FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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

Virtual Meeting

Tuesday, February 15, 2022

9:30 a.m. to 5:36 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

DR. BATEMAN: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email is currently displayed.

My name is Brian Bateman, and I'll be chairing this meeting. I will now call the February 15, 2022 Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to order. Dr. Moon Hee Choi is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. CHOI: Good morning. My name is Moon Hee Choi, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Bateman?

DR. BATEMAN: Good morning. Brian Bateman. I'm professor and chair of the Department of Anesthesiology, Perioperative, and Pain Medicine at Stanford University.

DR. CHOI: Dr. Goudra?

DR. JOWZA: Good morning. I'm Maryam Jowza. I'm the associate professor of Anesthesiology and Pain Management at UNC School of Medicine.

DR. CHOI: Thank you, Dr. Jowza. I was calling on Dr. Goudra.

DR. JOWZWA: Oh, I'm sorry.

DR. CHOI: No problem.

Dr. Basavana Goudra, please?

(No response.)

DR. CHOI: Dr. Goudra, you might be on mute.

(No response.)

DR. CHOI: Dr. Goudra, you might be on mute.

DR. GOUDRA: Do you hear me now?

DR. CHOI: Yes, we can.

DR. GOUDRA: Hello?

DR. CHOI: Yes. Please introduce yourself.

DR. GOUDRA: Yes. Basavana Goudra, anesthesiologist at Penn Medicine, Philadelphia.

DR. CHOI: Dr. Higgins?

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

DR. CHOI: Dr. Horrow?

DR. HORROW: Good morning. I'm Jay Horrow. I design and conduct clinical trials at Bristol-Myers Squibb, and I am clinical professor of Anesthesiology and Critical Care Medicine at the University of Pennsylvania.

DR. CHOI: Dr. Jowza?

DR. JOWZA: Good morning again. I'm Maryam Jowza. I'm associate professor of Anesthesiology and Pain Management at University of North Carolina.

DR. CHOI: Dr. McAuliffe?

DR. McAULIFFE: Good morning. I'm Maura McAuliffe. I'm professor of nursing and director of the Nurse Anesthesia Program at East Carolina University.

DR. CHOI: Dr. McCann?

(No response.)

DR. CHOI: Dr. McCann?

(No response.)

DR. CHOI: It looks like you're on mute, Dr. McCann.

(No response.)

DR. CHOI: Dr. McCann, can you hear me?

(No response.)

DR. CHOI: Perhaps you might be double muted.

DR. McCANN: I'm not muted at all.

DR. CHOI: Okay. We can hear you now. Can you please introduce yourself?

DR. McCANN: Okay. I'm Dr. Mary Ellen McCann at Harvard Medical School, associate professor, and I work at Boston Children's Hospital. I apologize.

DR. CHOI: Thank you.

Dr. Richmond?

DR. RICHMOND: Good morning. I'm Rebecca Richmond, associate chief pharmacy officer at Duke University Hospital in Durham, North Carolina.

DR. CHOI: Dr. Shoben?

DR. SHOBEN: Hi. I'm Abby Shoben. I'm an associate professor of biostatistics at The Ohio State University.

DR. CHOI: Dr. Sprintz?

DR. SPRINTZ: Hi. This is Michael Sprintz. I'm an anesthesiologist, pain medicine specialist, and addiction medicine specialist at the Sprintz Center for Pain, and I'm a clinical assistant professor at University of Texas Health Science in Houston.

DR. CHOI: Dr. Zaafran?

(No response.)

DR. CHOI: Dr. Zaafran?

(No response.)

DR. CHOI: It looks like Dr. Zaafran may not be on yet, so I will go back to him.

Dr. Calis?

DR. CALIS: Good morning. This is Karim Calis. I'm director of Clinical Research and Compliance for the National Institute of Child Health and Human Development at NIH, and I'm also

chair of the NIH Intramural IRB.

DR. CHOI: Dr. Griffin?

DR. GRIFFIN: Yes. Good morning. This is Marie Griffin. I'm an internist and pharmacoepidemiologist and professor emerita of Health Policy at Vanderbilt University.

DR. CHOI: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Good morning. Sonia Hernandez-Diaz. I'm professor of pharmacoepidemiology at the Harvard Chan School of Public Health in Boston.

DR. CHOI: Dr. Hertig?

DR. HERTIG: Good morning. John Hertig. I'm associate professor and vice chair of Pharmacy Practice at Butler University College of Pharmacy and Health Sciences in Indianapolis.

DR. CHOI: Dr. Hovinga?

(No response.)

DR. CHOI: Dr. Hovinga?

DR. HOVINGA: Sorry. I was double-muted. Can you hear me?

DR. CHOI: Yes, we can. Can you please

introduce yourself?

DR. HOVINGA: I'm Collin Hovinga. I'm clinical associate professor at the UT College of Pharmacy in Austin, Texas, and I'm senior vice president for Clinical and Scientific Development at I-ACT for Children. Thank you.

DR. CHOI: Dr. Huybrechts?

DR. HUYBRECHTS: Good morning. I'm Krista Huybrechts. I'm a pharmacoepidemiologist in the Division of Pharmacoepidemiology at Brigham and Women's Hospital, and associate professor of medicine at Harvard Medical School.

DR. CHOI: Dr. Lo Re?

DR LO RE: Hi. I'm Vincent Lo Re. I'm in the Center for Clinical Epidemiology and Biostatistics the Center for Pharmacoepi Research and Training in the Division of Infectious Diseases at the University of Pennsylvania.

DR. CHOI: Dr. McAdams DeMarco?

DR. McADAMS DeMARCO: Hi. I'm Mara McAdams DeMarco, and I'm an epidemiologist and the associate professor and associate chair of research

at the New York University Department of surgery in New York City.

DR. CHOI: Dr. Mehta?

DR. MEHTA: Hi. Good morning. I'm Reema Mehta, and I am head of Risk Assessment and Management at Pfizer, and I am the non-voting industry rep.

DR. CHOI: Ms. Robotti?

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I'm the founder and president of MedShadow Foundation and the executive director of DES Action USA.

DR. CHOI: Mr. O'Brien?

MR. O'BRIEN: Good morning. I'm Joe O'Brien. I'm president and CEO of the National Scoliosis Foundation, and I am the patient representative.

DR. CHOI: Dr. Ruha?

DR. RUHA: Hi. I'm Anne-Michelle Ruha. I'm the chief of the Department of Medical Toxicology at Banner University Medical Center in Phoenix and professor of medicine and emergency medicine at the University of Arizona College of Medicine in

Phoenix.

DR. CHOI: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Good morning. Kevin Zacharoff. My expertise is in anesthesiology and pain medicine. I'm the course director of Pain and Addiction at the Renaissance School of Medicine at Stony Brook University.

DR. CHOI: Dr. Roca?

DR. ROCA: Good morning. My name is Rigo Roca. I am the division director for the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of Neuroscience.

DR. CHOI: Dr. Wiltrout?

DR. WILTROUT: Good morning. My name is Dr. Lisa Wiltrout. I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of Neuroscience.

DR. CHOI: Dr. Staffa?

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. CHOI: Dr. Meyer?

DR. MEYER: Good morning. I'm the associate director for Nonmedical Drug Use in the Division of Epidemiology in the Office of Surveillance and Epidemiology also in CDER.

DR. CHOI: Dr. Chiapperino?

DR. CHIAPPERINO: Good morning. I'm Dominic Chiapperino. I'm the director of the Controlled Substance Staff in the Drug Center. Thank you.

DR. CHOI: Okay. I'm sorry. We need to go back.

Dr. Zaafran, it looks like you're on. If you can please introduce yourself by stating your name and affiliation.

DR. ZAAFRAN: Thank you. Good morning. This is Dr. Zaafran. I'm with US Anesthesia Partners and also the president of the Texas Medical Board.

DR. CHOI: Thank you.

DR. BATEMAN: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite

strongly held. Our goal is that this 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 the 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, 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 topic during the breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of

Interest Statement for the meeting.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration, FDA, is convening today's joint meeting of the Anesthetic and Analgesic Drugs 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 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 special government employee'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 the 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 or 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 the discussion of new drug application NDA 213231 for tramadol hydrochloride injection submitted by Avenue Therapeutics, Incorporated, for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting.

The issues for the committees to discuss include the clinical relevance of tramadol hydrochloride injection, an opioid intended for management of acute pain in a medically supervised healthcare setting, when its onset of action is delayed and its proposed dosing is a fixed-dosing regimen.

This is a particular matters meeting during which specific matters related to Avenue Therapeutics' 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 product at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Jay Horrow and Reema Mehta are participating. in this meeting as non-voting industry representatives acting on behalf of regulated industry. Drs. Horrow and Mehta's role at this meeting is to represent industry in general and not any particular company. Dr. Horrow is employed by Bristol-Myers Squibb and Dr. Mehta is employed by Pfizer.

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 an 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: For today's meeting, the meeting DFO will read a statement on the formal dispute resolution request.

Dr. Moon Hee Choi, please proceed.

Statement on Formal Dispute Resolution Request

DR. CHOI: During the course of review of a new drug application, a wide variety of important scientific and medical issues are considered that are central to product development, including issues related to a product's safety and efficacy. Sometimes an applicant may disagree with the agency on a matter, and a dispute arises. These disputes often involve complex scientific and medical matters. Formal Dispute Resolution, FDR, is a pathway in CDER by which applicants may seek to resolve scientific and medical disputes that cannot be resolved at the division level.

FDR provides a mechanism for an applicant to

obtain formal review of a decision by raising the matter with the next management level in the center chain of command above the level at which the decision being appealed was made. The deciding authority, during review of an FDR request, may determine that additional input is needed from an appropriate advisory committee before making a determination regarding the dispute.

Today's joint meeting of the AADPAC and DsARM was requested by Dr. Mary Thanh Hai, the deputy director of the Office of New Drugs, who is the deciding authority for the FDR request submitted by Avenue Therapeutics regarding the Complete Response letter issued by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine for tramadol injection, NDA 213231. Dr. Thanh Hai requested the advisory committee meeting in order to seek additional input on scientific and medical issues relevant for the dispute.

The AADPAC and DsARM committee members will be asked to consider and vote on questions related

to the medical and scientific issues to be discussed in detail today. The advisory committee members will not be asked to vote on whether the FDRR should be granted or denied. Dr. Thanh Hai will carefully consider the advice of the AADPAC and DsARM committee members on these medical and scientific issues when reaching a decision regarding the formal dispute resolution request.

DR. BATEMAN: We will now proceed with the FDA introductory remarks from Dr. Roca.

FDA Opening Remarks – Rigoberto Roca

DR. ROCA: Good morning, Dr. Bateman, members of the AADPAC and DSaRM committees, and invited guests. My name is Rigo Roca. I am the division director of the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Office of Neuroscience.

Today we will be discussing the application by Avenue Therapeutics for an intravenous formulation of tramadol for the indication that was just noted by Dr. Choi. In the next few minutes, I would like to briefly review the agenda for today's

meeting.

After the applicant's presentation and period for clarification questions, Drs. Wiltrout, Tolliver, and Greene will present the FDA perspective. That will be followed by lunch and the open public hearing. After the open public hearing, I will give the charge to the committee.

As you listen to the presentations and engage in your discussions, the points that I would like you to keep in mind are the following: the importance of time to onset of action and risks related to delayed onset of action for tramadol IV when used for the management of moderate-to-severe acute pain in the inpatient setting such as postoperative or acute severe injury setting.

