologic and blood chemistry values during the study. Toxicity grading for the trial was based on the National Cancer Institute common toxicity criteria. Three patients had laboratory toxicity grades greater than or equal to 3 after baseline, including an 8-year-old patient with neutropenia with underlying Ewing's sarcoma and chemotherapy treatment, a 13-year-old with low hemoglobin with underlying sickle cell anemia, and a 12-year-old with a single elevated ALT and AST

without an associated elevation of bilirubin or alkaline phosphatase. Those values returned to normal while the patient was receiving Butrans.

There were no unexpected safety findings in the pediatric population. No new safety issues specific to pediatric patients were identified that were not already established as part of the Butrans safety profile for adults.

The reported adverse events for the 12- to 16-year age group were consistent with the known safety profile of Butrans observed in the adult clinical trials and our postmarketing experience. There were not enough patients to draw conclusions in the 7- to 11-year age group.

In conclusion, the PK data for children 12 to 16 years of age who are at least 50 kilograms suggest that no dose modification is needed from adult dosing. For children 12 to 16 years of age who are under 50 kilograms, the PK data suggests that half of the adult dose should be used. There were no new safety issues identified.

I would like to thank all of our patients,

their parents and caregivers, for their participation in this important study. Their commitment and generosity contributed to the advancement of research in the treatment of pain in pediatric patients.

The pediatric study data on Butrans provides information for prescribers as they make challenging decisions about the care of the small number of children with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

We have with us today a number of respondents who are available to answer your questions. Thank you.

Clarifying Questions

DR. BATEMAN: Are there any clarifying questions for Purdue? Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Dr. Emala?

DR. EMALA: Hi. Charles Emala from Columbia

University. I guess my question is for the most recent speaker, and it's in reference to a figure in the briefing document from Purdue, which is figure 2 on page 34 of the briefing document, which is a visual analog scale reading of patients over the 24-week period in the 12 to 16 age group.

My question really comes down to the context of safety. And realizing that these children were also receiving supplemental analgesics, I'm wondering whether they really had a sufficient exposure to Butrans to interpret whether they were receiving a therapeutic level, and thus can we assess safety from that, realizing that on page 48 of the presentation, we alluded to the fact that the QT prolongation identified in the adult population occurred at levels of 40 mics per hour.

So I'm trying to reconcile whether in fact they're receiving a high enough dose to make an assessment of safety based on the visual analog scale.

MS. BALDRIDGE: I will first speak to the visual analog scale diagram. If you could bring up

slide 2, please.?

Exploration of analgesic activity was a secondary objective of the trial for informational purposes since efficacy can be extrapolated from the adult population. And as the speaker mentioned, the majority of these patients were receiving supplemental analgesia, most receiving supplemental immediate-release opioids during the study.

Regarding exposure of patients to evaluate safety, I'll ask Dr. Ram Kapil to speak to the exposure data obtained in the pharmacokinetic analysis.

DR. KAPIL: Ram Kapil, clinical pharmacology, Purdue. Can we pull up slide CP-13, please? These are the five subjects in question. So you see we have the respective age, weight, subject's first dose, and the last dose, and their respective clearance for each suspect, and maximum observed plasma concentration as shown in the middle of the column, and also the predicted area under the curve after the last dose. The second to

last column is the AUC projected at 5 micrograms per hour dose.

Just to draw your attention on the bottom of the table, we have PK information from the thorough QTc trial, where we saw prolongation of QTc at 40 micrograms per hour. The mean Cmax was 931 picograms per mL, and the area under the curve was 116.

If you could just look at the yellow shaded areas for these 2 patients with QTcs, they are below this so-called systemic exposure where QTc occurred. If you look at the very second to last column, the AUC steady state predicted at a 5-microgram per-hour dose is comparable to the human adult targeted exposure with the exception of the second row. But if we focus on these two subjects, the systemic exposure is comparable to the adult doses, and it's far below the QTc levels.

DR. EMALA: If I could just follow up, I understand that we didn't achieve those levels. My concern was, were the children exposed to a therapeutic dose of Butrans, because the visual

analog scale suggests that there were some improvements. But the text of the description of the figure talked about maintained pain scores rather than improvement in pain scores. And realizing that the children are getting additional drugs in addition to Butrans, I'm wondering if they were really exposed to a high enough level to assess safety if Butrans was being used as this whole analgesic.

MS. BALDRIDGE: The design of this clinical trial and others allow for use of supplemental analgesia and informative exploration of efficacy. Most 39 patients were receiving opioids at baseline, so they had a baseline pain score that indicated that their pain was generally maintained. When they transitioned to Butrans, they were allowed supplemental analgesia, so that is a factor in considering the pain scores.

I will ask Dr. Kapil to speak further about the exposure data for all patients in the study.

DR. KAPIL: Could you pull slide CP-25, please? So if we focus on the very last column,

the last column basically reflects the area under the curve at steady state, projected at 5 micrograms per hour dose for all of these 38 subjects. And the target there was to compare it to the target adult exposure at 5 micrograms, which was 17.

If you go to slide 24 to look at the statistics, if you bring that one up, as you can just see, the median exposure across all 38 subjects is around 19, which is comparable to the adult exposure. And if we look at the coefficient of variation here, it's about 21 percent, which is also comparable to what we see in adults.

So our data suggests that we have comparable exposure across all the kids.

MS. BALDRIDGE: Dr. Fanelli?

DR. FANELLI: Regarding the therapeutic level and whether Butrans -- at the levels we saw, as Dr. Kapil said, they're comparable to the adults.

In this trial, efficacy as a secondary measure, the subjects came in, the vast majority,

all but very few patients, on an opioid, so they were being maintained. They had pain relief with that application. Then they were tapered down, and a Butrans patch was applied.

So very similar to clinical practice, where there's supplemental analgesic given, the fact that the blood levels were similar to adults and that they maintained the pain scores, even though it was just secondary, we did not see a loss of analgesia when the Butrans patch was applied. It is consistent with the fact that there was therapeutic efficacy in those subjects.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: Good morning. Thank you. Ms. Baldridge, I had a question about the sicklers. It must be so hard to do a study like this. As a formal clinical trialist, I just can't imagine trying to coordinate this among centers. And I know it must have been very difficult to recruit non-cancer patients.

I take care of a lot of cancer patients, and I can't think of one that's not on ondansetron, so

you would have had to obviously recruit other kinds. You have 5 sicklers here, and 2 are listed in slide CC-45. Both of those had two crises I guess while on Butrans.

I'm just curious. At first blush, you look at some of these adverse effects, and like say appendicitis, obviously Butrans can't cause appendicitis and the same for the crisis. But on the 16-year-old female, it was stopped permanently.

Do you know if there's any reason that they said to themselves, "Could this crisis be related to the Butrans?"

MS. BALDRIDGE: Bear with me one minute.

DR. LITMAN: Yes, no problem.

MS. BALDRIDGE: I'm going to speak about that patient. So particularly for the patient with sickle cell anemia and multiple -- I think two events of vaso-occlusive crisis, the 16-year-old, the discontinuation was actually her choice. And we had other discontinuations that could have been related to the events or related possibly to lack of therapeutic effect or multiple doses of the

drug. That patient did discontinue due to lack of adequate pain control.

DR. LITMAN: Thank you. I just have one more question about the QT prolongation. As a pediatric anesthesiologist, this has plagued us for years. In fact, every day I'm in the OR, I give sevoflurane and ondansetron to everybody.

It really just makes me wonder. And maybe this is for you or Dr. Iyer, but when you were recruiting these patients, I would imagine that many of them who are already on opioid therapy had also already been on ondansetron. So for the purposes of the protocol, did you just stop it before they were entered into the study?

MS. BALDRIDGE: So for the purposes of the protocol specifically regarding ondansetron, they had to be free of ondansetron for 7 days prior to entering this study. There were a little less conservative criteria for medications considered additional QT prolongers. Ondansetron is a known prolonger, so they should have been off of that for at least 7 days before starting Butrans.

DR. LITMAN: Looking back on the patients, were there any that accidentally received both at the same time? I'm trying to get an idea. What would actually happen? Not everyone reads the label, of course, and it's bound to happen that someone's going to get this while also receiving ondansetron.

MS. BALDRIDGE: So we had very diligent monitoring and education of the investigators. But as you described, there were isolated events where ondansetron was administered to a patient on the study. One of those in particular was for one of our sickle cell patients who came into the hospital over the weekend in vaso-occlusive crisis, and the emergency room physician treated that patient.

Those were isolated events. We documented those closely. For certain patients, depending on the dose, or the ondansetron, or other medications given, they may have received extra safety or cardiac monitoring. But those were isolated events, which we dealt with education and reinforcing the prohibited medication list on the

study.

DR. LITMAN: Is there any cases out there that you know about where Butrans affected QT prolongation in a clinical way, any kind of clinical events?

MS. BALDRIDGE: I'll ask Dr. Iyer to speak to that question.

DR. IYER: Ramesh Iyer, pediatric electrophysiologist, Children's Hospital, Philadelphia. I am the cardiovascular safety consultant for the study. And my disclosures, I do not have any financial interest in the company or the outcome of this meeting.

With regards to any clinical cases where we had QTc prolongation, in my clinical practice, I am not aware of any. With regards to the 2 patients, I can describe the more details of what had happened.

I'm sorry. That's your question? I just wanted to clarify.

DR. LITMAN: No, that's okay. I was just curious. Obviously, most of us in this room, for

many years have been plagued by this QT prolongation without a lot of knowledge like what does it really mean. So I was just curious if there's been ever any clinical events associated with Butrans.

DR. IYER: I have one other comment about the ondansetron, which has been used in some of our patients with prolonged QT syndrome. So it does prolong. I'm not aware of a combination of the Butrans and ondansetron.

DR. LITMAN: Thanks very much.

MS. BALDRIDGE: I'll ask Dr. Paul Coplan. He has data on clinical events, and he can speak to that for your question.

DR. COPLAN: Thank you. Paul Coplan, epidemiologist. Could I have the first slide on the adverse events of interest?

One of the questions is, does the QTc prolongation translate into an adverse event, a clinical adverse event associated with that prolongation such as Torsades de pointes and cardiac death.

So the FDA looked at that for sublingual buprenorphine tablets, which are administered at a dosage strength that's 5 to 10 times higher than that of the highest dose of Butrans in adults. So we have to look at adult data to try to get an answer to your question, Dr. Litman, and to see in adults, is there an indication of the QTc prolongation translating into real-world events.

So in order to do that, we can look at postmarketing data. A study was done in the FAERs system by Dr. Cao with the FDA. I think Dr. Staffa is a co-author on that, I think. And they looked at whether there was a signal of QTc prolongation for buprenorphine as compared to methadone. And what they found was that there was a signal of sudden cardiac death in Torsades de pointes and other clinical adverse events for methadone, which is known as QTc prolongation, a molecule. But the buprenorphine did not show an increase.

However, they pointed out that there was a problem -- that their conclusions didn't translate to the patch. So we undertook a study to see

whether there was a particular issue with the patch. We used the MedDRA terms in the FDA adverse event reporting system. We used a narrow term, which is specifically for QTc, and then a broader term which looked at a broader array of clinical adverse events.

Could have slide 1, please? This is the data from that study published, and the bars on the far left in orange are the buprenorphine patch, Butrans. Those immediately to the right are other buprenorphine formulations. And the two peaks that are increased are for methadone, which was our positive control in the study and was at a negative control of fentanyl patch.

There's a broad term and a narrow term, so the broad term is more sensitive. The narrow term is more specific. As would be expected for methadone, the narrow term, the more specific term shows a stronger effect. For fentanyl patch on the far right, we don't see an effect. That's our negative control. You can see for Butrans, there does not appear to be an increase.

Now, the 2, the redline at the 2, is the criteria that's used. This is a geometric mean using a Bayesian smoothing measure, and as long as the confidence interval doesn't exceed a 2, then that is your signal.

Now, that doesn't quite get at your question, Dr. Litman, because how many of these people are already cancer patients and could be using ondansetron? So we looked at the U.K. data. So in the U.K., there's a buprenorphine patch called Transtec.

Can I have the next slide? This is an analysis that was done by the Uppsala Monitoring Center in Sweden using the Vg database. And again, we used methadone as a positive control. You can see the criterion. And they used the information criterion, and the lower bound of the 95 percent confidence intervals needed to be above 1 for a signal. So if you look on the far right, you can see, for methadone, it shows up pretty extensively.

The Transtec patch, which is used at a 35- to 70-microgram per-hour dosage strength, which is

substantially higher than the 20-microgram, which is the maximum dose in the U.S., the Transtec is specifically indicated for cancer patients. And there we don't see any increase in any of the clinical adverse events associated with proarrhythmia that we would expect if the QTc prolongation was translating into a clinical concern in these cancer patients. Thank you.

DR. LITMAN: Thanks very much.

DR. BATEMAN: We'll come back to remaining questions later this morning. So we'll now proceed with the FDA presentations, starting with Dr. Fields.

FDA Presentation - Sharon Hertz

DR. HERTZ: Hi. This is Dr. Hertz. Dr. Fields was unable to come today, so I'm going to present her slides.

What I'm going to cover is just a lot of the background that I think is important to consider when we're talking about pediatric development in analgesics, but particularly opioid analgesics.

This is what this talk is going to cover,

general pediatric drug development specifically as it pertains to analgesics, some discussion about our study requirements. I'll go more into opioids. We had an advisory committee specifically on the topic of pediatric opioid analgesic development, so I'll review that, and where we see ourselves moving forward.

You heard a little bit about this from the sponsor. I'm going to go into it in a little bit more depth. There's some general principles for pediatric drug development. Two key principles are children should have access to products that have been appropriately evaluated, and there should be thoughtful drug development and inclusion of children in trials, and that's critical to pediatric health.

So you heard a little bit about the pediatric legislation. There's two particular areas that cover drug development in children, Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

Best Pharmaceuticals for Children Act, BPCA, is

a voluntary system that sponsor can request. It results in issuing of a written request, and that's an extensive evaluation program that involves the actual moiety. It's not specific to the existing approved indication in adults, so it can be quite expansive.

We issue these when we think there's a public health need for that information in children, and it also provides a process for studying off-patent drugs, which can be challenging. And it's rewarded for someone who undertakes this type of development program with six months of marketing exclusivity if the terms are met, the terms of the written request. That's important.

As you heard, PREA, that's a requirement. We require pediatric assessment at the time the application is initially submitted, but we also have criteria to waive or defer pediatric studies. This legislation also created the Pediatric Review Committee, and that committee works with us, with the divisions, as we review pediatric plans and

assessments and also the waivers and deferrals.

With regard to pediatric analgesic drug development, it is clearly an unmet need for information about products used for pediatric pain management. Few products have pediatric indications or labeling. Most analgesic use is off-label in children. And although pediatric studies have been required since 2003, few studies have been completed.

Most infants and children are healthy and experience brief pain episodes, but it's important to remember that some have very severely painful conditions and really do require analgesics at the level of opioid analgesics.

These are the products that have pediatric labeling, and you can see there's very few opioids here. It's mostly NSAIDs, and that's in the area of JIA, juvenile inflammatory arthritis. We have a few of the combination opioid products that have some labeling, but you can see that these are generally not popular or more modern products. And of course, we've modified what's going on with

codeine now.

Here is a list of drugs in general that have no pediatric language. You can see that there are a number of products here that are used in children, and the way in which they're used is based on the education and experience of individual providers.

With regard to the study requirements for developing analgesics for children, prior to 2010, we were pretty strict. We required not only pharmacokinetic data, but efficacy and safety studies, and that's efficacy from adequate and well-controlled studies for almost all analgesics and all age groups.

Companies were very reluctant to undertake this. There were a lot of challenges, ethical concerns expressed from IRBs and investigators regarding the use of placebo or allowing children to experience more than mild pain. Clearly, this led to challenges with enrollment, concerns from parents, study sites, investigators, and there were just a limited number of patients in general.

Clearly, with neonates, it's a whole other story. They undergo painful procedures, and the experience of pain for the children is also an experience of pain for the parents.

We were getting nowhere or very little progress with obtaining important information for the use of analgesics in pediatric patients, so we needed to take a step back and look at what was the current state of the science and how could that help understand the discipline needed. So we convened a scientific workshop, and we asked leading pediatric, analgesic, and clinical trial design experts and clinical pain experts to come together and discuss what is the science behind extrapolation of analgesics for pediatrics and what is the science that helps us decide how to differentiate the different age groups? Then, if there are areas where there isn't science to support extrapolation, what kind of data is possible to obtain?

There was some discussion of extrapolation, and as you know, an adequate and well-controlled

efficacy trial was not required for Butrans in their PREA requirements.

Why is extrapolation an important concept in this area? Children are considered a vulnerable population and that results in the requirement for additional safeguards in studies. Particularly, they can't consent and also there can be, as they get younger, challenges with communicating symptoms. We also need to consider that they're developing, especially their nervous systems.

So extrapolation of efficacy is important when it's possible because studies in children can be difficult. There's a limited number of patients available to enroll, and extrapolation permits smaller studies that enroll fewer patients.

This is established by legislation, and it's a very specific situation in which extrapolation is allowed and here is the language there, so the disease and the effects of the drug are sufficiently similar in adults and pediatric patients so that we as an agency can conclude that pediatric effectiveness can be extrapolated from

adequate and well-controlled studies in adults. And that's usually supplemented with other information obtained in pediatric patients such as pharmacokinetic studies.

Just for your reference, the results of the scientific workshop was written up and published, so you can see more about the discussion that occurred at that time.

Since 2010, we have thought about how to apply the science to our requirements for studies in analgesics in children. Opioids, non-steroidal anti-inflammatory drugs, acetaminophen, and local anesthetics, we think that with the same exposure and in conditions where we think the pain has a similar mechanism, and the characteristics of the pain are similar, we can expect the effect of these products to be similar. And that's in the setting of understanding the pharmacokinetic exposure and also obtaining independent safety information in children. We don't extrapolate safety. We get additional safety information in pediatrics.

It seems that the science could support

extrapolation of efficacy for these types of drugs down to the age of 2, but based on a variety of physiologic factors, below the age of 2, really, attempts should be made to try and get actual efficacy data.

For other classes of drugs, including novel analgesics, we don't know whether or not extrapolation would be appropriate, so we start with the idea that demonstration of efficacy as well as pharmacokinetics and safety would be required across the age range. And then when it comes to chronic pain and the use of extended-release analgesics, there's very little use of this below the age of 7, and it's just not practical to even consider conducting studies.

I'm going to approach this drug-use data a little bit differently than you heard to show you the current landscape. We have national estimates of total pediatric patients in the zero to 16 age range who have received dispensed prescriptions for opioid analgesics from outpatient retail pharmacies. It's a very specific group that the

data sources cited here can provide information for.

What you can see is between the years of 2011 and 2015, overall there's been a decline in the use of opioid analgesics. And I think that's an important recognition that many uses of opioid analgesics in pediatric populations can be avoided, which is always a good thing, and we can see the decrease predominantly in the 7- to 16-year-olds, and that in the younger age groups, there's very little use of this data.

So here's the graph of the number of children with dispensed prescriptions, and it's just a way to break down IR versus extended-release and long-acting opioids. It's separated by age group. I think that when you're looking at the zero to 1, you may be thinking how is an ER used in this age range? And I think what that probably reflects is long-acting opioids, the use of methadone, and/or buprenorphine in the very young to treat things such as neonatal abstinence syndrome or opioid withdrawal syndrome.

The use of opioids in the middle age group, 2 to 6, is predominantly IR, immediate-release products. Even in the older children, use is really overwhelmingly immediate-release. And I think this speaks to a lot of the difficulties we've seen in various development programs trying to explore newer products in pediatric populations.

Which opioids are currently being used in pediatric populations? Here's a list for the IRs. It's predominantly far and away the hydrocodone-acetaminophen combination opioid products, opioid-non-opioid products as well as codeine-acetaminophen products.

This was in 2015. We're obviously going to expect the codeine numbers to change based on the more recent activities. And here is a distribution of what's being used with the extended-release and long-acting products. And you can see it's just a small amount, and it's mostly with the products described here.

Again, you can see that the methadone is, by percentage, greater in the zero to 1 compared to

the other opioids. I can't believe the zero to 1 in the transdermal fentanyl is an accurate representation of use, but the methadone, again, is probably not used for analgesia.

So you heard there's not a lot of Butrans use in pediatric patients. It's been approved since 2010. There's very little use. In some of the data systems, the number is so low that a reliable estimate can't even be generated.

So basically, to summarize that, use of opioids is on the decline. Their use is predominantly immediate release, and there's very little experience or use of Butrans in the pediatric population.

I'm going to go over OxyContin. This is always a trigger point for many. I'm just going to contrast what we're doing today with Butrans with what we've done with OxyContin, just to make the differences clear. OxyContin had pediatric studies that were also required, and we approved an indication, to many people's dismay, in August of 2015.

This was based on a written request, so it was different than the PREA requirements, and several studies were conducted, both with oxycodone immediate-release and OxyContin as a formulation.

We approved a pediatric indication, and we thought it was important because the pediatric patient population that seemed to be appropriate when this level of analgesia and type of product was necessary was a more narrow, more limited population than in adults.

So in contrast, for pediatric patients over the age of 11, they would have to be already opioid tolerant and using a minimum of 20 milligrams of oxycodone per day. That's the lowest available amount for dosing with OxyContin, and we wanted patients to already be known to tolerate that or its equivalent before the extended-release formulation is used.

In fact, we had data on the use of OxyContin -- I'm going to show that in a minute -- and we did not think we were creating a new use for OxyContin, but there was a lot of

concern that even just the attention would expand the use. That's the labeling. It just shows what I described.

We instituted some novel PMRs, trying to understand the impact of this new indication. One study requires the company to assess a variety of important and serious adverse events, and not just in the 11 and older age group but also the entire age range, and also to understand what the use patterns for OxyContin are in children, both looking before and after the approval.

So here are national estimates of pediatric patients by age, and it's the same three age bands, zero to 1, 2 to 6, 7 to 16, who received prescriptions for oxycodone ER, which for most of this, the only one approved or marketed at the time was OxyContin, dispensed from outpatient retail pharmacies.

You can see that the number has consistently declined in the older age group that reflects the wider use of opioids in this age group, and you can see that there's exceedingly little in the lowest

age groups. Again, one has to consider these are national estimates, and the likelihood of OxyContin being dispensed for somebody without teeth is pretty unlikely; hence the zero to 1 is not likely to be an accurate representation.