The second one will be the benefits and risks of tramadol IV for acute pain management in the inpatient setting, considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.

Lastly, I would like you to keep in mind during the course of the discussion the relevance

of tramadol's abuse potential as a Schedule IV substance in the context of the proposed use; and with respect to that last point, any impact on a patient's subsequent risk of abuse, misuse, or the development of opioid-use disorder in the outpatient setting, as well as any comparative advantage over currently available Schedule II intravenous opioids approved for the management of acute pain in an inpatient setting.

We look forward to your discussion, and we thank you for taking the time away from your busy schedules to assist us. Thank you.

DR. BATEMAN: 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 that 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 relationships they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interests in the applicant, 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 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 will now proceed with Avenue Therapeutics' presentation.

Applicant Presentation – Lucy Lu

DR. LU: Good morning, ladies and gentlemen. My name is Lucy Lu. I'm the CEO of Avenue Therapeutics. I'd like to thank Dr. Bateman, advisory committee members, and the FDA for this opportunity to discuss intravenous, or IV, tramadol for the management of postoperative acute pain in a medically supervised setting.

We're here today to resolve a formal dispute resolution request with the FDA so that we can make IV tramadol available as an effective, well-known, Schedule IV analgesic with the potential to displace intravenous Schedule II opioids in patients with postoperative acute pain.

We submitted a new drug application for IV tramadol in 2019 and received two complete response letters from the division with the same core clinical deficiency. We appealed to the Office of New Drugs, whose deciding official asked for input from this advisory committee to make a decision on our appeal.

IV tramadol met regulatory standards for approval. It was safe and effective for the intended population with a clinically adequate onset of action. IV tramadol [indiscernible] to the multimodal analgesic approach, as it was adequately managed with NSAID rescue in our study. This is not a new molecule. Oral tramadol has had a 26-year history in the U.S., and IV formulation has been widely used in Europe and other

territories for 30 years.

Tramadol was fully assessed by the FDA and the DEA in 2014 before being placed in Schedule IV. By definition, it has a lower abuse potential than Schedule II opioids that are currently available in the U.S. hospital today. FDA's core clinical concern is that IV tramadol did not meet the division's expectation for onset of analgesia using the stopwatch metric despite compelling evidence from other measures of a clinically adequate onset of analgesia.

The division's position is that a delayed onset may require the need for early rescue with another opioid, otherwise referred to as opioid stacking, and this could potentially place patients at risk for opioid overdose once the tramadol analgesia takes effect. The division has also stated that rescue for an IV opioid should be another opioid, not a non-opioid such as an NSAID.

As we'll demonstrate today, the data supports a positive benefit-risk profile of IV tramadol and answers FDA's central concern. The

totality of our clinical data indicates an adequate onset of action. Our studies demonstrated no increased risk of opioid stacking, and clinical experience from Europe does not support a safety signal regarding overdose or harm from opioid stacking. IV tramadol's availability would reduce patients' exposure to Schedule II intravenous opioids. This is a benefit in our ongoing opioid crisis.

Let me also clarify issues related to the proposed indication. We have not had an opportunity to discuss labeling with the FDA. Avenue is willing to take the standard opioid indication.

This is what a standard opioid labeling would look like for IV tramadol, which is the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. We would accept this indication.

To provide a framework, Dr. Richard Langford will discuss the dual mechanism of IV tramadol and

a 30-year European experience. I will present data from our PK study and our phase 3 program, as well as the clinical issues in the complete response letters. Dr. Janetta Iwanicki will summarize the findings from an epidemiology study on the abuse of tramadol in the U.S. and in Europe. Finally, Dr. Harold Minkowitz will conclude with his perspective as an investigator in our phase 3 Program.

We also have additional experts here with us to answer your questions. Our statistician had a family emergency and cannot join us today. All external responders have been compensated for their time and expenses but do not have equity interest in the company.

I'll now turn the presentation over to Dr. Langford.

Applicant Presentation – Richard Langford

DR. LANGFORD: Good morning. Thank you.

My name is Professor Richard Langford. I am a practicing anesthesiologist and head of the inpatient pain service at a large hospital in

central London. I'm also a past president of the British Pain Society. I've known parenteral tramadol since participating in the pivotal clinical trial versus morphine for postoperative pain in 1991 and its subsequent introduction in the UK in 1994. I will present an overview based on our long-standing European experience, and in so doing address the FDA's two main areas of concern. But I'll start with tramadol's dual mechanisms of action, which underpin its atypical clinical profile.

We know from animal and human blocking studies that the monoaminergic and opioid mechanisms each provide approximately one-third of the total analgesic benefits of tramadol, and the final third derives from synergistic potentiation of the two mechanisms.

Tramadol's parent isomers are themselves analgesic with rapid onset after intravenous administration, devoid of reliance on metabolism or metabolic status. Intravenous dosing of tramadol results in rapid presence of the parent isomers in

the CNS, which contributes to both opioid and non-opioid mechanisms of analgesic action.

Monoamine reuptake inhibition, in particular norepinephrine, blocks afferent pain signal transmission in the spinal cord. The dual mechanisms have been confirmed in animal and human studies using selective blockade. Further opioid-based activity follows as a result of metabolism in the liver to the M1 metabolite.

Now, regarding the clinical profile, it has been widely used in Europe for 30 years with about 370 million doses of IV tramadol administered from 2010-2019. It is used in a wide range of postoperative settings, and when used with non-opioid analgesics, minimizes the use of opioids with stronger abuse potential.

Intravenous tramadol has had a regular place in my clinical practice since its authorization in the UK in 1994. Although we've steadily improved our perioperative analgesic strategies by targeting different parts of the pain pathway with multimodal analgesia, non-opioid analgesics are typically not

sufficient to effectively manage pain following medium or major surgical procedures, where repeated doses of opioids, in addition to NSAIDs and acetaminophen, are commonly required.

For many patients, intravenous tramadol effectively manages pain while reducing the need for conventional opioid analgesia. Clinically, systemic multimodal pharmacotherapy, in conjunction with nerve blocks and infiltrated local anesthetics, play an important role in surgical pain management. We maximize multimodal therapy, combining non-opioid and opioid analgesics when patients undergo painful surgical procedures.

Intravenous tramadol provides an option that precludes an initial use of a Schedule II opioid. We should also remember that in the postoperative setting, we're not starting from zero. These patients already have analgesic drugs on board during surgery. From that perspective, intravenous tramadol is safer because it only acts partly by opioid mechanism. Patients are commonly sent home on oral tramadol after intravenous tramadol,

therefore entirely avoiding conventional opioids.

Having intravenous tramadol as a therapeutic option in the U.S. would help physicians avoid exposing their patients to drugs with higher abuse liability. I'll turn now to the first of the two main issues under consideration, namely the onset of action.

Although this is in stark contrast to the reported stopwatch data from the sponsor, my experience in common with many colleagues is that intravenous tramadol does have an appropriate and acceptable onset of action for use in acute pain, usually working within 30 minutes. We would not use it if the onset was truly delayed. My clinical experience is consistent with the clinical endpoints of Study 102 and 103, which support that tramadol, even at low levels of its active metabolite M1, provides patients with pain relief at early timepoints.

With regard to opioid stacking, I understand the concern that it might lead to overdose, but in my 27 years of experience with IV tramadol in the

UK, I've not seen or heard a problem with opioid stacking causing a bad outcome. IV tramadol is widely adopted in many countries with acceptance of considerable benefit.

Opioid rescue is commonly practiced in the medically supervised postoperative setting. Both the nurses and doctors are proficient at matching the appropriate drug and dosing to a patient, and patients are regularly observed for sedation and vital signs, including physiological monitoring. Central nervous system complications are no more likely with IV tramadol than with other opioids; in fact, less so with published evidence with tramadol to support this.

Specific to this proposal, we should also recognize that 50 milligrams of tramadol is a medium-sized dose sufficient for meaningful analgesia but relatively modest in terms of opioid activity.

To put this in perspective, 50 milligrams is equivalent in analgesia to 4 or 5 milligrams of morphine, and in terms of opioid activity, even

less, given tramadol's non-opioid component. I therefore believe that these factors explain why parenteral tramadol has a long-standing reputation for being relatively safe and effective in postoperative analgesic practice.

So to summarize, tramadol's pharmacokinetics and dual mechanisms confer adequate onset and duration of effect with reduced opioid-related risks, including respiratory depression and abuse potential. In the hospital setting, staff competent postoperative pain management will be able to safely incorporate tramadol into their practice, and peer-reviewed evidence and more than 30 years of experience support tramadol as an effective component in real-world, multimodal, perioperative pain management.

Thank you. I'll now turn the presentation back to Dr. Lu.

Applicant Presentation – Lucy Lu

DR. LU: Thank you, Dr. Langford.

Let's review the clinical data, beginning with the pharmacokinetic profile of IV tramadol.

In our PK study, IV tramadol was given as a fixed-dosing regimen, 15 milligram at baseline, 2 hours, 4 hours, and then once every 4 hours. As a comparator, oral tramadol was given according to the FDA-approved dosage, 100 milligrams once every 6 hours.

Shown here are the blood levels of parent compound tramadol from both IV administration, shown with the dotted line, and oral administration, shown with the light brown triangle line. As expected, IV tramadol [inaudible] higher blood levels of compound tramadol compared to oral tramadol at early timepoints. The parent compound tramadol provides pain relief via a non-opioid mechanism, as well as the opioid mechanism.

Now, let's look at the active metabolite M1 from IV and oral administration. M1 from the IV tramadol regimen rises gradually with less accumulation after 12 hours than oral tramadol. The overall levels are lower, reflective of the lack of first-pass metabolism. As stated in the Ultram label, the relative contribution of both

tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Let's review the PK in more detail. The IV tramadol dosing regimen has a predictable PK profile. It provides a similar Cmax and AUC of the parent compound compared to oral tramadol 100 milligrams every 6 hours. However, the Cmax of M1 from IV tramadol is about 30 percent lower than that of oral tramadol and AUC is about 20 percent lower. Therefore, in terms of mu agonist activity, IV tramadol provides a smaller dose than oral tramadol, 100 milligram every 6 hours [inaudible]

Turning now to the phase 3 study, our phase 3 program was designed with division guidance. It achieved two purposes. The first is that in registrational programs, analgesics are generally tested as monotherapy to determine whether the drug is effective. In these studies, pain medications and nerve blocks were withheld after surgery, so patients' pain levels can go up to moderate-to-severe levels, they became eligible for dosing.

Studies do not reflect the real-world practice. They isolate the efficacy and safety of the drug and define the drug's independent effect. We did that for IV tramadol through the two adequate and well-controlled efficacy studies in two different surgical models, bunionectomy and abdominoplasty, and the abdominoplasty study included morphine as an active comparator.

The design and endpoints are similar to those in a trial [inaudible] approvals of IV meloxicam and an NSAID and IV oliceridine Schedule II opioid in 2020. In our efficacy studies, rescue was oral ibuprofen 400 milligram every 4 hours as needed. In all studies, patients knew that they could discontinue at any time to receive other opioids. How many of them did that can tell us the need for opioid rescue.

The second goal of our phase 3 program was to assess IV tramadol in a setting similar to anticipated real-world use. This was done in the open-label safety study, which assessed IV tramadol's safety and effectiveness [inaudible]

multimodal analgesia without another opioid, following a variety of surgeries with 251 patients.