So there was a lot of consternation about this. We decided to review our approach for the development of analgesics in children at an advisory committee. This was held in 2016.

Some of the topics that were discussed at this meeting were the fact that there's still a lot of challenges in developing analgesics for or studying analgesics in children. There's still a lot of trouble enrolling patients. And I think this reflects the use patterns that we saw. There's not a lot of use overall, and there's really not a lot of use below the age of 7.

So there's too few patients. The parental concerns remain, and of course they're legitimate. Then the ethical and logistical concerns still remain, particularly when we're looking at neonates or the very young. It took four years to complete

the OxyContin studies, and we didn't get the full enrollment that was initially specified.

Also, in general, the understanding of the use of opioids in children is very difficult. I think the headlines that some of us saw around the time of the OxyContin approval really underscores how there's not a good understanding of the management of children with serious pain.

So we did this review, and this was also part of the commissioner at the time. Dr. Califf announced an agency opioid action plan, and what was included in there was that we would take pediatric programs to advisory committee. The committees would include representation from at least these three advisory committees, and if necessary, from others. We heard from, at this meeting, a number of FDA and outside speakers. Here's a link if you want to look at some of the details.

Just some highlights. There was overwhelming -- and many of you participated -- support for the need for data.

Children should not be treated based on just experience if there is an opportunity to also provide healthcare teams with the appropriate information about individual products.

It was also discussed that there are in fact pediatric patients whose analgesic needs include opioid analgesics for a variety of conditions, and we had some very interesting contrasts.

On the one hand, untreated or poorly treated pain in children can have a lasting effect, even irreversible effects, including sensitization to greater risk of chronic pain in the future. Pediatric patients are also vulnerable to problems with drug use and addiction, opioid use disorder, particularly and differently from adults because of ongoing brain development.

This really requires an understanding of how to properly manage pain, properly select patients for whom an opioid is appropriate when we're dealing with children, and to have a lot of education for the prescribers, for the patients, and for their families. Approvals will continue

where appropriate when we have enough information based on postmarketing requirements in other studies to assess the safety of these products in children.

So which patients are currently being treated with opioid analgesics? I mentioned this earlier, but there are chronic pain conditions or pain conditions that require treatment for two or more weeks. There are not a lot of children who require months or years of analgesics, but some conditions can require weeks or months. For those children, opioids may be appropriate. This includes, of course, cancer and end-of-care type of palliative treatment, post-op pain after extensive surgeries.

Really, it's hard to imagine putting a child through spinal orthopedic procedures, cardiothoracic procedures, other types of major surgeries, and not manage their pain post-op. Those types of major surgeries, major corrections, the pain can last for weeks at a pretty serious level.

But there's also the acute pain conditions for lesser types of surgeries, many injury or trauma settings, burns and dressing changes. Obviously, we've already mentioned sickle cell, which can have both acute and chronic needs, the key being particularly in studies, but of course in practice that the appropriate patient population be selected. Generally, for these extended-release and long-acting products, enrollment criteria include the need for an opioid for at least 2 weeks.

The same challenges remain, and we're continuing to work in a variety of settings with companies when we have particular product programs and also through other avenues with pain specialists and academic institutions to try and address some of the challenges with pediatric pain analgesic development.

Overall, we have important information gaps that still need to be filled regarding the use of opioid analgesics in patients, how to study these products, and how to use them most safely in

children. Currently, we have no evidence that labeling a product with an opioid indication for pediatric patients increases the use. We're continuing to watch that, though, and we'll continue to work with sponsors. We're open to looking at innovative approaches to this type of study, and we are committed to bringing these applications to advisory committees for further discussion, and a list of useful references. Thanks.

DR. BATEMAN: So the next presentation will be from Dr. Levin from the FDA.

FDA Presentation - Robert Levin

DR. LEVIN: Good morning. My name is Robert Levin. I'm a medical officer in the Division of Anesthesia, Analgesia, and Addiction Products. This morning I will be talking about the PREA requirement, and since Purdue has already covered the protocol in detail, I will be skipping those slides and proceeding to results of the study, and then finishing with a discussion.

In the Butrans approval letter from 2010,

the PREA requirement was issued, a PK and safety study for the treatment of moderate to severe or chronic pain requiring continuous around-the-clock opioid treatment for extended period of time in pediatric patients ages 7 through 16.

The study was deferred because the product was ready for approval in adults. We decided that an open-label study would be adequate because, as you heard, efficacy can be extrapolated from pediatric patients as young as two years of age.

The pediatric requirement for ages birth through 6 years was waived because the number of patients meeting the indication was too small to make studies feasible.

We told Purdue that 40 completers with at least 6 months of exposure would be needed to assess safety. As we have heard previously, our policy with regard to studies of opioid analgesics in the pediatric population have evolved since the Butrans approval.

Our current recommendations for pediatric studies of extended-release long-acting opioids

have changed, and we now require a larger safety database than what was previously told Purdue. We have also learned that it's difficult for pediatric patients to remain in an analgesic study for 6 months, and we currently request a 2-week minimum treatment duration.

I will be skipping the next three slides on study design and proceeding with the results.

The study was conducted over a period of 3 years and 9 months. We wanted to have an even distribution of patients across ages, but enrollment was more in the older ages since it is harder to recruit younger patients who meet the inclusion criteria. This is not uncommon in opioid analgesic trials.

Of the 41 patients exposed to at least one dose of Butrans, only 6 patients were in the 7- to 11-year age group, and those patients were in the older portion of the 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.

As you can see from this table, which summarizes exposure, older children had a longer duration of treatment. 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 information regarding the painful condition that qualified patients for the study raised questions for us. For example, we do not believe that migraine is an appropriate condition for enrolling subjects in a study for use of this kind of product.

I reviewed the reasons for pain at study entry and here is how I tabulated them. We also note that some of the diagnoses do not provide an explanation for the pain. For example, 2 subjects were listed as having Crohn's disease. While one subject was reported as having painful mouth ulcers, which may have been the reason for the pain, the other patient had no additional medical history.

We were able to review the medical records

for the patients enrolled at one site in study 3031. A review showed that, at study entry, there were limited options beyond opioids for these patients. We now request that the reason for opioid treatment be carefully documented for each patient.

We reviewed all the narratives carefully and don't think Butrans was responsible for any serious adverse events, but may have exacerbated the SAE of hypersomnolence. The remainder of the treatment-emergent adverse events were not unexpected for a product like this.

I would now like to summarize our findings. We do not recommend Butrans receive an indication for pediatric pain. As we heard earlier, the requirements for the approval of an ER/LA opioid in the pediatric population has evolved from when the Butrans pediatric study was designed and initiated. Most notably, we now require a larger database.

I further note that the number of patients in the younger age stratum was very small. Thus, there are inadequate safety information to support

an approval in the pediatric population.

I do note that in the limited database from this study, there were no unexpected safety issues. We intend to add information about Butrans from study 3031 to the pediatric section of the label.

Finally, we believe it is important for future opioid studies to recruit patients with appropriate diagnoses for treatment with opioids and carefully document the reasons for pain. This concludes my presentation. Thank you.

DR. BATEMAN: The next presentation is from Dr. Gottipati from the FDA.

FDA Presentation - Gopichand Gottipati

DR. GOTTIPATI: Good morning, everyone. My name is Gopichand Gottipati, and I'm a pharmacometrics reviewer in the Division of Pharmacometrics, Office of Clinical Pharmacology.

In the talk this morning, I'm going to cover the considerations for the pediatric extrapolation and FDA's assessment of the applicant's analysis with a specific focus on pediatric pharmacokinetics in study 3031.

As summarized by Dr. Hertz in her talk, a full extrapolation approach is acceptable for Butrans. Though Dr. Hertz touched upon extrapolation, I would like to highlight a few key elements of the full extrapolation approach in this slide and as outlined in the pediatric clinical pharmacology guidance.

The key questions to address when considering a full extrapolation approach are whether there is similarity in disease progression, response to the intervention, similar exposure response relationship, and if the drug or the active metabolite concentrations are measurable, and they're predictive of the clinical response.

If the answer is yes to all of the above, efficacy can be extrapolated from adequate and well-controlled trials in adults to pediatric population.

Two original considerations for a further pediatric extrapolation approach are around dose selection and safety. First, pharmacokinetic studies may be needed to support the selection of a

target pediatric dose or dosing regimen, which results in an exposure range or distribution that is comparable to adults.

In this regard, modeling and simulation can be used as a powerful tool to aid in the identification of the target pediatric dose or dosing regimen. When it comes to safety, it cannot be extrapolated, and the safety database needs to be evaluated at all the proposed doses to be used in the pediatric patients.

Switching gears, I'll be presenting a brief regulatory history around Butrans. The buprenorphine transdermal system was approved in adults at doses ranging between 5 and 20 micrograms per hour. A snapshot of the clinical pharmacology highlights the absolute bioavailability is around 15 percent. Dose proportionality was established in the range of 5 to 20 micrograms per hour.

Buprenorphine undergoes hepatic metabolism by a CYP3A4 pathway, which is assumed to be mature by the age of 7 years. The steady-state exposure levels were achieved in 2 to 3 days.

This slide shows the adult pharmacokinetics in adults following 3 successive 7-day buprenorphine Butrans 10 micrograms per hour application. The Y-axis represents the plasma buprenorphine concentrations and X-axis is time. We can see that the Tmax is achieved in around 2 to 3 days.

Since most of the information was presented in the preceding talks, I would like to draw your attention to two aspects in this light. In the younger age cohort, the dose was initiated at 2.5 micrograms per hour, while in the older age cohort, it was initiated at 5 micrograms per hour. The dose titration was based on tolerability and inadequate pain control. It was titrated up to the next higher dose at least 72 hours after treatment, and it was down-titrated again based on tolerability or adverse events.

A quick peek into the pediatric PK database, first, the PK blood samples were collected at 5 intervals 18 to 24 hours after the first application of Butrans, end of week 1; 2 to 3 days

after end of weeks 1, 2, and 3, or a discontinuation if it happens prior to the last scheduled draw.

The analysis data set consisted of 41 subjects who received treatment, 6 belonged to the younger age cohort while 35 belonged to the older age cohort, and the final pediatric PK data set consisted of 38 patients and a total of 151 plasma concentrations.

This table illustrates the distribution of the final titrated dose across the two age cohorts. Younger is shown in blue and the older age cohort is shown in red. What we can see here is that in the younger age cohort, the dose spanned between 2.5 to 5 micrograms per hour, while the older age cohort spanned from 2.5 to 20 micrograms per hour.

A closer look at the respective plasma buprenorphine concentrations in these age cohorts is shown in this slide. The Y-axis are the plasma buprenorphine concentrations, and on the X-axis is time after dose. The solid lines represent the mean adult pharmacokinetic steady-state exposures

at the recommended dose range of 5, which is on the lower end, and on the upper end is 20 micrograms per hour. The data points represent the pediatric buprenorphine exposures after the final titrated dose.

The take-home message from this slide is that the buprenorphine exposures observed in the pediatric population from this study are consistent with the observed exposures in adults following the recommended dosing range of 5 to 20 micrograms per hour.

Overall, a population pharmacokinetic 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 the exposures that are comparable to observe in adults. Furthermore, the body weight-based dosing recommendations can be derived to match the pediatric exposures to adults.

In line with what was presented by Dr. Levin, due to the small safety database, we did not propose specific dosing recommendations for

Butrans. Thank you.

DR. BATEMAN: We'll now take a 10-minute break. When we return, we'll do clarifying questions for the FDA.

Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:10.

(Whereupon, at 9:59 a.m., a recess was taken.)

Clarifying Questions

DR. BATEMAN: Welcome back. So we'll now have clarifying questions for the FDA. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Are there questions for the FDA? Dr. Greene?

DR. GREENE: Yes. Forgive me that I've failed to recognize the name of the last presenter on the pharmacokinetic data.

On the pharmacokinetic observations related

to the pediatric concentrations over time in this pediatric database, is there any evidence of differences in serum concentrations achieved in those patients who were on the therapy for a more prolonged period of time as compared to the shorter courses in some form of fashion?

DR. GOTTIPATI: This is Gopichand Gottipati, the pharmacometrics reviewer. We actually did not look at the data, but the plot that I showed is after the final titrated dose.

DR. GREENE: In that plot, there's great variability in serum concentrations achieved. And even though the best fit lines kind of look nice and achievable, it certainly gives me some pause to be concerned about some variability there.

DR. GOTTIPATI: Yes. That is correct. And I would like to also mention that that's the mean adult PK profile. And as you said, there will be some variability on that.

DR. BATEMAN: Dr. Ruha?

DR. RUHA: I'm sorry. I was still thinking of the Purdue questions.

DR. BATEMAN: We'll come back to Purdue questions later. Dr. Litman?

DR. LITMAN: Thank you. So intravenous buprenorphine is approved for pediatric labeling. I assume that's Sharon's slide number 8. Is there any mechanistic plausible reason why the efficacy or safety would be different for a patch vis a vis the actual IV injection?

DR. HERTZ: This is Sharon Hertz. We think that based on the available data, the efficacy for the product is extrapolatable. The PK, the absorption across the skin, we do need to understand that there are pediatric differences with the very young, but this isn't really used there. So from the efficacy perspective, no. We think that we can extrapolate.

From a safety perspective, we're not allowed to extrapolate data, so we put specific safety measures into the protocol and try to maximize the safety of any patients enrolled. And then within that context, we try to explore what the safety is and if it differs from adults.

DR. LITMAN: Thank you.

DR. BATEMAN: Dr. Flick?

DR. FLICK: Sharon or Ellen, can you tell me how you arrived at a sample size of 40? What drove the sample size, which I think is probably the central question here.

DR. HERTZ: This is Sharon Hertz. The sample size was driven by a lack of experience in what could be possible because, at the time it was approved -- Butrans was approved in 2010 -- we really had no sense of whether it would be something that would be useful in children, and we were struggling to have any studies completed. So it was an estimate, not a calculated population size.

We have changed what we've been asking for subsequently, so we do ask for more exposure, particularly across different age groups. But even then, it's a balance between the amount of information one would like to have to understand safety and the feasibility of collecting data across the age group.

DR. FLICK: So I guess what you're saying is that there was no primary outcome here in terms of safety, so the frequency of adverse events in buprenorphine in adults wasn't used to drive a sample size calculation or anything. This was just chosen based on your expectation of the ability to recruit patients?

DR. HERTZ: Yes.

DR. BATEMAN: Dr. Havens?

DR. HAVENS: Thank you. I had a question about the PK modeling. On slide 10, you suggest that modeling based on body weight could be done. Was it done and what were the results?

DR. GOTTIPATI: Based on the sponsor's analysis, they found that the ideal body weight was one of the important covariates, and that was presented by the sponsor.

DR. HAVENS: No, it wasn't. They said it, but they never presented the data. So you did not do an independent analysis of that?

DR. GOTTIPATI: They believed that the body weight is an important covariate.

DR. HAVENS: Well, they said ideal body weight. The backgrounder said ideal body weight. Your slide says body weight, but you did not do an independent analysis to look at that?

DR. GOTTIPATI: No, we did not look at the ideal body weight. We think body weight can be used.

DR. HAVENS: So when you did the body weight analysis, what's the appropriate dose that you suggested based on body weight? Does it break at 50 kilos like the sponsor suggests? Does it break at 40 kilos? What is the body weight to match the adult PK?

One of the things you can get from these kinds of studies is an appropriate PK analysis, which is done based on body weight or body surface area, or ideal body weight in certain circumstances, but not based on patient age, given that, as you point out, CYP3A4 is probably okay after a certain age.

So then the key parameters of interest are the dose given based on body weight or body surface

area, and then the exposure of interest, which in this case you've shown us.

So did we do that analysis?

DR. HERTZ: This is Sharon Hertz. We don't think we have enough data to put pharmacokinetic information in the labeling based on what was available.

DR. HAVENS: Okay.

DR. HERTZ: We reviewed the analyses that were conducted. We don't disagree with them, but it's not enough for us to confirm that we think there's enough information from PK, but especially from safety, to inform labeling.

DR. BATEMAN: Dr. Patrick?

DR. PATRICK: Stephen Patrick. I'm curious if we have safety information from other indications like opioid use disorder in adolescents, any other safety data for buprenorphine in adolescents from other studies that we can utilize in this, or is that not able to be utilized in these discussions?

DR. HERTZ: In the context of using

buprenorphine for other indications, it's challenging to use that in this setting because in opioid use disorder, obviously the safety profile is going to reflect that difference in the population, and in the management of analgesics, it's different.

The differences in the population, that I think are critical for not relying on one to support the other, would be the fact that in opioid use disorder, there may be exposure to other illicit substances, other co-occurring use disorders. And in the analgesic setting, it's going to be important to consider what the underlying condition is and how the effects of titrating the opioid to effect impact the overall safety.

The dosing paradigm for pain is different than the dosing paradigm for opioid use disorder. In opioid use disorder, you're going to target potentially a blocking dose, at least early on, and in analgesia, you're really managing according to symptoms.

So I think, in general, we're reluctant to use that to support use. It's important to use it for signal detection if there was anything specific that we needed to worry about.

DR. PATRICK: Sorry. Just a quick follow-up. That's actually part of what I'm asking about, some of the signals that we see with QT prolongation. Do we see similar trends in the data at least that are available, if there are data available, for adolescents and other indications?

DR. HERTZ: I have to go back and look to see what the data are for the PK prolongation in adolescents, but the amount of data available for that population is still fairly limited.

DR. BATEMAN: Ms. Robotti?

MS. ROBOTTI: I'm concerned about the extended and constant exposure to opioids in developing brains as compared to mature brains, and this is something that's perhaps known, but it's not known to me. I'm not a medical doctor.

But do we know anything about the effect of instant-release opioids on children and their

developing brains versus the constant regular exposure that a transdermal patch would give, and what the long-term effects are on addiction or pain reaction, anything like that?

DR. HERTZ: This is Sharon Hertz. We explored that in our 2016 advisory committee, and I can't do justice to that presentation. But your concern is appropriate that exposing the adolescent brain to opioids can have repercussions regarding risk for opioid use disorders in the future.

With regard to whether an immediate release versus extended release impacts that, I don't believe the data drill down adequately to separate that. However, in general, one should never use an extended-release product or a long-acting product if an immediate-release product dosed as needed is suitable.

What we hope occurs with dosing opioids, both in children but also adults, is that first the decision to use an opioid is based on a series of factors: is an opioid necessary; can non-opioid measures be used? If non-opioid, or even non-

pharmacologic approaches, are inadequate and an opioid is initiated, it should be started carefully with perhaps combination opioid/non-opioid products, which have dose limitations based on the non-opioid. And it should be used as needed unless around-the-clock analgesia is necessary.

For instance, post-op pain doesn't stop when you go to sleep, but some musculoskeletal pains may not be as intense when people are at rest and not weight bearing.

So as clinicians choose to initiate opioid therapy, we hope that there's not a situation in which intermittent dosing with an immediate-release product is overlooked and replaced by extended-release, around-the-clock dosing.

So in that light, hopefully if a pediatric patient is managed with an extended-release product, it's really because their pain is around the clock, their pain is at the level requiring an opioid and can't be managed with other products, that the dose is carefully titrated and the duration of use is limited to absolutely only as

long as necessary. And then the distinction of the effect of the IR versus the ER type of product becomes secondary because in that setting, the IR on an intermittent basis would not be sufficient.

DR. STAFFA: This is Judy Staffa. I'd just like to follow up and add just one more piece to that. In support of that meeting last September, our office tried to look into the question of, if we expose children to therapeutic analgesics, does that increase their risk for misusing or abusing, becoming addicted down the road in the future.

We found only one study that has actually addressed that. It's from Monitoring the Future, where 12th graders were asked about having a therapeutic prescription for analgesia of an opioid, and then looked at the risk in the next year or two for developing misuse or abuse behaviors. And the risk was about a 33 percent increase.

So it's not huge, it's not small, it's one study. We'd love to see more work in that area, and there was no ability to look at which agent,

what formulation, or any other details of that. But that's about all we know.

Open Public Hearing

DR. BATEMAN: We'll now move on to the open public hearing. Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA

encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organizations you represent for the record.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a senior fellow at the National Center for Health Research, and I previously trained at Johns Hopkins University School of Medicine.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from industry, so I have no conflicts of interest.

Our center strongly supports the purpose of the pediatric assessments under the Pediatric Research Equity Act to obtain data that will support the safe and effective use of new drugs in pediatric patients who already use or who may benefit from their use. We also support the purpose of this FDA meeting to discuss potential additions to the labeling of an opioid analgesic intended for use in children ages 7 to 16.

It is important to address the medical needs of children as effectively and safely as possible. Most opioid analgesic products have not been

studied in pediatric populations, and there is a lack of pediatric use information in drug product labeling. It is critical to provide clinicians with age-appropriate information regarding the safety and pharmacokinetics of opioid analgesics. This is only possible when we have evidence from high-quality clinical trials in children.

We are concerned that study 3031 is too small, too short, and includes some patients who are not appropriate to be in it. Despite what the company described as extensive recruitment efforts, the current required postmarket study included only 41 patients, 35 of whom were ages 12 to 16 and only 6 patients were ages 7 to 11.

Although the total sample size meets the initial requirement for the study, the recommended size of the sample has subsequently increased from 40 to 125 patients for the 12 to 17 age group and 50 patients for the 7 to 11 age group.

FDA's advice for the study was that 40 completers have at least 6 months of exposure in order to assess safety. However, only 12 patients

were exposed to Butrans for 24 weeks or longer, all of whom were in the 12- to 16-year-old age group.

In addition, patients in this trial had 19 different primary conditions that various investigators judged to meet the eligibility criteria for the study. FDA reviewers noted that some of these conditions do not generally reflect the currently accepted indications for the use of ER/LA opioids for children and adolescents.

Our questions are, why include information about a study that is flawed and does not meet current standards? Will the proposed labeling be helpful for providers and patients in real-world clinical settings? Will it be misleading?

We are concerned that including the information will tend to encourage physicians to prescribe the drug to children. The small sample size and duration of treatment for most children are not adequate to provide evidence that this drug is safe for children. For example, 5 patients discontinued trial participation due to ECG-related adverse events, and Butrans could not be ruled out

as a contributor for three of these patients.