As with efficacy trials, patients were instructed that they could discontinue at any time to receive other opioids. Again, how many of them did that can tell us the need for opioid rescue, and no patients did. This study demonstrated safe and effective use of IV tramadol and established that its benefits outweighed risks. Results of the safety study will be reviewed when we discuss onset.

First, let me go through the top five results of the efficacy studies based on IV tramadol as a monotherapy. IV tramadol met the primary endpoints in both surgical models. There is no disagreement with the division on this point. In the bunionectomy study, the primary endpoint was the sum of pain intensity differences, SPID, over 0 to 48 hours; in the abdominoplasty study, SPID over 0 to 24 hours.

Let's look closer at the results from Study 103, as they included an active comparator.

Study 103 demonstrates similar overall efficacy of IV tramadol and IV morphine on the primary endpoint of SPID-24 and key secondary endpoint of SPID-48. IV morphine was included for assay sensitivity and to assess the safety of IV tramadol relative to an approved therapy.

There was no formal statistical comparison being the two active arms. Study 103 allowed a general comparison of both the safety and efficacy of IV tramadol and IV morphine. There was never an expectation that tramadol would be equivalent or superior to IV morphine in all aspects, and of course there's no requirement that it has to.

On this pain intensity difference, or PID, over time graph, IV tramadol is aligned with the green circles [inaudible] and IV morphine is aligned with the yellow triangles. Again, we see similar overall efficacy between IV tramadol and IV morphine. IV morphine has a faster onset than IV tramadol, but IV tramadol did begin to separate from placebo early, as will be seen in greater detail.

Now, let's review the adverse event profile of IV tramadol as a monotherapy relative to IV morphine [inaudible]. This is a graph that shows when patients experienced adverse events in Study 103. The green is tramadol and the yellow is morphine. Patients were not given preventative [inaudible] in the study.

In the first hour, there was a higher rate of nausea in the IV tramadol arm, but after 1 hour, nausea and other opioid-related adverse events, or ORAEs, occurred at a similar rate [inaudible]. Overall, tramadol and morphine showed a similar pattern of adverse events, including sedation/somnolence with no late peak of these infrequent adverse events. No patients had respiratory depression or hypoxia requiring reversal of naloxone.

These data tell us that the parent compound tramadol is active, [inaudible] its monoaminergic mode of action in the early hours, and that the OREAs caused by IV tramadol are similar to IV morphine.

To put the AEs in perspective, let's review how many patients had to discontinue due to AEs. The most common reason for IV tramadol patients to discontinue the study was GI related, such as nausea and vomiting, 3.3 percent of tramadol patients versus 2.2 percent in the IV morphine arm. The next most common reason was hypoxia-related AEs. This was driven by pulse oximetry [inaudible], and no patient required naloxone; 2.8 percent of tramadol patients versus 3.2 percent of morphine patients discontinued for this reason.

Now, let's review the issues in the complete response letters. The division concluded that IV tramadol's onset leads to an increased risk of opioid stacking and related risk of overdose [inaudible] agree. The totality of data support a clinically acceptable time to onset of analgesia, and there's no evidence that there is a late onset affecting need for rescue analgesics.

Let me first explain the stopwatch metric. [Inaudible] two stopwatches started at the start of dosing. Patients are instructed to stop the first

stopwatch when they first perceive pain relief, and to stop the second stopwatch when they feel meaningful pain relief.

The median time to meaningful pain relief [inaudible] the onset of analgesia. In the absence of clear guidance from the FDA, different sponsors have taken different approaches to data collection and data analysis on the stopwatch metric. The FDA has accepted these various methods even though they can yield very different results.

For example, our intent was to understand meaningful pain relief driven by IV tramadol without rescue. If a patient took rescue ibuprofen [inaudible] and they felt meaningful pain relief, the protocol stated that they were not allowed to stop the second stopwatch, and these patients were counted as not achieving meaningful pain relief. They were automatically assigned to a time to meaningful relief of 6 hours, the end time for the endpoint.

This is in contrast to the stopwatch metric for IV meloxicam, which was used for approval and

labeling by the FDA in 2020, where patients were allowed to stop the second stopwatch without regard for rescue use; or if the second stopwatch was never pressed, patients were censored at the time of rescue.

Let me show you how these differences affect [inaudible] stopwatch results. This table is from our results in an NDA that used very conservative methods for both data collection and data analysis. Results show a delayed onset, and the division quoted these numbers in the second complete response as the basis for not approving IV tramadol.

It is not possible to know what our stopwatch metric would look like, so we used the data collection method in the IV meloxicam NDA, however, we were able to reanalyze the results using their analysis method. By this analysis method, the median time to meaningful pain relief was much shorter for IV tramadol, 135 minutes in Study 102 and 81 minutes in Study 103. IV morphine remained the same, as very few patients needed a

rescue in the first 42 minutes.

Please note that this analysis has not been submitted to the NDA. It is only presented here to demonstrate that a different statistical methodology can have a dramatic influence on the stopwatch result. This is one of the reasons why the stopwatch data should be reviewed along with other clinical endpoints for an accurate assessment of onset. In fact, the FDA stated that they're open to other approaches to assess onset of analgesia beyond the two stopwatch methods in their guidance for non-opioid analgesics for [inaudible] that was just released last week.

In our case, the stopwatch metric is an outlier and did not reflect the fact that patients had clinically meaningful relief at early timepoints. In contrast, the three endpoints also provide information about onset of clinical benefits in efficacy studies. Clinical endpoints are patient reported pain intensity difference, time to first rescue, and satisfaction with their medication during the first 24 hours.

Here you can see the pain intensity difference, or PID, from baseline over time in the first 4 hours. In Study 102, IV tramadol separated from placebo early, as is clearly demonstrated at 30 minutes. The decrease in pain levels continues throughout the early timepoint. In Study 103, the IV tramadol curve also separated from placebo by 30 minutes, but not as much as the IV morphine curve.

In addition, the median time to first rescue was much longer in the IV tramadol arm than placebo in both studies. In Study 102, the median time to rescue was approximately 5 hours compared to less than 2.5 hours [inaudible]. In Study 103, the median time to rescue was approximately 23 hours, much longer than the 1.7 hours for placebo [inaudible]. These results confirm adequate onset and are consistent with the PID and PGA-24 results, which were better in the IV tramadol group than placebo patients in the study.

To summarize the results from the efficacy studies, in contrast to the stopwatch data, which

can be significantly influenced by methodology, IV tramadol provided meaningful pain relief at early timepoints on three clinical endpoints that informed the onset of [inaudible].

The parent compound tramadol, and not just M1, provides clinically apparent pain relief at early timepoints via the monoaminergic and opioid mechanism. This is consistent with the known pharmacology of tramadol and the PK observed with IV tramadol, and is evident on patient-reported PID, time to rescue, and patient perception regarding their pain relief. In addition, very few patients discontinued in the absence of another opioid, which we'll discuss in more detail.

Next, we'll see that Study 104 demonstrates that IV tramadol can be used safely and effectively in real-world clinical practice, and there are no concerns about onset of action. Study 104, our phase 3 open-label safety study -- that assessed IV tramadol in a setting similar to anticipated clinical use -- demonstrates that IV tramadol can be used safely and effectively with multimodal

analgesia, and further supports a favorable benefit-risk balance, the clinical utility model, and successful postoperative analgesia without Schedule II opioids.

Study 104, IV tramadol was used [inaudible] another opioid following [inaudible] -- that are invasive are usually managed with postoperative Schedule II analgesics. Non-opioids were permitted as needed, and patients knew that they could leave the study at any time to get another opioid. We did not collect pain intensity scores, as the goal of the study is not to determine pain [inaudible] -- that was demonstrated in the efficacy studies.

In Study 104, since pain was treated prophylactically, one would expect the standard of care medical practices [inaudible]. PGA was used after a patient's satisfaction. A key takeaway from this study was that none of the 251 patients [inaudible] to request another opioid. Here are the results of the PGA upon discharge from Study 104. Out of the 251 patients, 95 percent

were satisfied with pain relief without the need for rescue doses [inaudible] Schedule II opioids. The study demonstrated the utility of IV tramadol [inaudible] in managing postoperative pain, allowing patients to avoid Schedule II opioids.

In the study, IV tramadol displays the use of Schedule II opioids, and patients were highly satisfied. When we got these results, we were excited, as these results [inaudible] U.S. population are consistent with decades of the European [inaudible] experience and how IV tramadol is used outside the U.S. We feel that Study 104 answers the question of the use of [inaudible] IV tramadol in the multimodal paradigm in real-world [inaudible].

Next, we disagree with the division's conclusion that the use of IV tramadol results in early use of opioid rescue and its related harm. The division's concern is on both increased need for opioid rescue when patients are given IV tramadol as well as the harm it may cause. Opioid rescue on top of an opioid is a legitimate concern

for all [inaudible] opioids. All opioids are subject to the stacking and [inaudible] patients' variable response to them, however, there is no evidence in the phase 3 program that the use of IV tramadol will cause increased rescue use.

In the efficacy studies, a vast majority of patients were adequately managed with IV tramadol and NSAID rescue. Only 2 percent of patients [inaudible] another opioid, and none of them had a serious AE [inaudible]. In the open-label safety study, none of the 251 patients [inaudible] get another opioid. After painful surgery, patients reported high levels of satisfaction with knowledge that some patients will get another opioid, as is the case with all opioids today [inaudible].

As for the concern of harm resulting from opioid stacking, this can be addressed with the European experience with IV tramadol having been widely used for 30 years, [inaudible] hundreds of millions of doses over the last 10 years. There's not a safety signal related to opioid stacking in the literature from Europe or any of the other

territories. The drug is [inaudible].

Of interest, a follow-up literature search found no publication [inaudible] with any reference to opioid stacking [inaudible] for IV tramadol. In fact, we found only one review that discussed combining tramadol [inaudible] with morphine, and there was no mention of any opioid stacking safety signal [inaudible].

As Dr. Langford mentioned, this is a medium-dose opioid, so the risk of a rescue dose of an opioid on top of IV tramadol can be effectively managed in a medically supervised setting by clinicians' experience in management. In addition, AE assessment of VigiBase and the WHO global database of individual case safety reports [inaudible] from 2009 to 2019 did not reveal any unexpected findings or signals of concern.

Let me go through the use of rescue in the IV tramadol arm and IV morphine arm at early timepoints in Study 103. Using table 8 in the FDA's briefing document, there were patients in all treatment groups who received NSAID rescue as early

as the first 30 minutes. The proportion of morphine and tramadol patients needing rescue was similar through one hour, approximately 17 percent. The proportion of tramadol patients receiving a rescue NSAID did exceed the morphine group at the 2-hour timepoint, which is when the tramadol dosing regimen called for a second dose.

Overall, the mean use of rescue was low, indicating many patients required little to no rescue. It is also important to point out that in Study 103, IV tramadol patients were able to avoid postoperative exposure [inaudible] of Schedule II opioids.

Let me also address the metabolism issue. M1 formation from tramadol is mediated by CYP2D6 in the liver. While CYP2D6 phenotypes can impact many drugs, including tramadol, clinically, this variability does not pose an undue [inaudible] for IV tramadol. With poor metabolizers, there will be low levels of M1 throughout the treatment. Patients are at low risk for additive effects from an opioid rescue.

With the ultra-rapid metabolizers, M1 levels are expected to be higher and earlier, and these patients are less likely to request rescue medication. Elevated M1 levels from IV tramadol for these patients are unlikely to result in harm, as these patients will be in a monitored setting where sedation or respiratory depression can be managed. Additionally, the M1 levels in these patients will still be lower than oral tramadol at dosages that are FDA approved.