Serious adverse events also led to study discontinuation for three other patients. Twenty percent of patients experienced treatment-emergent serious adverse events that were more common in the 7- to 11-year-old age group. The researchers concluded that events were not caused by the drug.

It is important for this panel and the FDA to make decisions about drug labeling based on good science and strong data. We concur with the 2016 advisory committee that because pediatric patients are vulnerable to drug use and addiction due to ongoing brain development, proper prescribing, patient selection, and education are crucial to optimize safety in this population.

Results of study 3031 do not provide sufficient evidence to inform healthcare providers about the safe use and proper dosing of Butrans in the management of pain for pediatric patients. We urge this advisory committee to advocate for pediatric patient safety and urge the FDA to require that the drug be appropriately evaluated

before allowing information about Butrans to the pediatric section of the labeling.

Thank you for the opportunity to share our perspective.

DR. BATEMAN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you represent for the record. Speaker number 2?

(No response.)

Clarifying Questions (continued)

DR. BATEMAN: That concludes the open public hearing. We'll now move on to questions for the sponsor, remaining questions for Purdue. Dr. Ruha?

DR. RUHA: Yes. I was just curious. This is Michelle Ruha. We heard that most of the children enrolled were previously on opioids, and several times it was mentioned that the opioids were tapered down. I just wanted to clarify, were they tapered off or down? And if they were still on opioids, did any of the children have withdrawal syndrome when the Butrans was initiated?

MS. BALDRIDGE: So by protocol, there were a couple of different parameters for that incoming opioid and the taper. First, patients 7 to 11 had to be on doses of under 40 milligrams a day of morphine equivalent to be considered. Patients in the 12- to 16-year age group had to be on less than 80 milligrams a day of morphine.

If they were at those higher doses, they were tapered down, not off, for the older age group tapered down to 30 milligrams a day of morphine or equivalent, and the younger age group tapered down to 15 milligrams a day of morphine or equivalent, and then initiated therapy on Butrans.

Adverse events were monitored throughout the study. There were no events of withdrawal. That was monitored at clinic visits through clinical assessment and judgment of the investigator, and those events were not described in the study.

DR. BATEMAN: Dr. McCann?

DR. MCCANN: Hi. I actually have two questions. One is for Dr. Fanelli, slide 10. Did you look at how many pediatric patients were

getting both opioids and ondansetron? Do you have any information about that?

DR. FANELLI: This data is the data that Dr. Hertz was also mentioning that was done by FDA. But in terms of in this database, I'm not aware that those combinations were studied.

MS. BALDRIDGE: It's my understanding that this database was exploring utilization of opioids. I'll let Dr. Hertz or Dr. Staffa speak to it.

DR. HERTZ: We don't have that information. We did not conduct that analysis.

DR. MCCANN: My second question is for Ms. Baldridge, slide 49. So it looks to me that 2 out of the 41 patients had mild prolongation of their QT. Is that the same? It works out to be about 5 percent, and I realize it's a very small sample. Is that what you find in adults?

MS. BALDRIDGE: I will ask Dr. Iyer to speak to our adult data. We have some information about the rate of frequency in adults, and then we also have information about clinical events if we need to look at that as well. Dr. Iyer?

DR. IYER: Slide 1 up, please. There were two detailed thorough QTc adult studies performed. In the first study, the 1011 did not show any evidence of QT prolongation with 10 micrograms per hour. But with the supertherapeutic doses of 40 micrograms and 80 micrograms per hour, there was a 9.2- and 11.4-millisecond increase in the maximum mean QTc.

Now, when we look at the ICH E14 guidelines, less than 5-millisecond increase is not proarrhythmic. Greater than 20-millisecond increase in the mean QTc is associated with proarrhythmic events. Any number between 5 and 20 is inconclusive. This was the adult data.

Slide 2 up, please. In the pediatric data, the mean change was negative 4.1 milliseconds in the 7 to 11 age group and a 5.8-millisecond increase in the 12 to 16 years' age group.

Compare the adult data, which was not a thorough QT study, but looking at 5, 10, and 20 micrograms per hour and measuring the placebo-corrected QTc, the increase was minimal.

So the answer to the question, if we compare the two studies apples to apples, the adult QTc data, this study and the pediatric study, the QTc increase is minimal. The two patients that had QTc prolongation were also unfortunately on other medications that potentially could explain, but our criteria to discontinue therapy were very conservative.

DR. MCCANN: But wasn't that an exclusion criteria if they were on medications that could prolong QTc?

DR. IYER: Yes, it was.

DR. BATEMAN: Dr. Havens?

DR. HAVENS: Thank you. I'd be interested to see the results of the dosing or the exposure data by weight, weight-based dosing. Do you have that.

MS. BALDRIDGE: Dr. Kapil?

DR. HAVENS: Then if you could show us why you decided that ideal body weight-based dosing is better than plain body-weight dosing, that would also be interesting.

DR. KAPIL: Thank you. Consistent with the guidance, we leveraged adult pop PK data, which we had available, and from this study 3031, we were able to get sparse sampling, which is one the approaches for pediatrics. So we had about 151 samples, PK samples.

We used the simulation approach where what we did was we leveraged adult data where we adjusted for the PK parameters like clearance and volume distribution, adjusted to the body weight using a fixed allometric exponent. For clearance, we used 0.75; for volume distribution, we used 1.

So we did extensive simulations, and at that stage, we used ideal body weight to gauge an idea. This was to initiate therapy, where prior information in pediatrics was not available. We were leveraging adult data.

With that in mind to answer your question, if we go to slide CP-3, if possible, these are the results of our simulation based on adjusting the body weight. I apologize for the extensive data, but what we are showing here is using national

averages for age 7 to 16, and what their median ideal body weight is, and based on a model, what will be the projected dose.

This example shows where we are trying to target an adult dose of 10 micrograms per hour. So if we focus on the last rows here, you can just see that the ideal weight for 7- to 11-year age group is around 34. And if you go to this matrix, it turns out to match the 10-microgram per-hour dose in adult, you would require around a 5.9-microgram per-hour dose for the smaller age group.

Similarly, when you look at 12 to 16 years old, the model predicted that you would require 8.6 to match the systemic exposure. And if we look at the whole panel, you could also see where we end up for sudden AUCs, whether we use 2.5 all the way to 20 micrograms per hour, and based on the ideal weight, what will be systemic exposure in this shot.

So this was what was used to initiate therapy. And once we initiated the therapy -- and I would like to draw your attention to CP-25,

please. This is all the data set we have. The one shown in yellow is the subjects from 7- to 11-year age category. As you'll recall, we initiated both sets of ages at two sets of doses. The 7 to 11 was initiated at 5, and then they were titrated based on their analgesic needs. The 12- to 16-year-olds were titrated up to the needs of their analgesic needs.

Now, if we focus here, this example here shows where we would be because the initial adult dose is 5 micrograms per hour, and at 5 micrograms, adult dose, our targeted area under the curve at steady state is 17 nanograms per hour per mL, which is shown right here on the left-hand side.

If I could draw your attention to the last column, this is how all 38 subjects ended up, based on the model and based on the individual rate of each. Now, we are talking total body weight, not the ideal weight, the body weight of each individual across these 38 subjects, and then we use their observed plasma concentrations.

The expected area under the curve at steady

state at a 5-microgram per-hour dose is shown in the last column. If you focus on the blue area, that represents the range of expected area. Our goal was to target 17. And if you look at the yellow area, the expectations are as predicted, that they are 2X of the adult exposure.

So again, that was very consistent with our study where we initiated the lower age group at 2.5 micrograms, which is what our model predicted, and you can see the exposure.

If we could summarize this, and slide 1 up, please? Our target here, as shown in the blue on the right-hand side, is 17 nanograms hour per mL. This is the AUC for adult when you give a 5-microgram per-hour dose. And based on our study in 38 subjects, we were able to match that with the two sets of dosing conditions as shown.

DR. HAVENS: Can I ask a follow-up? Can we go back to that prior slide?

So the 22-kilo kid had an AUC of 49? If I remember, that is similar to the AUC that you would expect to see in somebody who's getting the

40-microgram per-hour patch as an adult. Is that right? So could we say here that dosing children at body -- you're focused on age. Let's focus on body weight for a little bit. And you've got those kids at the lowest body weight. Some of them are 22 kilos, pretty small. His AUC is 46.

Is that the one who had the QT prolongation? Is there a PK/PD relationship that we can find between drug exposure and toxicity in this data set? You seem to suggest that that relationship exists because you don't use an adult dose greater than 40 micrograms per whatever it is, hour, so that suggests that there is an exposure response relationship to toxicity.

Is that the kid? The slide that we saw from the FDA suggested there were two people with these very high exposures that were outside of the standard adult range. Are those the kids who had the QT prolongation?

DR. KAPIL: If we could go to slide --

MS. BALDRIDGE: I'll let Dr. Kapil follow up, and he's going to speak to the PK exposure in

patients with the cardiac AEs. That younger patient with the weight of 22 kilos was not one of the patients with QT prolongation. It did not occur in the younger population.

In pediatrics, age is often used as a proxy for weight. In the protocol, initial dosing was determined by age, but then the PK modeling gave us additional information about the influence of weight in the model. And I'll let Dr. Kapil follow up on that.

DR. KAPIL: I was just going to add one thing, that interindividual variability is pretty inherent. And when we look at the patch data in adults, when we look at the data at 20 micrograms per hour, a 20-microgram per-hour patch versus 40, you will always find some overlap, which we see that in the context that there are some, for lack of a better word, outliers, which we cannot ascertain why the levels were higher.

But to answer your other question about the relationship, as you recall, the data is sparse, and the design of the study was focused on

comparable exposure to adults at this point.

DR. HAVENS: But the other issue that comes up is you didn't really do an ideal body weight analysis. But because in a transdermal system, if you're under weight from your ideal body weight, you may absorb more, and if you're over weight from your ideal body weight, you may absorb less. So that would become an important consideration in this kind of an analysis.

So that's why I was interested. And I really, really appreciate your showing these data. Thank you very much.

DR. KAPIL: We fully appreciate your questions. Thank you.

DR. BATEMAN: So I have a question for Ms. Baldridge. Can we pull up slide CC-30? As I understand it, the lowest dose that's available on the market is 5 micrograms per hour. When the protocol was designed, why did you allow for dosing at 2.5 micrograms per hour in the older age group? I mean, I see here that 15 of the 35 patients were titrated down to that lower dose.

So if we're doing a safety study, trying to evaluate the medication, it's a bit concerning to me that half the cohort received a dose that wouldn't be accessible to clinicians.

MS. BALDRIDGE: So I have a couple of points to address that question. In the older age group, the use of the 2.5-microgram per-hour patch was in one patient used as a starting dose, which was a special exception to the protocol starting dose.

The remainder of those patients, that was used at the end of therapy as patients had to be tapered down off of the product. We initiated the 2.5-microgram per-hour dose in the trial to allow recruitment of that younger patient population because that was the appropriate starting dose.

DR. BATEMAN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. Ms. Baldridge, since you're up there, I have a couple questions. I'll start with you.

You mentioned in the course of your presentation about supplemental pain medication being administered to the study subjects,

presumably for breakthrough pain?

MS. BALDRIDGE: Correct.

DR. ZACHAROFF: Do you have some more information regarding what was used and some data regarding needs for supplemental pain medication?

MS. BALDRIDGE: I do. So by protocol, supplemental immediate-release opioids were allowed as patients were on Butrans. We didn't have any restrictions about rescue analgesia used on the study.

Slide 1, please? This slide shows a summary of supplemental pain medication in both age groups. The most commonly used immediate-release opioids while patients were on study were Vicodin, tramadol, and oxycodone. And as you can see in the top line of the table, 40 patients of 41 took some supplemental analgesic during the trial.

Patients also took non-opioids. I can provide that summary as well, but this is limited to the opioids used on study.

DR. ZACHAROFF: So all of those were administered orally?

MS. BALDRIDGE: Correct.

DR. ZACHAROFF: Thank you. Then I have a question for Dr. Fanelli.

Dr. Fanelli, in your second slide of the product description, it said, "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."

Would treatment with IR formulations of opioids be included in alternative treatment options that are inadequate?

DR. FANELLI: Yes, it would. And that is the revised indication for these products.

DR. ZACHAROFF: Okay. So in my mind, then, someone who is tolerating and being well managed on immediate-release opioid therapy would not necessarily be a candidate for this medication?

DR. FANELLI: Yes, that's correct.

DR. ZACHAROFF: Then with respect to the long-term opioid treatment, I've heard post-operative pain mentioned a couple of times here today. And as a pediatric anesthesiologist, I'm

not a hundred percent sure that I consider post-surgical pain to be something that I would consider to be a requirement for long-term opioid treatment.

I'd just like some clarification with respect to that because I would be very concerned if somebody said that they were going to use this medication as something right out of the gate, that they would want to use it to treat post-surgical pain in a pediatric patient population.

MS. BALDRIDGE: So in the protocol, eligibility was determined by patients with moderate to severe pain requiring or anticipated to require at least 2 weeks of treatment. So for some very complicated surgical procedures, it is possible that pain can persist beyond 2 weeks.

We did have patients post-surgical procedure enrolled on the study. The first was a patient who underwent a repair of pectus excavatum. The second was a patient with a hemipelvectomy with underlying Ewing's sarcoma. And we had 2 patients who had traumatic injuries, one with a gunshot wound and one with a limb-crushing injury who also had some

associated surgery.

So these were complex patients who were expected to need at least 2 weeks of around-the-clock opioids, and they had to be at least 48 hours from the surgical procedure to be considered for enrollment.

DR. HERTZ: Excuse me. This is Dr. Hertz. And I'd just like to speak to this a little bit as well because that language and how we've integrated that language is not a program-specific concept.

When we were deciding whether or not it was appropriate to study extended-release or long-acting products in pediatric age ranges, what we did was we looked at utilization data to see if it was being used because the underlying concept of when to study products in pediatric age groups is based on whether or not there's a need. If there was no need for any of these products to be studied in these age groups, we would not request or require them.

So for instance, we don't request or require studies for these extended-release products below

the age of 7. The use is exceedingly limited, and the studies are not really even feasible. But we do know that there is use of these products in a subset of pediatric patients with pain over the age of 7. So we do require companies to attempt to study these products in that age range because we anticipate there could be use, and we want information available to prescribers.

When we explored the data about how these products were being used and when we spoke with different clinicians, what we found was that there are patients with cancer and other diagnoses that are consistent with the use in adults, the appropriate use of these products in adults. But there was a pattern of use in certain post-operative patients, particularly in this setting, or the setting that was described, that these patients typically require 2 to 4 weeks of treatment with an opioid, and clinicians were selecting extended-release products because they basically wanted to allow the children to be dosed less frequently and to have less interrupted sleep.

So in order to get information from the relevant population where we thought these products would be used based on existing practice patterns, we described in our PMRs, our postmarketing requirements, and in other settings like the studies described in written requests that this population would be acceptable to help fulfill enrollment and understand the safety and PK.

DR. ZACHAROFF: So with respect to using these patients as study participants, it totally makes sense, but I'm used to the term "long-term opioid treatment" meaning something else in the context of chronic opioid analgesic therapy.

DR. HERTZ: That's true. And the other distinction with the adult population is when we do these studies in children, it's not the first opioid. Somebody who has failed, an adult who has failed immediate-release opioids used on an intermittent basis or a more regular basis can be moved on to an extended-release product. But there are some adults who develop a condition where their pain is suitable for around-the-clock treatment

early on, and many of the extended-release products come in low enough doses, strengths, to be safe to initiate treatment. But that's a much harder situation to consider in children because of their smaller size, their smaller weights, their younger age.

So we want to know that the children can tolerate a dose of opioid that's as consistent as can be calculated with the lowest available dose of the opioid or that can be created in an age-appropriate formulation, hence the 2.5 dose with this product.

Companies are required to create an age-appropriate formulation when it's necessary because the existing adult or the existing marketed doses are too high. They are not required to market those doses, but they are required to develop them for these studies.

The only time when that doesn't occur is when the formulation cannot be developed in a lower strength, and that's based on the chemistry and manufacturing parameters. And we actually require

submission of a development report to support any contention that that lower strength could not be formulated.

DR. BATEMAN: Dr. Flick?

DR. FLICK: My question was answered.

DR. BATEMAN: Dr. Schmid?

DR. SCHMID: Yes. Chris Schmid. I just wanted to verify the 7- to 11-year-olds, there were 6 of them. Correct?

MS. BALDRIDGE: Correct.

DR. SCHMID: The mean age was 10.3. So there was only 1 child under the age of 10, is that correct, and 1 child who was 10?

MS. BALDRIDGE: There was an 8-year-old, and if we can, pull up the demographic slide, or if we have the slide on age and weight. I'm trying to work from memory, but that sounds accurate. I think there was one 8 year-old, two or three 10 year-olds, and an 11 year-old?

DR. SCHMID: Yes. Well, the way I calculate it, there's one 8, one 10, and then the others are 11, I think.

MS. BALDRIDGE: I apologize. I don't have those details.

DR. SCHMID: Thanks.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: My question has been answered.

DR. BATEMAN: Ms. Robotti?

MS. ROBOTTI: My question's been answered.

DR. BATEMAN: Dr. Greene?

DR. GREENE: So I have two questions just to be clear. Dr. Kapil I believe will have to address this. But just help me to fully understand this sparse sampling strategy for pharmacokinetics. It's really kind of -- I'm not sure what you're trying to tell me about that.

MS. BALDRIDGE: Sure. I'll ask Dr. Kapil to give the details, but in the study, we applied the sparse sampling, which means there were few samples for each patient, not intense sampling over sequential repeated hours of sampling and over 24 hours.

The patients had up to 5 samples during the first 4 weeks of treatment. Four of those samples

were obtained after a steady state was achieved, so after 3 days on treatment, the subsequent samples were achieved at steady state. I'll let Dr. Kapil speak to the rationale for that approach and support of the study.

DR. KAPIL: Thank you. Because of ethical reasons and because of consent, it's becoming very clear that there are only so many samples we can take. And in the emerging field of pharmacometrics, which our agency is really on top, they have put in the guidance that you can leverage adult data to get things going.

It has also become very clear that size matters. Body weight plays a big role. So what we did was in our so-called population pharmacokinetic model from adults, we leveraged that data and incorporated -- adjusted the PK parameters for body weight.

When we did, and we then followed up again per guidance simulation -- that's another technique which is becoming very common, modeling and simulation -- in that spirit, we were able to

generate data where we maximized what we had. We had 38 patients with 151 PK samples. And when we simulated the data, what we did was we relied on each -- that's how we initiated the therapy, and then we collected the samples, and then we revisited the data.

What we found, our study suggested was that body weight -- if you could recall, age and body weight are very closely correlated in this small age span of 7 and 16, so we didn't have to add age as a covariate. Body weight basically explained everything, and we used that technique. And it's a well-accepted technique where we take sparse sampling in children and then leverage prior data.

DR. GREENE: But again, just to be clear, we had a standardized approach to drug concentration sampling, and we had samples in every patient.

MS. BALDRIDGE: We had samples in 38 patients, 151 samples. We sampled all patients, and levels of quantifiable samples were present in 38 patients.

DR. GREENE: Great. One other question,

then, for you, Stacy, if you don't mind.

I know you're saying that patients were not supposed to be enrolled if they were on medications that prolong QTc, and yet, you indicate that some patients were exposed to other drugs that prolong QT.

So I guess the question I have is, what is the experience? In the real world, we're not going to be able to, pragmatically -- we're going to struggle with preventing patients from getting those concurrent therapies if we say this drug can be used.

So our experience in this population being exposed inadvertently, or whatever, is very important, to me at least. So is there enough data to actually describe in X number of patients there was concurrent exposure and these were the outcomes?

MS. BALDRIDGE: So we do not have that analysis at this time. We could provide it to the agency at a later date. I will say, at study entry, the restriction of protocol restricted

concomitant medications, there was great compliance at study entry. The challenge came when these kids presented to the emergency room or were potentially treated by another physician, but it was still limited.

Investigators were able to follow the protocol, and in addition, that list changed. That list of prohibited medications changed throughout the course of the study. It was very intense education and awareness for the investigators and study staff, but there were isolated incidents. We did not analyze those separately, but could take that under consideration.

DR. GREENE: I just think that would be meaningful information because that's going to happen in real life.

DR. BATEMAN: Any further questions for the sponsor or for FDA?

(No response.)

DR. BATEMAN: So if not, we'll move to the charge to committee. Dr. Sharon Hertz will now provide us with the charge.

Charge to the Committee - Sharon Hertz

DR. HERTZ: It's been very interesting to hear the questions and the discussion, and I thank you for the careful attention that's being paid to this application.

We're going to ask you about any concerns regarding the data. Now, obviously, we're all aware that the study itself was small and limited, so what are concerns? And then discuss whether information should be added to the label.

Let me just say that we have a number of options and we didn't specify them in detail. But what we can do and what we often do when we have studies that are not sufficient to support an indication is a variety. There's a range.

We can say that a study was conducted, describe it briefly, and then we can say whether or not it supports any conclusions. We can provide a lot of information if we think the information is as good as will be gotten and is important for the labeling. Basically, at this point, given what you've heard about the use of the product, the

information that could be obtained, that's the background we'd like you to consider as we go through these discussion points.

There's no vote here because there's not a new indication to vote on. There's not an approval of sorts in that context. It's really whether the study should be represented in some manner, and if so, we'd like to hear your thoughts.

Questions to the Committee and Discussion

DR. BATEMAN: We'll now proceed with questions to the committee and panel discussions. I'd like to remind the public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So discussion question 1, discuss any concerns you have regarding the data from the evaluation of Butrans in pediatric patients. Are there any questions or concerns regarding the wording of the question?

(No response.)

DR. BATEMAN: So if not, we'll now open the

question to discussion. Dr. Greene?

DR. GREENE: I guess I'll go ahead and just express some concerns that I have in the beginning. It seems that even though the numbers are small in this data set, we're missing the opportunity to address at least some information by not having better analysis of those patients that were continued beyond some 2-week, 4-week, whatever period of time instead of just that limited first two weeks.

Then secondly, the comments that I made about the QT-prolonging drugs that were given in the data seems to me to be information we ought to have.

DR. BATEMAN: Other comments? Dr. Patrick?