In our program, we saw no patients with signs of excessive opioid agonist activity requiring naloxone [inaudible]. IV tramadol is widely used in territories with different ethnicities enriched with different 2D6 phenotypes [inaudible]. Postmarketing safety data and the available literature have not identified the safety signal for IV tramadol to 2D6 phenotype variability. Oral tramadol continues to be used safely in most adults without prior determination of 2D6 phenotype.

IV tramadol will be used only in a medically

supervised setting, which are hospitals and surgical centers. As the clinicians who work in the setting know, multiple opioids can be used to achieve adequate analgesia, and patients are closely monitored and managed by clinicians experienced in pain management.

As Dr. Minkowitz will discuss later, not only are clinicians highly experienced in perioperative pain management, but there are protocols in place [inaudible] safe use of IV opioids. In fact, monitoring following IV opioid therapy is mandatory at every hospital and surgical center. Healthcare professionals, not patients, administer IV opioids in this setting.

It is known that there is a need at times to use concomitant opioids to manage patients' pain because of their variable response to opioids. This has been recognized and managed with class labeling for all opioids, warning prescribers about the concomitant use of opioids and other CNS depressants, including other opioids.

Let me discuss the abuse potential of

IV tramadol in comparison to Schedule II opioids. Oral tramadol has been approved in the U.S. since 1995 and is listed as a Schedule IV drug. The scheduling definition is found in the box. The scheduling of tramadol was based on eight factor analyses conducted by the FDA and by the DEA. Similar to the FDA analysis, the DEA analysis relies on published case reports, case series, and databases, including the Drug Abuse Warning Network and the National Survey of Drug Use and Health.

In addition, the DEA reviewed nonclinical drug [inaudible], drug self-administration studies, as well as post-approval human abuse potential studies. The DEA concluded that tramadol has an abuse potential less than Schedule II morphine and oxycodone, and buprenorphine. This is consistent with information in the FDA briefing document that noted it takes supratherapeutic doses of oral tramadol to [inaudible] a drug-liking effect as the therapeutic dose of oxycodone.

This study evaluated drug liking among recreational drug users and 20 milligrams of

oxycodone compared to a therapeutic dose of 200 milligrams of oral tramadol, shown in green. [Inaudible] with a difference in scheduling, drug liking is lower for tramadol, and the time to peak is [inaudible] tramadol, even when using for therapeutic dose. Importantly, it's likely that IV tramadol would be even lower due to the delayed and reduce M1 formation.

The lower abuse potential and reinforcing effect with IV tramadol was [inaudible] by a crossover study comparing IV morphine 100 and 200 doses of IV tramadol with experienced drug users. This study assessed both drug liking and euphoria following 5-minute infusions compared to placebo. As shown in both graphs, the scores for either 100- or 200-milligram IV tramadol was similar to placebo, while morphine was significantly higher.

Importantly, we do not see a dose-dependent increase in opioid-like effects with IV tramadol, which is different than reported with oral tramadol. The authors concluded that unlike other

opioids, tramadol's abuse potential indices [inaudible] appeared low relative to its analgesic indices [inaudible], at least by the parenteral route. This supports the Schedule IV designation that sets tramadol apart from Schedule II opioids, having a less reinforcing effect and less abuse potential.

Due to the lack of first-pass metabolism, IV tramadol has less opioid activity than oral tramadol. The WHO expert committee stated that parenterally administered tramadol is less likely to be identified as an opioid because M1 production is minimalized [inaudible]. This is supported by studies that showed that parenteral tramadol produced lower readings of high and liking than morphine. Study participants did not reliably classify parenteral tramadol as an opioid.

As you may know, the abuse potential of a drug is determined, in part, by how high the rewarding effect is and how fast it gets to that onset [inaudible]. It is well documented that opioids with a fast onset and a big rewarding

effect have the highest risk of abuse. The experience of a rewarding effect from an opioid [inaudible] later non-medical use. IV tramadol has little potential for a rush of rewarding effect based on the dose being administered for 15 minutes and later slower and comparatively low M1 levels with IV tramadol [inaudible].

With every drug, there's always a trade-off. IV fentanyl provides fast pain relief, but it also delivers the most rewarding effect with high-peak and fast onset. In our case IV tramadol provides good, overall pain relief, as evidenced in our studies, with a clinically adequate onset, however, the onset is slower than intravenous Schedule II opioids. This is a trade-off for a less rewarding effect and a lower abuse potential.

Weighing the trade-off, I hope that you'll consider two aspects. First, decades of European experience with parenteral tramadol do not support the concern of increased adverse event risk from opioid stacking. Second, European physicians have had an alternative Schedule II opioid 370 million

times in the last 10 years. As you will hear, clinicians can properly determine when to use the Schedule IV option instead of opioids such as IV fentanyl.

Next, I'd like to discuss the division's position regarding the use of non-opioid analgesics with IV opioids. By the division's statement, "Combination therapy of an opioid with a non-opioid is not consistent with the intended use of intravenous opioids in our complete response." Recent FDA approvals allow such combination. We provided some examples in the briefing document.

The division's position is inconsistent with successful management of patients' pain in our clinical trials with IV tramadol and NSAID rescue, or with the opinion expressed by experts by the HHS in 2019. The experts said that it is important to explore the benefits of multimodal non-opioid approaches in acute pain [inaudible] management in conjunction with possible therapy.

In light of the national effort to address the opioid epidemic, clinicians are moving pain

management away from monotherapy with opioids and toward multimodal analgesia and products with lower abuse potential. IV tramadol as a Schedule IV opioids offer U.S. clinicians and patients safe and effective Schedule IV options for multimodal analgesia with less rewarding effect and lower abuse potential.

Decades of European experience support the safety and utility of IV tramadol. Therefore, the benefit of IV tramadol in helping patients avoid Schedule II opioids outweighs the division's perceived safety concern.

With that, I'd like to turn the presentation over to Dr. Iwanicki to discuss the epidemiology of the abuse of tramadol.

Applicant Presentation – Janetta Iwanicki

DR. IWANICKI: Thank you, Dr. Lu.

My name is Dr. Janetta Iwanicki, and I am the chief scientific officer at Rocky Mountain Poison and Drug Safety. I am a board certified physician in emergency medicine and medical toxicology [inaudible]. I've been conducting

mosaic epidemiologic research on opioids since 2014, with a focus on data from the RADARS program and public health implications.

Today, I'll be discussing the real-world evidence related to tramadol misuse and abuse. The sponsor conducted a collection of epidemiological studies, gathering data from multiple sources, both U.S. and globally. First, we used the mosaic approach to evaluate drug's misuse and abuse from several different angles using several data sources because no single data source tells the whole story of real-world behavior.

Next, I will review RADARS data from the U.S., where only oral tramadol is available, and Europe where tramadol is available in [inaudible]. Finally, I will review tramadol abuse by the injection route compared to the oral route. The epidemiological work was very extensive. Please note that similar results were seen with other data sources. They are in the briefing book.

For today's discussion, I'd like to provide a framework for how we think about non-medical use

prescription drugs. Non-medical use is a term that encompasses both misuse and abuse. Misuse is the intentional therapeutic use of a drug in a way other than prescribed or for whom it was not prescribed. Abuse is the intentional non-therapeutic use, even once, for its desirable, psychological, or physiological effects.

Different data sources collect a variety of these outcomes, but today we will focus on rates adjusted for drug availability by using the number of pills dispensed of a product since each pill dispensed is an opportunity for misuse, abuse, and diversion. The briefing book has a good summary of the report. Those that have misuse, abuse and diversion, and non-medical use of oral tramadol in the U.S. are low compared to [inaudible].

Let's review the abuse of tramadol in European countries for both oral and IV tramadol that are widely available. A survey of non-medical use of prescription drugs, or NMURx, collects data from the general population. Standard units include all available formulations for that

particular country. Again, abuse of tramadol is low compared to other opioids in all of these countries.

Similarly, we can look more closely at intravenous-use behaviors associated with opioid in NMURx. Here we use the broader non-medical use to make a more informative comparison of tramadol and other opioids to account for the rarity of injection behavior. Again, we see that even in countries with IV tramadol formulations, non-medical use of tramadol via injection is rare, especially when compared to a conventional opioid [inaudible] such as morphine.

Now, let's evaluate the intravenous abuse of tramadol. Consistent with the pharmacokinetic and pharmacodynamic properties of tramadol, the rates of intravenous abuse is low in the U.S. RADARS poison data system. Abuse of oral tramadol by injection was rare and accounted for a very small proportion. Out of the 4,753 cases involving oral tramadol abuse, the proportion of cases involving tramadol abuse via injection was 0.005. Compare

this to other opioids; for the proportion of abuse, the injection is plenty times higher and 10 times higher [inaudible].

In summary, tramadol has lower drug liking and abuse liability compared to other opioids, based on laboratory evidence and human abuse potential. Additionally, the pharmacokinetic and pharmacodynamic properties lead to less mu activiation by the intravenous route than oral tramadol and other opioids due to the lack of first-pass metabolism. Overall, real-world evidence shows low rates of tramadol abuse, including by the IV route, compared to other opioids.

Thank you. Next, I'd like to invite Dr. Minkowitz to [inaudible].

Applicant Presentation – Harold Minkowitz

DR. MINKOWITZ: Thank you.

My name is Dr. Harold Minkowitz, a board certified anesthesiologist and adjunct professor of anesthesiology and perioperative medicine at MD Anderson, and also president of Analgesics

Perioperative and Hospital Based Research at HD Research.

I've been involved in acute pain research for over 30 years and studied almost every mu acute pain therapy, both opioid and non-opioid, under evaluation for approval in the U.S. I was also a principal investigator in the phase 3 program for IV tramadol. Based on what I've seen over my years researching this [inaudible], I'm here today to explain a real need for Schedule IV [inaudible] postoperative pain management that can minimize the use of Schedule II opioids in that setting.

As you can see on this slide, IV tramadol with its dual mechanisms of action fills an unmet need and delivers opioid efficacy with less abuse potential and less risk of dependence compared to conventional opioids. IV tramadol fills in the current gap of acute pain management. It is to be used to treat pain after non-opioids prior to conventional Schedule II opioid administration, and also a potential new option for patients with contraindications to non-steroidals who don't

tolerate or don't desire strong narcotics.

The question is, how well does it work? Well, let me share my experience with you. I was involved with a double-blinded, pivotal abdominoplasty trial, as well as the open-label safety study. Let me share my impressions of these studies; first, the abdominoplasty study.

When I saw that patients receiving IV tramadol had similar pain scores to those receiving IV morphine, I was really encouraged. To have an agent that demonstrates similar overall pain relief to IV morphine that is not a Schedule II opioid would be a very valuable tool in our toolbox.

Now, turning to the open-label safety study, where our site enrolled about 100 adult patients who had undergone a variety of painful procedures, most patients underwent total joint replacement. It's a very painful surgery and typically requires Schedule II opioids as a regimen to control pain.

IV tramadol was added to the baseline multimodal therapy currently used in practice.

This regimen could not control their pain. They could request conventional opioids and at any time exit the study. The data showed, and I personally saw, my patients experienced sustained pain relief at a high-level of satisfaction.

I expected some patients to require at least some additional opioid to control their pain after having undergone such major surgeries, but not one patient required conventional opioids. Staff taking care of these patients were pleased with the patients' response and that they were able to undergo physical therapy and discharge in a timely manner.