DR. PATRICK: Stephen Patrick. I think my concern is with the QT prolongation, and the limited amount of data that we have, and also which population is going to be utilizing this medication.

It strikes me that it's a population that's going to be fourth line, that's going to be

commonly prescribed other medications. So I just wonder about the practical application and worry about broad mission creep, where we see this medication being used more broadly in other populations. But it just strikes me that we don't have enough data on the QT prolongation issue and what that actually means.

DR. BATEMAN: Dr. Flick?

DR. FLICK: It seems that the sponsor was asked or required to perform this study, was given a sample size. The sample size was too small from the outset. The population under study is not the population likely to use this medication in the future. In fact, many of the patients in this study are, in my view, inappropriate for this medication.

It seems that if the primary question here is safety, then the study ought to focus around endpoints that represent what we would consider to be likely causes of serious adverse events. Hypersomnolence, it's hard for me to imagine that hypersomnolence is not associated with the

medication even though it's suggested that it was not medication effect; in some situations, prolonged QT.

Those would be the two endpoints that one would think that the study should be built around if it's considering safety. Clearly, the numbers or the sample size would have to be substantially larger than it is.

DR. BATEMAN: Dr. Havens?

DR. HAVENS: So there are a lot of drug measurements taken, but the way that data are presented, it's really quite difficult for me to understand what the PK really is because the people who started at 2.5 moved to 5. The data that might be presented might have been on the 5. It's hard for me to tell.

While I understand that age and weight are usually matched, often they're not. And faced with any patient, usually we care -- within this broad age range, call it, 6 to 18, weight is more important than age. So the data need to be analyzed based on weight.

In a transdermal system, something needs to be considered about skin depth, obese or not obese, so ideal body weight or not, depending on how that might control the drug exposure.

So there is potentially a lot of data here that could inform the interested clinician in knowing that in a 50-kilo child who is in the median for body weight, the drug exposure at 5 would be expected to be similar in this child compared to an adult.

That's often the beginning of this extrapolation process, to get exposure data based on small PK studies in children. But the way the data are presented here doesn't even allow that.

DR. BATEMAN: Dr. Portis?

MS. PORTIS: Yes. I want to echo some of the concerns. I think we really don't have adequate safety data, and I know someone mentioned that we can't extrapolate and assume that children are little adults. That's really important in terms of the weight issues, and the issues of the developing brain, and later impact. None of that

is addressed and I think those are really important safety concerns.

I think Dr. Flick also touched on that, that we're not really looking at the population that would most use these drugs. There is a little bit of mention about end-of-life care and children with cancer, and that's a whole different picture than in terms of what the needs are there and addressing the needs of those kids.

DR. BATEMAN: Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. I was struck by the fact that all the children needed supplemental analgesia at various times, and I'm not clear on how that compares to adult supplementation with the same patch. But it would indicate to me that it's quite possible that therapeutic levels were not achieved, that potentially the same amount of drug in a child's body does not give the same amount of relief.

I don't think that was made clear that the children were getting the kind of relief that they wanted, and clearly we couldn't give them more. It

wouldn't be safe.

DR. BATEMAN: Other comments?

(No response.)

DR. BATEMAN: So to summarize the committee's discussion on question 1, there was a specific concern that the study was small, that the population included may not be representative of the patients who had received the treatment in the real world, patients who have cancer, who are at the end of life, who may be co-exposed to other medications, particularly medications that prolong the QTc.

There was a mention that perhaps these types of studies should be focused on particular endpoints that are of concern, like somnolence and prolonged QT, and that the studies should be adequately powered to address those issues.

There was a noted difficulty in interpreting some of the PK data due to shifting doses and the fact that weight was not always accounted for in the analyses. There was thought that additional analyses could be conducted given the data that

were collected, particularly focused around weight.

At least one member of the committee raised the concern that two patients were disenrolled due to prolonged QTc, suggesting a potential safety signal, but clearly we don't have enough data to fully evaluate this risk.

There was also some concern raised about the efficacy of the doses at which Butrans was administered, given the amount of supplementation that was required with additional analgesics.

Any other points that should be added to the summary?

(No response.)

DR. BATEMAN: So we'll move on to discussion question 2. Discuss whether the information from study 3031 should be added to section 8.4, pediatric use, in the Butrans label.

I'm just going to add to that, perhaps it would be useful to the FDA if we commented on the proposed language for the Butrans label that was provided by the sponsor in appendix C.

Ms. Higgins?

DR. HIGGINS: I am concerned that if we did move in this direction, it would encourage more generous use of the medication by treating physicians. As a consumer rep, that's something that gives me pause.

DR. BATEMAN: Dr. Zacharoff?

DR. ZACHAROFF: Kevin Zacharoff. I'm fully cognizant of the fact that we need to start studying these medications in kids, and we need to start thinking about releasing information about how medications are being tested in children to start chipping away at some of the barriers we've been living with for the majority of our careers.

So I think it would be valuable to add information from this study to this section about pediatric use, but I would also think that there should be clear statements about the fact that representative pain models were used in order to facilitate the study that may not necessarily be representative of clinical applications for this medication.

Also, clarification of the term "long-term

use," as I discussed earlier, for fear that people might think that even in an institutional setting, this might be the treatment of choice. And thirdly, clarification of the fact that in this study, supplemental analgesic therapy was utilized and as detailed as is possible be mentioned about that fact.

DR. BATEMAN: Dr. Ruha?

DR. RUHA: Hi. Michelle Ruha. I agree. I think it would be important to add some of the information from this study to the pediatric information. I don't think we can really say anything about efficacy or safety based on this study. However, there is some limited pharmacokinetic data that I think could be added because I don't necessarily think use will increase because the labeling is there, but if people are using it in children and there is pharmacokinetic data that we have, then I think we should share that in the labeling.

However, I do have concern that a 2.5-microgram dose that isn't available might have

been used to obtain that pharmacokinetic data, so I wonder if that data should be looked at again without the 2.5-microgram doses and then used in the information in the labeling.

DR. BATEMAN: Dr. Emala?

DR. EMALA: So I have some concerns about adding any of the language to the pediatric labeling because while in the case of the agency I'm sure there's a strong understanding of the difference between an indication and then adding labeling under pediatric use, I wonder, in the average prescriber's hands, if that distinction is really that clear.

I would be concerned that having information from what I think is a woefully inadequate study, conveying the suggestion that this has been studied and that some safety criteria have been satisfied, I think could give a very wrong misimpression.

So I feel pretty strongly that adding any language would indicate that some sort of adequate study has been done, which I think is not the case here.

DR. BATEMAN: Dr. Flick?

DR. FLICK: I think the sponsor has made a valiant attempt to comply with what was requested by the agency. Unfortunately, I think the question is, does adding this information to the label inform the prescriber or misinform the prescriber.

I think that there's risks here that this is misinformation or information that is so incomplete as to mislead the prescriber and suggest that the study implies in some way that this medication has been adequately studied in children when it clearly has not.

So I would think that this is probably not something that should be added to the label.

DR. BATEMAN: Dr. Portis?

MS. PORTIS: I agree. I think that we really don't have enough data, and we need to use an abundance of caution here. Jennifer, your comments about we don't want to encourage more generous use I think is very important, that we do have a lack of data.

Yet, I also want to say that I appreciate

that the sponsor said they're not going to start encouraging this, that their goal is not to market this for more wide use. I hope that we will keep looking at this because, as the patient representative, the number one thing I hear from patients, and families, and parents of young patients is about pain, and especially in cancer and end-of-life care, that there will be pain that isn't controlled.

So it is a really important issue that we try to get adequate data so that doctors have at their disposal every available and appropriate medication to help because I think we really do need to be able to assure these patients that there are ways to appropriately and safely control their pain and the pain of their children.

DR. BATEMAN: Dr. Havens?

DR. HAVENS: Thank you. I do think there might be some additions or changes to what the company proposes that could allow you to put some of that data in, specifically, further, a more complete description of the study, pointing out

that baseline prolongation of the QT is a contraindication of the use of the drug in children under age 16 would be a reasonable thing to say.

The company states in what they've presented here that there's no increase in safety signal, but in fact there is because two people of a very small study were stopped because of QT prolongation, which is an important issue.

The baseline for forbidding use of drugs that might prolong QT, if you're going to put something in, should also be in the label to fully describe the population of study. And I think, importantly, while you can say you can use it in somebody over 50 kilos, you can make a strong statement that you shouldn't use it in somebody under 50 kilos because there's inadequate data, and there may be high drug exposure, and there's no appropriate dosing formulation for that.

So there would be ways to modify this to allow it to be used, but it would have to be very carefully structured to limit its use.

Can I ask a question? Has the company

satisfied PREA only if something gets in the label, or does doing the FDA-required study satisfy the company's PREA requirements? And I can understand if the FDA doesn't want to answer that question.

DR. HERTZ: Hi. This is Sharon Hertz. No, I do want to answer that for the record. Completing the studies that are described in PREA PMRs, PREA postmarketing requirements, satisfies the requirements independent of what is chosen for labeling.

DR. HAVENS: Good. Thank you. So in follow-up to that, then, to understand the evolution of the FDA requirements for postmarketing requirements for PREA studies might be interesting, what are the specifics of doing that.

Has that been published, just this argument about age, and weight, and BMI versus body surface area?

DR. HERTZ: This is Sharon Hertz. I don't know what's been published in a general way regarding that.

DR. HAVENS: Right. So this gets to

Dr. -- kind of the opening gambit here, that this is sort of an ad hoc study number chosen so that we could do this.

DR. HERTZ: I'm sorry. I just needed to confer with a colleague. There is a guidance, a clinical pharmacology guidance, that does describe some of these parameters and how to evaluate them in this setting.

DR. BATEMAN: Dr. Greene?

DR. GREENE: As I sit in an organization where we're very active at defining drug-use policy and we deal with very difficult and challenging patient care situations, the availability of data, whatever the data may show, is important to us, yet we have to be careful to interpret that.

We also recognize that maybe in the general population, I'll say, we have plenty of evidence that providing data in the wrong way to indiscriminate prescribers or indiscriminate salesmen clearly correlates with increased use of drugs in the wrong way.

So there's this conflict within me to know

that we need the data to be able to understand how we can better deal with difficult situations. On the other hand, we know that making the data available may pose risks. And I guess I want to echo Dr. Havens's requests.

It seems to me prudent that we want to somehow make this data available to careful clinicians, but be very, very careful to change the way it's described to cite its many flaws and limitations. I don't know how better to summarize that.

DR. BATEMAN: Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. I do agree with many of the opinions of the panel that have cited the lack of the data and the inadequacy of this very difficult trial to do, but I do respectfully disagree with the overall risk-benefit ratio.

I think that any data that we can get on pediatric patients should be given to practitioners. When I look at the overall risk of using this versus the benefit to some patients, ,

remember, this is a drug that's not used very often. It's a drug that's mostly going to be used by specialists in pediatric pain or hematology, oncology. And I do believe this data should be somehow listed, but I also agree that there has to be some clarifiers, perhaps additional language about careful monitoring of the things we're concerned about, whether it's hypersomnolence or the QT interval.

But what we didn't really discuss here today is the advantages of buprenorphine over other opioids, but I think that if a clinician wants the option of using this patch for 7 days on a child with pretty bad pain that they're having trouble controlling, any additional data we can give them would be helpful.