I started the trial expecting a dropout rate of about 20 percent or so, as these patients were undergoing painful major surgeries, and typically Schedule II opioids would be part of their regimen for pain control. As more patients were enrolled, I began to see a consistent pattern. Patients were comfortable, happy with their pain management, and were able to undergo their rehabilitation without requiring conventional opioids to control their

pain patients.

Patients tolerated IV tramadol well with no observed safety signal. Ninety-five percent of the patients in the study reported that the IV tramadol-based regimen is good, very good, or excellent at the end of the study. A few patients who actually had undergone a similar surgery in the past without this regimen were pleasantly surprised by the enhanced analgesia they experienced this time around and preferred this pain regimen.

In clinical practice, a rapid onset is not needed for drugs given in the fixed-dose regimen. Clinicians choose a drug that has the best clinical effect for a particular patient's needs. For example, if we want a rapid onset of analgesia but the duration of analgesia is not as important, we'll commonly use a drug like fentanyl.

Now that IV tramadol's characteristics have been defined in the same fashion as all other approved drugs have been, it would be quite easy to incorporate it into a multimodal therapy, as has been done in Europe. Similarly, if a drug is

administered around the clock -- the fixed-dosing regimen, typically with a multi-modal regimen as I saw in the safety study -- a slower onset time is not as relevant. Clinicians in this setting experienced in pain management formulate a regimen to provide adequate coverage with our patients in our [inaudible].

There are substantial differences in treatment effectiveness. Prevention, assessment, and treatment of pain is a persistent challenge for clinicians and health systems. All hospitals have protocols and controls explicitly for pain management that includes continuous assessment of analgesic efficacy and patient safety.

Our inpatients are monitored, and the analgesia is assessed and reassessed throughout their stay. We use multimodal, non-opioid therapy from the start, relying on non-opioid options when possible, trying to limit opioids and less needed. All treatments are tracked in our system and our patients are continuously assessed for comfort and safety.

Importantly, using multiple opioids is common practice in the standard of care in most facilities. In the perioperative setting, most hospitals use a pain management algorithm similar to what you see here. This is an example of what is used at MD Anderson Cancer Center and allows a safety dose of various opioids at different doses. As healthcare professionals, we know how to use opioid rescue and add it to background opioid therapy.

In summary, IV tramadol could displace Scheduled II opioids for patients with postoperative pain. I always maximize non-opioid medicines and techniques to first line. Some procedures will require an opioid as part of the regimen for pain control. If IV tramadol is available, we could use the Schedule IV option, therefore delaying or negating the need for conventional opioids.

Having IV tramadol as a therapeutic option really helps physicians avoid exposing their patients to drugs with a higher abuse liability.

Importantly, there would be no increase in opioid use because IV tramadol would replace the use of Schedule II conventional opioids. So from my experience, I found IV tramadol provided meaningful pain control for my patients. It delivered similar pain relief to IV morphine, but is a Schedule IV drug. The drug works well, and its onset was not an issue in clinical trials.

For 30 years in clinical practice, I realize there are multiple ways to manage pain. We try a multimodal approach, but for many of our patients, non-opioids are just not enough. They need a day or two of opioids while they're in the hospital.

Opioid rescue for IV tramadol is not an additional safety concern. Patients are in a medically supervised setting and routinely get additional doses of the same or additional opioids to help manage pain. The value of having access to a Schedule IV opioid for postoperative pain far outweighs the low potential risk of opioid stacking theorized by the FDA.

Thank you. Now, I'd like to invite Dr. Lu

to conclude the presentation.

DR. LU: Thank you, Minkowitz.

In conclusion, IV tramadol provides a Schedule IV option for patients whose pain cannot be adequately controlled with non-opioids. We're seeking approval based on two well-controlled phase 3 pivotal studies that demonstrated the efficacy and safety of IV tramadol at the proposed dosing. The open-label safety study further demonstrates its utility, a multimodal analgesia without another opioid.

This is not a new medication. IV tramadol has had a 30-year history in Europe and a 26-year history of oral use in the U.S. The availability of IV tramadol in a medically supervised setting will reduce the reliance on Schedule II intravenous opioids. It gives clinicians and option to use a drug with lower abuse potential than what they have today when non-opioids are inadequate.

Again, please consider the fact that decades of European experience with parenteral tramadol do not support the division's central concern of

increased adverse event risk due to opioid stacking, and in the FDA's own words, "There's likely no potential for a rush of the rewarding effect from tramadol IV."

Please consider that European physicians had this alternative, Schedule II opioids, 370 million times in the last 10 years. In contradiction to most advisory committee meetings, where the focus can be on safety unknowns or the evaluation of a new molecule, this meeting is asking your opinion regarding the safety of a well-established, well-known drug with decades of oral use in the U.S. and decades of intravenous use in Europe.

As you heard, there's substantial evidence of safe use and benefit and decades and hundreds of millions of doses of intravenous tramadol used in Europe to answer the theoretical concerns posed by the division and for which, as part of the formal dispute resolution process, the Office of New Drugs is asking you to consider.

With that, we'll be happy to take your questions.

Clarifying Questions for Applicant

DR. BATEMAN: Thank you.

We'll now take clarifying questions for Avenue. Please use the raised-hand icon to indicate that you have a question and remember to lower your hand by clicking the raised-hand icon again after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. McCann?

DR. McCANN: Can you hear me? This is Dr. McCann from Boston Children's Hospital.

DR. BATEMAN: Yes, we can.

DR. McCANN: Good.

I have several questions for Dr. Langford. Question number one is, clinically, when you give patients an antiemetic prophylactically, is there noticeable nausea and vomiting over, say, your clinical experience with giving standard narcotics during a procedure? That's question number one.

Question number two, is IV tramadol given intraoperatively so that you can get it on board before the patient fully wakes up, so that you decrease the time of non-activity?

The last question is, are practitioners cognizant of stacking concerns? Do they hold back on treating with opioids because they know that IV tramadol will eventually kick in? In PACU, are practitioners more likely to use a short-acting opioid like fentanyl rather than a long-acting one?

So those are my three questions. So if Dr. Langford could answer, it would be wonderful.

DR. LU: Thank you. Let me just quickly repeat for everyone, and Dr. Langford can come and address these questions.

The first one is, if you were to use

antiemetic on a prophylactic basis, will they reduce the nausea and vomiting rate? The second one is, if you have any comments regarding the use of IV tramadol intraoperatively; and the third question is if practitioners are understanding the risk of opioid stacking, especially in PACU.

DR. McCANN: Thank you.

DR. LANGFORD: Thank you. Dr. Langford speaking again.

Taking them point by point, yes, we do a normal routine practice and regularly use prophylactic antiemetics, and that does reduce the nausea and vomiting rate. In terms of when we dose, that's a very interesting, very important question. Of course in the pivotal trials, 102-103, it was necessary to allow the patients to develop moderately severe to severe pain, and of course that's the very opposite of what we aim for in our normal clinical practice.

So it varies a bit, but in many people's practice, they would wish to give, obviously, the infused tramadol much earlier than that, sometimes

intraoperatively, although that's probably not quite as common as either at the very end of surgery or the very beginning of the patient's time in the PACU, in the recovery room.

So although, obviously, there is a slightly more gradual onset of action with tramadol, which is actually a very good thing in terms of adverse events, that is absolutely mitigated by giving it a bit earlier. So in essence, actually when we looked at the data, it looks as though most patients in routine practice would get the tramadol about 45 to 50 minutes earlier than was the case in the pivotal trials, which were necessarily obviously artificial. And we're all used to doing these studies where the patients are on monotherapy, and the doses are given only when a certain baseline is reached to show change from baseline.

Finally, the stacking concerns, of course, obviously, as anesthesiologists, we are -- as you know, as all of us working in this area know -- amongst the most, if not the most, safety

conscious of all physicians, and of course we are mindful of issues, especially when we are combining medicines which will have additive effects in the central nervous system. That, nevertheless, absolutely does not inhibit us from treating the patient's pain when necessary.

Our first mission, of course, is to keep the patients safe and comfortable. So there is, on a regular basis, the need to rescue patients from pain episodes, and on those occasions, a number of times, either it will be a further dose of the same medicine or a different medicine, an opioid medicine. But it is all done, as I mentioned in my presentation, with care to titrate according to the patient's need. And of course in this supervised setting, the patients are very carefully monitored. Thank you.

DR. McCANN: Thank you. That was very helpful. But specifically, do you avoid long-acting opioids?

DR. LANGFORD: If by long-acting opioids you mean sustained-release, modified-release opioids?

DR. McCANN: No, something like hydromorphone as opposed to fentanyl.

DR. LANGFORD: Right. Well, we don't use hydromorphone, particularly, but if one, for example, were to look at, say, oxycodone or morphine versus fentanyl, it's horses for courses as we might say.

If a patient is in extreme pain, we would probably -- or I personally, and many of my colleagues, would use incremental doses of fentanyl to titrate and bring the patient's pain down to a suitable level. On the other hand, if the patient were developing a pain score of 3 or 4 and beginning to suggest that they might need something more, then on those sorts of occasions, intravenous tramadol would be a perfectly acceptable option.

DR. McCANN: Thank you very much. You've answered my questions.

DR. LANGFORD: Thank you.

DR. BATEMAN: Thank you. This is Brian Bateman. I'd like to ask a question directed to Dr. Lu.

The focus of your presentation on the benefits of tramadol really centered around the reduced abuse liability relative to Schedule II opioids, and the epidemiologic studies that were reviewed are obviously focused on tramadol use in non-medical settings.

So my question is, are you aware of any data to suggest that the choice of inpatient opioid, or even the use of inpatient opioid, is associated with subsequent abuse or misuse? I am aware of some data looking at opioid-sparing approaches used in inpatient settings -- for example, regional anesthetic approaches and persistent opioid use -- and there the studies didn't see a persistent effect of reducing long-term opioid use.

So again, the question is, does it really matter which type of inpatient opioid we administer or whether opioids are administered in terms of long-term misuse or abuse?

DR. LU: The drug data, to answer your question, Dr. Bateman, has not been collected. What you are asking is so important and so relevant

to today's discussion, I actually would like to have two of my experts here to answer questions. One aspect is, from a patient's perspective, the reinforcing rewarding effect. I'd like Dr. Jody Green to talk about that, whether or not that's relevant to our discussion today.

The second part is how the availability of intravenous tramadol may impact physicians' prescribing decision for deciding what opioid to send patients home with, and I'd like Dr. Minkowitz to address that aspect.

So I'd like to address your question, if I may, from both the patients' perspective and their experience, as well as the physicians' comfort level.

Go ahead, Jody.

DR. GREEN: Jody Green from Inflexxion. To your point, there are no direct studies that would say for certain what an exposure or medical setting looks like or leads to in such behaviors. What we do know is that tramadol as a Schedule IV drug does have a lower abuse potential than any Scheduled II

drug.

What we also know is most of that, a lot of that, is based upon those reinforcing effects, the diminished reinforcing effects with tramadol as opposed to a Schedule II, and also knowing that those reinforcing effects may influence subsequent behaviors of abuse-misuse.

We found in the core presentation, based upon the drug-liking effect, we do see demonstrated here the oral tramadol is significantly lower than any other C2 exposure, a lower peak drug-liking score, and lower time to tramadol peak liking. We also know from a systemic view from Dunn, et al. that not only is there lower drug liking, but also an unreliable identification of tramadol as an opioid, where most individuals can identify Schedule II opioids reliably.