DR. BATEMAN: Dr. Patrick?

DR. PATRICK: I echo some of the concerns earlier raised about, again, the population that was studied and how this is actually applied. I worry that the labeling at least appears to be an endorsement. I wonder if there are other

mechanisms to provide these data because I generally agree that data are what they are and putting them out there is helpful. I wonder about -- maybe it's not the appropriate venue to ask -- peer-reviewed publication of these data to be out there, or if there are other venues other than labeling.

That aside, I think perhaps more detail on what potential labeling options there are to provide some data to the public without some of the statements that are here, that are listed as a potential candidate.

DR. BATEMAN: Sharon, do you want to comment on that?

DR. HERTZ: I'd like perhaps clarification on the question a little bit more.

DR. PATRICK: I guess the question is, what are the options in terms of what is put in the -- because there are so many things that appear that they could be on the label. We have this sort of extraordinary effort that was undertaken to gather these data, and there's the desire from all

of us to share these data to clinicians, as well as this worry that the underlying population isn't necessarily representative of who this would be utilized in.

Is there a way to provide the appropriate warnings with still sharing these data? How is this typically done?

DR. HERTZ: I'll avoid commenting on what's typically done because pediatric labeling is going to be based on a number of factors that can often be specific to the situation.

We have a very large range of options, literally from nothing to full-indication clinical trials represented in section 14, which is the clinical trials section, full pharmacokinetic data in section 12, and additional information in section 8 for pediatric labeling, as well as in the adverse event labeling.

So that is the range. The challenge is what to do when we have limited data and how to balance the concerns described here, the need to convey as much information as is available for use by

thoughtful clinicians versus conveying information that may not be stable or reliable, or that may not be clear enough to be used by the prescribing population. When the data are limited, we will often not include it if we don't think it's sufficient for decision-making.

For instance -- and I'm going to give general things here not specific to this application and comments -- if the PK data are not reliable enough to support dosing and administration instructions, we generally do not include it. I can think of one example where that's not what we did in my division.

So even to say that there are general approaches, sometimes there are underlying circumstances that have to be taken into consideration.

In the case of the exception, while the studies themselves that were conducted didn't provide a full picture, there was such extensive use of the product and data from other sources that we decided to include a lot more in the label.

This one is more challenging because there is not extensive use. It's not clear whether or not more data will be collected based on feasibility of more studies.

Conceptually, it would take years to enroll enough patients to get more data, and as you've seen, the use of these products, of opioids in pediatric patients, is declining, so that makes the decision harder. Does the fact that we don't think we'll be able to get more information make it more or less important to put what we have in the label?

So options in this type of setting could include limited information. But I will tell you that when we try to provide context in labeling about limitations, they're not necessarily received by the people we want to receive them.

Labeling is our primary means of communication, but we know that people don't read labels. We know that people don't understand the differences in a box warning, a warning, representation of adverse events, even contraindications. So it's always a challenge to

balance all of these different elements.

DR. PATRICK: Just to follow back up, I think with that context, the concerns about the PK data, particularly in the population I think may utilize this, that may be under weight, the concerns about safety, I think I wouldn't support including the data on the label.

DR. BATEMAN: Dr. Havens?

DR. HAVENS: But in terms of other places to present the data, one of the anesthesia crowd here must write guidelines, or textbooks, or the St. Jude's you can use this drug in my hospital guideline.

So then the question is, what is the source of data that you use to do that, and would having this discussion or a standard review on the FDA website allow you to draw from that?

So the access data website has been revised. They now put the summary review and the initial review. So on Butrans from 2010, you can see all of the review that's there.

Will this review go on that website for the

2017 discussion, even if the label is not changed? The reason I ask is because I participate in guidelines writings for children with HIV, and there's often a dramatic difference between what is in the label for children and what the guidelines say, and we often use these kinds of FDA review documents to inform. So it's not just me saying this is okay, the FDA has the data.

So that would be another way to hide the data somewhere for the thoughtful guideline-writing crowd to say, "I'm not going to put that in because that's crazy," or "Make your own decision."

So where will all these data go?

DR. HERTZ: We're in a public meeting. All of this information is currently either available publicly through our Web based on the background packages. That's all available. The meeting is going to be transcribed. So this information is now public.

With regard to our reviews, our reviews ultimately get posted. They go up on the Web when we approve an application, but not when we take a

type of non-approval action called a "complete response."

So whether our reviews get posted depends on our ultimate action, and I don't know what that is now. We're going to think about everything that we've heard today and use that in our decision-making for label for the action. It will be incorporated into our thinking as conveyed in our reviews.

DR. BATEMAN: Dr. Flick?

DR. FLICK: I'm going to persist in suggesting that this not go on the label, notwithstanding my good and friend and colleague, Dr. Litman. I worry that the only thing that people will read is the dose. They will go to the dose. They'll decide they're going to use this formulation, and they'll go and use that dose.

I'm not sure that any one of us, Peter, would be comfortable with that. I agree that having the information available is in general a good thing, but again, I'm not sure that this information really informs. It may misinform.

With regard to guidelines, the Society of Pediatric Anesthesia just published a set of guidelines around opioid use in children. This obviously was not included in that. The problem is you I'm sure know in HIV work, the numbers are very small, and it's very difficult to write evidence-based guidelines when there is very little evidence.

So I still have to say that this probably doesn't belong in the label. If you look at the current label, what it says is "Safety and effectiveness of Butrans have not been established in patients below 18 years." I think that statement stands and should remain.

DR. BATEMAN: Any additional comments on question 2? Dr. McCann?

DR. MCCANN: Mary Ellen McCann. I just want to reiterate what Randy said. I'm a pediatrician as well as a pediatric anesthesiologist, and I've had the occasion to write prescriptions for drugs that I wasn't that familiar with. And my inclination -- and you can call it laziness if you

want -- is to go to the labeling. If there's a lot of information there, I don't read it. It just sort of is a shortcut for me, incorrectly, that the FDA has studied this extensively. They've actually written two to three pages about whatever the drug is, and then I go to the dosing. I may go quickly to the adverse reactions, but very quickly scan them. And it's a rare drug that I will read the labeling from start to finish.

So I think putting this information in falsely to perhaps lazy practitioners gives them false assurance.

DR. FLICK: Brian, can I make one other quick comment? So Ron said that the use of this drug will be by pain providers, which I think is probably not the case. So we saw in this study that those enrolled were probably many of them, inappropriate, for the use of this medication.

If we look at the postmarketing data for OxyContin, we see inappropriate use as common, post-operative pain as Dr. Zacharoff pointed out. These ER/LA-class opiates are not appropriate for

most patients.

The sponsor pointed out that a pectus repair is an appropriate patient for an ER/LA-class opiate. That is clearly inappropriate. It is not a complex surgery; it's an everyday procedure in pediatric patients. It's painful, but it certainly doesn't require an ER/LA-class opiate.

So this formulation will be used in patients where it's inappropriate or marginally appropriate by non-pain providers. So we have to keep that in mind, as Dr. McCann points out, that they will go to this, look at the dose, and use that dose as a starting point.

DR. BATEMAN: Any additional comments?

(No response.)

DR. BATEMAN: So to summarize, I think there were mixed opinions amongst the committee members as to whether information from study 3031 should be included in the label. Many on the committee voiced concerns that including information on the label will suggest that there are robust safety and efficacy data in pediatrics, which would be an

inappropriate conclusion, given some of the limitations associated with this study.

There was concern that the providers and the public may not make the distinction between an indication and information on the labeling, and that providers will frequently just look to the label for information on dosing and not read through the details where the limitations associated with the study would be expressed.

Some on the committee thought that the information might be valuable to providers, and therefore advocated for including information about the study in the label. I think in general people felt if there is information included, there should be clear statements beyond what's currently in the proposed label about the restrictions in the population that were included in the trial, noting that many patients were excluded because they were on drugs that prolonged the QTc, or had prolonged QTc, or other contraindications to participation, and that that should be put front and center on the label.

People also felt that information on the doses used in the studies should be clearly expressed, the fact that patients frequently required supplemental analgesics and a clear statement that the safety data are indeed limited.

The conclusion of the currently proposed label suggests that there aren't additional safety concerns that have been raised on the basis of this study, and several people suggested that that should be amended to note that several patients had ECG changes that were concerning and potentially related to exposure to the drug. Then finally, one member of the committee suggested that clear weight-based dosing information should be provided once those analyses are completed.

Any additional things to add to the summary or amendments?

(No response.)

DR. BATEMAN: So we'll move on to our final discussion, question 3. Discuss whether any additional labeling changes are supported by the data from study 3031. Are there any concerns or

clarifying questions regarding the discussion question? And to my mind, it heavily overlaps with our previous discussion. Dr. Zacharoff?

DR. ZACHAROFF: I keep hearing Sharon say that the spectrum of what could be mentioned is nothing to anything. And I'm wondering if there might be a way to make some mention of this information in the label without implying in any way, shape, or form how the medication should be dosed, and so on and so forth.

When Sharon said it, I was thinking exactly that. This is public information now. The study has been performed. The results are in. There's not enough data. I think we all agree about that. But is there a way possibly to just mention in some part of the label that this was done without giving clinicians the ability to mistakenly infer that these are marching orders and how the drug should be prescribed.

DR. BATEMAN: Other comments? Dr. Portis?

MS. PORTIS: I think that what you said -- I'm sorry, I don't know your name -- was

really important about physicians being very busy, and you're going to look quickly at the labeling and let that guide you. I look at even FDA's statement, and I think it's really clear that there really isn't sufficient data to describe the safety profile.

That's what I would want highlighted because of the fact that we're giving guidance to the physicians who are busy, and are going to look at that labeling, and maybe aren't going to dig into paragraph 3 of that information. So I think that's a really important comment, and I appreciate what you said.

DR. BATEMAN: Any other comments from the committee? Please?

DR. WADE: Dr. Hertz, I want to just say something, with all due respect. But in listening to this conversation, I'm struck by the challenges of this long QTc and the restriction of doing safety studies in the population who's receiving the drug, yet trying to do a safe study and limiting other prolonged QTc drugs, and we kind of

have to decide which safety data we want.

So I just wanted to put a plug in to considering these safety studies in these class of drugs that have the potential for prolonged QTc, and is it possible to come up with a design such that we could allow a drug like ondansetron and get into the population that's actually being exposed when we do these studies.

I just say that respectfully because I know that that is quite a challenge to design a safe study with multiple drugs that all may have a prolonged effect. But I think that I would feel better about this data if it was in a population of children with palliative care, or oncologic needs, or other needs that have them on concomitant medications that pose similar risks.

So I just wanted to say that that may be a consideration in future designs.

DR. BATEMAN: Any other comments?

(No response.)

DR. BATEMAN: Then before we adjourn, are there any last comments?

(No response.)

DR. BATEMAN: We need to mention Dr. Melody Cunningham had an emergency and was unable to attend today's meeting by telephone.

Before we adjourn, any last comments from the FDA?

DR. HERTZ: Just once again, I want to thank you all for taking time out of what I know are very busy schedules. This was really helpful, and safe travels home.

Adjournment

DR. BATEMAN: So panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so that it may be recycled. We will now adjourn the meeting. Thank you.

(Whereupon, at 11:59 a.m., the meeting was adjourned.)