This all ties into the epidemiological data presented by Dr. Iwanicki that we see in the real world, where the tramadol is much lower abuse, particularly by IV tramadol. So this all comes together to really reinforce the probability or

likelihood that diminished or lower subsequent use of abuse potential [inaudible], and I'll also ask [inaudible].

DR. MINKOWITZ: Thank you. Good morning. Dr. Minkowitz. As we've already alluded to, obviously our goal would be to have a patient experience with never getting a C2 exposure, and what we've seen is that in real-world settings for painful surgeries, I saw a total displacement of Schedule II opioids in every patient in the study, in our postoperative study, with major surgeries.

What we all want to do is to have patients comfortable when in the hospital and when they go home. Currently, we have no other option than a Schedule II opioid to control their pain should multimodal fail or not be adequate. So if patients were comfortable on IV tramadol, it would then be appropriate to transition patients to oral tramadol once we established that the pain was effectively managed without the need for Schedule II opioids, and that's what I saw in the 104 study.

So the benefit is that we can start off by

never exposing our patients to highly addictive opioids, and in Europe, as Dr. Langford mentioned, doctors have access to IV tramadol and can switch their patients routinely from IV tramadol to either oral tramadol or codeine on discharge. And I think in time in the U.S., physicians would learn that IV tramadol, and eventually oral tramadol, would be sufficient to control their patients' pain without ever exposing them to C2 opioids. Thank you.

DR. BATEMAN: Thank you.

Dr. Ruha?

DR. RUHA: Hi. Thank you. This is Michelle Ruha. I was wondering if we could pull up slide 33 of Dr. Lu's presentation. Maybe my question is best for Dr. Minkowitz, though.

I was just wondering, this is the earlier part of the study seeing that the tramadol separated from placebo. But I was wondering if you could clarify what is the clinically significant pain intensity difference. When I tried to find that information, I felt it looked like it may be 2, so I was just wondering what you consider to be

clinically meaningful.

DR. LU: If I may, Dr. Minkowitz, while you're walking up here, there is numerical separation at 30 minutes with a nominal p-value that's significant in Study 102, and it did start separating in 103, but it was not as good as morphine. Our view is that this is all consistent with lack of early rescue, as well as patients more or less being happy. But I think it's showing a clinically adequate onset, but I'd like Dr. Minkowitz to give [inaudible].

DR. MINKOWITZ: Thank you. Dr. Minkowitz.

You ask a very interesting question, and I think we always struggle to find that answer because it does depend on a number of factors. The one factor would be what is the starting pain score? Obviously, if it's going from a 10 to an 8, is that as significant as going down from a 4 to a 2?

So the question is relevant but difficult to answer in strictly numeric terms. However, what we do know is that we saw that the actual pain scores

did drop and separate from placebo. I think more importantly is what we saw clinically. In the phase 3 clinical trials, we did see that the IV tramadol was effective in treating the patients with moderate-to-severe pain.

Again, in the safety study, which I was involved with, with patients having major surgery, what I did was went to all the order sets for those particular patients, and every instance where we had Schedule II opioids, we deleted the order for Schedule II opioids and put in the IV tramadol program in those patients. Across the board, actually, all the patients had their pain well controlled with IV tramadol, and not one of them required rescue with C2 opioids. And that's kind of consistent with the randomized-controlled trials, where the IV tramadol patients required only low-dose opioids to control their pain.

So your question was a specific question regarding how much of a drop is relevant, and unfortunately all I can do is relate my clinical experience to me, showing that it is very clear

that IV tramadol was very effective as an analgesic for hospital-based patients, and was able to treat their pain and avoid Schedule II opioids. Thank you very much.

DR. RUHA: Okay. Thank you.

I did have just two other quick questions, mainly for Dr. Lu.

Just regarding the study protocols, for the efficacy studies, I assumed patients got other medications intraoperatively, or was there a time cutoff before they started the tramadol prior to which they could receive anything else? Then my second question was, were there any patients excluded based on use of other serotonin or the norepi [ph] reuptake inhibitors?

DR. LU: Let me show you the protocol for Study 103, quickly. These are the protocols. It's standardized in the study, and then patients were dosed once their pain level reached the moderate-to-severe level. And let me quickly show you, if I may, Study 102, the surgical and anesthetic protocol.

In Study 102, everyone, just like all the other studies, they had the block, and that block was withdrawn the next day at 4:00 a.m., and patients had to dose before noon. Most patients actually dosed within about 4 hours when the block was taken away. So the studies were done in a standardized fashion.

DR. RUHA: Okay. Thank you.

DR. LU: And what was your second question, please?

DR. RUHA: The second question was, I don't recall seeing whether use of serotonin or norepi reuptake inhibitors resulted in exclusion from participation in the study. I don't think it did; I just wanted to clarify.

DR. LU: Actually, because IV tramadol is a 505(b)(2) application with reference to Ultram, we did exclude patients with serotonin who are on the serotonin reuptake inhibitor in the study. We expect that if the drug is to get FDA approval, it would be used in the same patients who are eligible to receive oral tramadol.

DR. RUHA: Okay. Thank you. That answers my questions.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Thank you, and thank you, Dr. Lu, and Dr. Langford, and Iwanicki, and Minkowitz for the work you do in terms of the safety of patients, surgical patients.

I had a question, first of all, that's right basic. On your first introductory slide, slide 3, Dr. Lu, my first question was clarification on the indications that we're speaking of. Here you used the term "acute pain." The FDA in all of their supporting documentation primarily uses acute pain. However, in discussion of labeling and throughout your supporting documentation -- and on page 51, I believe it is, of that -- you refer to management of moderate to moderately severe pain.

I was very curious in terms of what the exact indications are for this and the difference between acute versus moderately severe, which actually seems to me to be an oxymoron. So I was just wondering if you could clarify the indications

that you're actually going for.

DR. LU: Thank you. First of all, Avenue would absolutely agree to the standard opioid label, and as the agency stated in the briefing document, there has not been any label negotiation.

The whole story is that when we submitted this NDA in 2019, because this is a 505(b)(2) application to Ultram, we used the original Ultram label. When we got the first complete response, when we met with the division during a Type A meeting, we thought that the division wanted us to add alone or in combination based on their comment. We thought that we had to align our labeling with IV meloxicam. So clearly, that was a miscommunication. We misunderstood what the division meant. That's very clear at this point.

But just to reiterate, this is an opioid. It should only be used when non-opioids are inadequate to treat pain. And therefore, we would absolutely accept the standard opioid label essentially that says only pain that warrants opioid-level analgesia for which alternative

treatments are inadequate.

MR. O'BRIEN: Okay. Thank you. I have a follow-up question to that, and that was the second part of it.

Obviously, the entire argument around here that is made by you, the sponsor, is the relative safety of a Schedule IV versus a Schedule II opioid. I found it interesting as I was going through, and I just need some clarification from you, and comment.

I've seen the epidemiology studies and the various pharmacological studies that are provided, and throughout your supporting documents, and in your slide 51, I think it was, you referred to the WHO committee report that was done in 2018, citing that it was relatively safer; yet that same report throughout it gives a variety of different warnings, as I read it.

In particular, on page 7, it specifically says, "There is growing evidence that the adverse effects of tramadol are consistent with the adverse effects associated with other opioids. Abuse,

dependence, and overdose of tramadol have become a serious public health concern in some African countries and parts of Western Asia." Now, I know in your epidemiology studies you had excluded Africa due to the potential of illicit drugs, which wasn't acting the same, but also in Iran and Western Asian countries, similar problems are there.

In addition to that, in the references that were used, there was a reference to a cohort study by Cornelius Thiels, et al, the chronic use of tramadol after acute pain episode. It was a 2019 study looking at the Medicare Advantage insurance claims for over 300,000 patients.

In that, the conclusion was that people receiving tramadol alone after surgery had similar to somewhat higher risks of prolonged opioid use compared with those receiving other short-acting opioids. "Federal government bodies should consider reclassifying tramadol, and providers should use as much caution with describing tramadol in the setting of acute pain, as for other short-

acting opioids."

That goes consistent with what Dr. Langford had indicated when he was discussing his slide 13, that it is very common that he sends home patients with oral tramadol. So I'm looking at it from a patient perspective and saying, are we just setting up for more of what Dr. Thiels and them had indicated in the United States; that while it's a small percentage of oral tramadol, are we now going to have a large percentage of oral tramadol and no difference in terms of what Schedule II opioids are? And I wish, if you could comment on that, please.

DR. LU: I'll be happy to, and I'll ask Dr. Janetta Iwanicki to comment.

Let me comment on your second question. We obviously read the Thiels' article with great interest. If you actually click on to their website, the BMJ website, there's an author response that was posted on January 3, 2020. I'm going to read what the author response was verbatim.

The author said, "Persistent treatment for pain is not the same as abuse or addiction. The study cannot conclude addiction or abuse is responsible for continued use. We do not at any point in this study conclude addiction or abuse is responsible for continued use. We completely agree that our study cannot and does not address this question," end quote. This is verbatim from an author response posted in January 2020.

I think these studies obviously provide little understanding of any causal relationship, but I actually want my opioid epidemiology expert, Dr. Janetta Iwanicki, to share thoughts on this point, as well as why we didn't include Africa in our survey.

DR. IWANICKI: Dr. Iwanicki.

Yes. Thank you for bringing up this important question. There are a couple of key points that I want to really focus on here, but the take-home message that I want us to start with is that, in general, tramadol, from what we see in the epidemiologic data in the postmarketing setting,

really does seem to act differently than Schedule II opioids.

Really, everything that we've seen so far, everything we've reviewed today, supports that, and that's consistent with what we see in the pharmacology, as well as in the human abuse potential studies. It has less misuse, abuse, and non-medical use.

Now, to bring that back around to where things may be different in certain countries, I think that's it's worth recognizing that that is true, and that there may be more factors that come into play there.

When we look at particularly the non-EU countries that you mentioned, Africa as well as countries in the Middle East, they're quite significant infrastructure differences and medical system differences that dramatically impact the availability of opioids in those countries. In fact, in some countries, you may not have access to any Schedule II, and that may drastically change the landscape of how a Schedule IV opioid such as

tramadol impacts that community. In particular, trends around misuse, abuse, non-medical use, and diversion are likely to be different.

More similar to what we see in the U.S. I actually think is the European experience. In particular, in Europe we have some availability of Schedule II and we have more common use of tramadol, both in the intravenous and in the outpatient [inaudible] setting, and in those countries we do not see a significant increase in those patterns, those outcomes that we're looking for, of abuse, misuse, and [inaudible].

So I think that's probably the closest parallel to what we can anticipate here in the United States, and I think the epidemiology really does support that tramadol acts as a Schedule IV opioid from everything we've seen. Thank you.

MR. O'BRIEN: Thank you.

DR. BATEMAN: Thank you.

Dr. Zaafran?

DR. ZAAFRAN: Good morning. Thank you. Sherif Zaafran in Houston, and actually a member of

the Inter-Agency Pain Management Task Force that was referenced in the presentation.

A question for Dr. Langford and for Dr. Minkowitz, just a couple of questions here. One, was the medication looked at in an ambulatory surgery center setting, and were their admissions because of issues with pain control being inadequate with the use of IV tramadol versus other Schedule II opioids? And conversely, was there an increased incidence of admissions with the use of Schedule II opioids because of sedation or not adequate pain control?

The second question is, obviously, we're looking at IV tramadol and not a PO tramadol, so is there any data on the abuse potential of a single dose of IV tramadol given in PACU, and is it any greater with tramadol than with the other Schedule II opioids?

Then the final question is, is there an equivalent weak opioid or Schedule IV opioid in the market that fills this gap between non-opioids and Schedule II opioids that currently exist in the

U.S.?

DR. MINKOWITZ: Thank you, Dr. Zaafran. For the first question regarding inadequate pain control requiring admission to the hospital afterwards, the patients were in a clinical research environment for the 102-103 studies, and as you can recall, the patients actually were successfully managed with rescue of only a few ibuprofen tablets as needed to control their pain in Studies 102-103, and no patient required readmission following those cases.

The second question?

DR. ZAAFRAN: The second question, Harold, was did you see issues with the use of Schedule II opioid versus tramadol in the need for increased monitoring, sedation issues, and stuff like that versus the tramadol group?

DR. MINKOWITZ: In the clinical program, we showed the patients didn't actually need to be rescued with a Schedule II opioid. They were controlled with either multimodal and IV tramadol or IV tramadol with the rescue with ibuprofen

alone. We did not see much of a difference in the 103 study when looking at the sedation rate in the respiratory parameters in those two trials when we compared the morphine arm and the IV tramadol arm.

The question with regard to another parenteral Schedule IV opioid, I'm not aware of any other. Maybe Dr. Langford in the UK -- you have none either. In the UK and Europe, there is no other Schedule IV opioid available.

DR. ZAAFRAN: Thanks.

The other question that I had asked was about the abuse potential. I'm just kind of curious because we are talking about IV tramadol that is typically a single-dose injection and not used at home. Is there any data about abuse potential with a single dose given in PACU versus with other Schedule II opioids? And if there is, is that potential abuse greater with IV tramadol versus other Schedule II opioids?

DR. LU: Dr. Jody Green to address your question.

DR. GREEN: Dr. Green from Inflexxion.

The question of the subsequent use of medication after [inaudible], it does come back to the abuse potential. Knowing and well established, that tramadol is this a Schedule IV, really has a lower likelihood of abuse potential [inaudible], based upon, too, the rewarding effects and reinforcing effects. What we do know is that those reinforcing effects can potentially [inaudible] in subsequent behaviors around seeking and using prescription opioids outside of a medical setting [inaudible].

So understanding that it's very complex pathways and influencers that lead someone to use any substance [inaudible], but recognizing if we can reduce those reinforced effects from the beginning, that [inaudible] theoretically, and the likelihood of them seeking prescription opioids afterwards has been diminished.

Again, I think that's really what we need [inaudible].

DR. BATEMAN: Thank you.

Dr. Sprintz?

(No response.)

DR. BATEMAN: Dr. Sprintz, you may be on mute.

DR. SPRINTZ: I am. Hi. Can you hear me?

DR. BATEMAN: Yes, we can hear you now.

DR. SPRINTZ: Okay. Thank you very much, and I appreciate everyone's presentation today; a lot of interesting concerns and questions.

One of my first questions for Dr. Lu, actually, is why did you not use the data collection methods used in the IV meloxicam for the stopwatch results? I noticed in your talk you mentioned that that they were different and were trying to compare those two. So why didn't you use those in the first place? That would be my first question.

Then my second question is for Dr. Minkowitz. On Study 104, you mentioned that in your studies that patients were not exposed to C2 opioids. So my first question is, with those, how many of the patients received regional anesthesia, and then also how many of those

patients had C2 opioids intraoperatively?

Then the final point is that I believe in Study 104, everyone stayed in-house in the healthcare facility, so people weren't discharged; and yet the indications that you had talked about is a medically supervised setting, which could be an ambulatory surgery center or an ER, and that's not an inpatient situation. That's all.

DR. LU: Okay. Let me start.

There's really no clear guidance, that we know of, of how to do the stopwatch metric. I think the way we did it was very conservative, and we were really trying to find out what is the independent effect of IV tramadol on the need for pain relief. As such, the minute someone takes rescue ibuprofen, their stopwatch was taken away, they were automatically assigned the worst possible outcome, and meaningful pain relief at 6 hours.

We thought that was the right way to do it. Clearly, there were other sponsors doing it other ways and, really, we did not realize this until we started preparing for this outcome. And when we

saw what IV meloxicam did, based on the clinical review posted on the FDA website, we realized that there were actually drastically different approaches to doing the stopwatch metric. In their case, they essentially allowed patients to take IV meloxicam and then oxycodone 5 milligram. They were still pressing the stopwatch, and it still counted. So clearly that's a difference.

The other one was the data analysis. We automatically assigned the worst outcome to whoever took rescue, but in their case, they were actually censoring patients and removing them from the pool, from the analysis pool, or the denominator, at the time of rescue, and therefore resulting in a much shorter time to onset. So I think both methods are correct. Obviously, the agency has accepted both of them.

Dr. Minkowitz, would you please address the second question?

DR. MINKOWITZ: Dr. Minkowitz. With regard to the question of the admitted supervised setting, this is intended to include both hospitals with an

inpatient facility, as well as outpatient surgery centers in basically places where people are used to providing parenteral opioids.

For your second question, the number of people that have blocks may have been a couple. I'm not quite sure if there were very many with blocks. We could always pull that [inaudible]. I don't have that information at hand.

With regard to the question to intraoperative opioids they may have received opioids intraoperatively, the protocol only specified postoperative termination [inaudible] of Schedule II opioids, which we succeeded in doing. And hopefully if people could see the efficacy of the IV tramadol successfully controlling the patient's pain, as we did in the study, it would be a transition to patients being discharged on non-C2 opioids and tramadol, or lesser agents, with home discharge.

DR. SPRINTZ: Okay. But I guess the question that I have, that I'm confused about, is if the indication that you're looking for is a

medically supervised setting, such as hospitals and inpatients -- that's how you did the study -- giving IV tramadol, even if you give it intraoperatively, as opposed to the end of the case, all of this was done with multiple fixed dosing. And if these patients are going home right after a procedure, we could have a potential of where they talk about the opioid stacking or you're not monitored when they go home.

So that was a concern of mine in terms of the labeling of what you defined as a medically supervised setting, that was concerning, versus a straight inpatient situation. And that's all for me.

DR. MINKOWITZ: No. I do hear your concern with regard to adequately monitoring patients after receiving any dose of opioid. As a standard across all institutions, there are guidelines for discharge following administration of any IV opioid prior to discharge home within a safe period of time. Obviously, that would have to be incorporated into any institution's discharge

criteria and practices. But I do agree with you that we do need to obviously maintain vigilance and care with all our patients, and this is no exception.

DR. BATEMAN: Thank you.

Dr. Goudra?

DR. GOUDRA: Basavana Goudra from Penn Medicine. I might be one of the unique physicians here. I worked in three continents. In fact, I used tramadol. But there are clear differences in patient expectations, physician compulsions, and even expectations of administrators when it comes to using U.S., and U.S. is also more multiethnic in terms of population.

So with that in mind, are there any questions, and are they having any studies looking at the abuse-risk potential across the races considering it's very well known that different races respond differently, both to pain, especially the emotional component of pain with Africans and them having a much lower threshold and responding differently?

My own study, in fact a retrospective study, showed a higher relative risk for opioid abuse among African American patients after intraoperative administration. So are there any studies looking at abuse potential across races and also incidence due to the euphoria experienced by patients across different races? I think that could be quite important from the prospective use in the United States. Thank you.

DR. LU: If I understand it correctly, the first question is on whether African Americans are in the trial? Is that correct?

DR. GOUDRA: Yes, or since the drug has been there for three decades, is there any sufficient data of how the drug has done in African countries?

DR. LU: Okay. I will ask Dr. Langford.

DR. LANGFORD: Yes. Thank you, and an interesting question. This is Dr. Langford speaking.

Of course there are variations across Europe in terms of the ethnic distribution, but if I just give my own personal account, working on the east

side of London actually for 25 years in Barts Health, which was Barts and the Royal London, we looked after a very large population -- 3 million -- with a very high percentage of Southeast Asian and African patients in the East London area. A goodly proportion of our patients were not Caucasian.

So just to say that I've experienced, and of course of course across other European countries, we have a very wide mix of ethnic groups. But I think I can say that tramadol proved to be perfectly acceptable in those situations.

DR. BATEMAN: Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. This is Suzanne Robotti. I have three questions.

It's been mentioned several times that patients were allowed to leave the study if they were not getting effective pain relief or for other reasons. I don't see how many patients did leave the four studies that have been reported today, and if they left for reasons other than ineffective

pain relief, I'd be interested in knowing what they are.

Two other questions. You have placebos in two of the trials. What were the placebos? The third question is, ibuprofen was used as a rescue drug, effectively, apparently. Has there been a study conducted comparing ibuprofen to IV tramadol as a replacement drug? If ibuprofen works, then why are we not using ibuprofen instead of tramadol or any opioid? That's it.

DR. LU: Great. Let me show you, on this slide is the study disposition in Study 102 and 103. These are the two efficacy trials. As you can see, there's the discontinuation rate among placebo patients, versus tramadol patients, versus morphine patients.

In Study 102, lack of efficacy, 11 patients in the placebo group discontinued versus one in the IV tramadol safety, and there was only one patient that discontinued due to an adverse event in Study 102 in the tramadol group, and it was due to vomiting. In Study 103, the percentages are listed

as shown, again. We can talk more about that if you have a specific question.

Then in Study 104, the safety study, the open-label, real-world safety study, we had zero patients that discontinued due to lack of efficacy, and 4.4 percent of patients discontinued due to adverse events, and here are some. Mostly it's GI-related adverse events such as nausea and vomiting, and then there are some procedural complications related.

I will ask Dr. Langford to address your other question.

DR. LANGFORD: Yes. Dr. Langford speaking again. You have a very interesting question about how tramadol compares, for example, to an anti-inflammatory. In fact, of course, the whole raison d'être of what we do is to provide non-opioid multimodal analgesia, including local anesthetics, and so on, in order to try and avoid exposure to opioids.

However, there are many intermediate and major surgical procedures which are just too

painful to be adequately managed with acetaminophen and an anti-inflammatory analgesic alone. And if one thinks of perhaps a major joint replacement, or thoracotomy, or abdominal surgery, one really would be serving our patients very badly if we did not provide them with some stronger analgesia.

Now, what we've shown -- or the sponsor has shown, rather, in these studies, and we have in our normal clinical practice, plus prior to that many studies have found -- is that in the multimodal setting, intravenous tramadol can provide that additional analgesia where necessary above and beyond what a non-opioid regimen can deliver. And of course, on occasion, one might need to reach for a Schedule II opioid -- that couldn't be denied -- but many, many patients are satisfied with the Schedule IV level of tramadol rather than having to escalate up to a Schedule II level.

I hope that answers your question.

MS. ROBOTTI: I just didn't know if you knew of a study that compared ibuprofen or acetaminophen to tramadol directly, IV tramadol, in a

noninferiority study or a superiority study.

DR. LANGFORD: Well, there are various studies in models of much lesser levels of pain, for example, in third-molar extractions, but that is not the setting we're talking about. We're talking about the types of patients who warrant stronger opioid analgesic management.

So in that setting, forgive me, but I think it wouldn't have been considered appropriate to compare an analgesic with the strength of ibuprofen or acetaminophen against something like tramadol or morphine, for example. Tramadol is being regularly compared to morphine, or oxycodone, or fentanyl, but not so much directly with anti-inflammatories. On the contrary, it has been trialed in association with those non-opioid medicines.

DR. BATEMAN: Thank you.

We have time for one more question. We're going to go to Dr. Lo Re, and then after the open public hearing, we'll circle back and get questions from Dr. Hernandez-Diaz and Dr. Huybrechts.

Dr. Lo Re, one short question, please.

DR. LO RE: Yes. Thank you. This is Vincent Lo Re from the University of Pennsylvania. My question regards slide CO-40, and it's either for Dr. Lu or Dr. Iwanicki.

In this slide, I'm trying to understand how the risk of opioid rescue stacking was determined here. If this is the data from Studies 102 and 103 that only allowed as rescue medication ibuprofen -- it seems like the second bullet under stacking is the open label, and I'm assuming that's Study 104, that only allowed non-opioid medications.

So I'm trying to understand how the risk of stacking was determined. I'm concerned that Studies 102, 103, and 104 might not necessarily reflect real-world experience, and I didn't really see real-world experience from European settings where the drug has been used for quite some time.

I'm wondering are there empirical pharmacoepidemiologic data that have reported the incidence of stacking with IV tramadol in real-world settings in Europe, and among those who

have evidence of stacking, has there been evidence on the incidence on harms in the outpatient setting, because we're trying to understand that in weighing the risks and the benefits, for me as a pharmacoepidemiologist, answering those questions would be helpful. Thank you.

DR. LU: Let me get started, and I will ask Dr. Langford to address the European reporting of stacking.

In terms of an increased risk of opioid rescue in clinical trials, you're correct that we didn't allow opioids to be the rescue. However, if patients needed additional pain control with opioids, they could discontinue at any time. If there's the need for a lot of opioid rescue, you would expect to see a big dropout rate from both the efficacy trials as well as the open-label safety studies [inaudible], and we just simply didn't see that.

I'd like to ask Dr. Langford to address your question in terms of our data collection and reporting our opioid stacking based on our European

experience.

DR. LANGFORD: Yes. Thank you.

Dr. Langford speaking again.

Well, to be frank, opioid stacking, or the deleterious outcomes of combining different opioids, just hasn't proved to generate any sort of safety signal. We have very sophisticated monitoring and safety systems and incident reporting systems, both institutionally in our hospitals. We have very good governance and quality control and a quality improvement program, and of course we have very well-regarded regulators such as the MHRA and EMA.

Despite vigilance over several decades and, as I said before, a very safety-conscious profession, i.e., anesthesiologists, there has not been a safety signal, and it wasn't anything therefore that generated interest in doing a study. So I'm afraid it's a negative answer, but with a positive background to it, if you see what I mean.

DR. LO RE: Thank you.

DR. BATEMAN: Thank you.

We'll now take a quick 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 11:57 a.m. Eastern time.

(Whereupon, at 11:47 a.m., a recess was taken.)

DR. BATEMAN: Welcome back. We will now proceed with the FDA presentations, starting with Dr. Lisa Wiltrout.

FDA Presentation – Lisa Wiltrout

DR. WILTROUT: Good afternoon. My name is Lisa Wiltrout, and I'm a medical officer in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine. I'm going to speak with you today about new drug application 213231, a submission for intravenous tramadol hydrochloride, also referred to as tramadol IV. The applicant is Avenue Therapeutics, Incorporated.

Here is an overview of FDA's presentation. I'll start by reviewing some of the regulatory history for tramadol IV. I will talk about

tramadol hydrochloride metabolism and mechanism of analgesia, I will review some of the efficacy and safety data, then I will discuss published literature and real-world data on intravenous tramadol use outside of the United States.

My colleague in the Controlled Substance Staff, Dr. James Tolliver, will speak about abuse liability considerations for tramadol IV, and Dr. Christina Greene from the Division of Epidemiology II, in the Office of Surveillance and Epidemiology, will speak about epidemiologic data and public health considerations in evaluating the benefit-risk of intravenous tramadol. Lastly, I will summarize tramadol IV's overall benefit-risk profile and conclude our presentation.

In December 2019, the applicant submitted a new drug application that relied, in part, on the FDA finding of safety and efficacy for Ultram, an oral formulation of tramadol hydrochloride. The proposed indication was management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The proposed dosing

regimen was tramadol 50 milligrams IV infusion over 15 minutes, at hour 0, hour 2, hour 4, and then every 4 hours thereafter.

In October 2020, the division issued a complete response letter to the applicant. We noted one product quality deficiency and one clinical deficiency with the NDA. The clinical deficiency was a safety issue. Tramadol IV's delayed onset of analgesia combined with its inability to be titrated to effect leads to a theoretical, yet serious, safety concern of additive opioid-related adverse events from use of opioids in succession, also referred to as opioid, stacking.

For patients whose pain is not adequately controlled with the first dose of tramadol IV, we anticipate they will likely receive another immediate-release opioid as rescue analgesia. This will result in opioid stacking and increase the potential for opioid-related adverse events. We stated that the applicant could address this deficiency by identifying a population for which

tramadol IV is both safe and effective for the acute pain indication.

In November 2020, we held a post-action meeting with the applicant. The applicant agreed with the division about tramadol IV's delayed onset of analgesia but disagreed with our thinking about the need for an immediate-release opioid as rescue analgesia and our concerns about opioid stacking. The applicant stated that patients in need of rescue analgesia could be adequately managed with another analgesic, and that use of most multiple opioids is customary in the hospital setting. The applicant proposed addressing the clinical deficiency with labeling revisions. The division agreed to review the applicant's proposed labeling revisions once submitted.

In February 2021, the applicant submitted a response to the division's complete response letter. The applicant's submission contained no new clinical data. The applicant addressed the product's quality deficiency, added language in the limitations of use, dosage and administration, and

clinical study sections of the label, and revised the indication. The revised proposed indication was management of moderate to moderately severe pain in adults in a medically supervised setting, alone or in combination with other analgesics.

In June 2021, the division issued a second complete response letter to the applicant. We stated that the information provided in the resubmission was not adequate to support the proposed indication for tramadol IV, which again was management of moderate to moderately severe pain in adults in a medically supervised setting, alone or in combination with other analgesics.

We restated our concern about tramadol IV's delayed onset of analgesia and the potential for opioid stacking and additive opioid-related adverse events. We also stated that the studies in the NDA were not designed to evaluate the analgesic benefit of tramadol IV in combination with another analgesic.

In summary, we concluded that tramadol IV's delayed onset of analgesia does not support its

benefit as a monotherapy in the acute pain population. Additionally, there was insufficient information in the NDA to support the conclusion that tramadol IV in combination with other analgesics is safe and effective for the intended patient population.

In July 2021, we held a second post-action meeting with the applicant. The applicant stated that the totality of the data, looking at endpoints other than time to meaningful pain relief, supports approval of tramadol IV. The applicant also stated that opioid stacking was not identified as a safety concern in the NDA, nor has opioid stacking been a safety concern in countries outside the United States where intravenous tramadol is utilized.

The applicant submitted a formal dispute resolution request to the Office of Neuroscience on July 27, 2021. The Office of Neuroscience reviewed the formal dispute resolution request and issued a dispute appeal denied letter on August 26, 2021, stating that tramadol IV's delayed onset of effect raises a safety concern about the risk of opioid

stacking that has not been adequately addressed in the NDA.

The applicant submitted a formal dispute resolution request to the Office of New Drugs on August 31, 2021. The Office of New Drugs reviewed the formal dispute resolution request and issued a dispute appeal interim response letter on October 21, 2021, stating that input from the advisory committee was needed to reach a decision on the formal dispute resolution request.

Tramadol hydrochloride is an atypical opioid analgesic. It is not only a mu opioid receptor agonist but also a weak norepinephrine and serotonin reuptake inhibitor. It is in Schedule IV under the federal Controlled Substances Act. Tramadol is metabolized in the liver primarily via the CYP2D6 enzyme from the parent compound, an extremely weak opioid antagonist to its major metabolite M1, a more potent opioid agonist. Therefore, tramadol exerts much of its opioid-related analgesic effect through M1.

With IV administration of tramadol,

first-pass metabolism is bypassed and there is delayed formation of M1. Delayed M1 formation appears to contribute to the delay in tramadol IV's onset of effects.

The applicant conducted two adequate and well-controlled phase 3 studies in support of the efficacy of tramadol IV. Both were randomized, double-blind, three-arm, multicenter studies designed to compare tramadol 50 milligrams IV infusion to placebo.

The first, Avenue 901-102, also referred to as Study 102, was a dose-finding study in a bunionectomy pain model that included a lower dose of tramadol IV, 25 milligrams, in addition to tramadol IV 50 milligrams. The primary endpoint was the time-weighted summed pain intensity difference from baseline over 48 hours or SPID-48.

The second, Avenue 901-103, also referred to as Study 103, was a placebo-controlled study in an abdominoplasty pain model that included morphine 4 milligrams IV push in addition to tramadol IV 50 milligrams. The primary endpoint

was the time-weighted summed pain intensity difference from baseline over 24 hours or SPID-24.

Given the different pain models, the approach to pain management during and immediately after surgery was different for the two studies. In the bunionectomy study, patients received both general and regional anesthesia. A popliteal block was administered before surgery. The popliteal block was maintained after surgery with a continuous subcutaneous infusion of anesthetic.

At 4 to 5 a.m. on the day following surgery, the popliteal block was withdrawn. Patients then had to report a moderate or severe rating on a 4-point categorical rating scale and a numerical pain rating scale, or NPRS, score of 5 or greater within 8 hours of removal of the popliteal block to be eligible for the first dose of study drug.

In the abdominoplasty study, patients received general anesthesia but no regional anesthesia. Patients' pain during surgery and in the immediate postoperative period was managed with intravenous fentanyl. Patients had to report a

moderate or severe rating on a 4-point categorical rating scale and an NPRS score of 5 or greater within 3 hours following end of surgery to be eligible for the first dose of study drug. Patients were also required to have an NPRS score of 5 or greater at baseline time 0 before study drug administration.

The only allowed rescue medication was oral ibuprofen 400 milligrams every 4 hours as needed for pain. Patients were encouraged to wait at least 60 minutes after first dose of study drug before they received rescue medication. Use of opioids was not allowed.

Results from Studies 102 and 103 provided substantial evidence of the efficacy of tramadol IV 50 milligrams for the acute pain indication. The results of both studies showed a statistically significant difference between tramadol 50 milligrams and placebo for the primary and secondary endpoints listed here. However, the division's analyses of time to first rescue use and time to meaningful pain relief using the two

stopwatch method suggested that tramadol IV 50 milligrams has a delayed onset of analgesia likely beyond 2 hours. Tramadol IV's delayed onset of analgesia is an aspect of the product's efficacy profile that has safety implications for the treatment of acute pain.

We evaluated whether tramadol IV provided adequate analgesia over the first dosing interval by analyzing the number of patients who used first rescue medication within 2 hours of initiating study drug. Note again that patients were encouraged to wait at least 60 minutes after first dose of study drug before they received rescue medication.

In the bunionectomy study, the percentage of patients using rescue within the first 2 hours was highest in the placebo arm, 45 percent, followed by the tramadol 25-milligram arm, 42 percent, which is similar to that reported in the placebo arm, and then the tramadol 50-milligram arm, 33 percent.

In the abdominoplasty study, the percentage of patients using rescue within the first 2 hours was highest in the placebo arm, 51 percent,

followed by the tramadol 50-milligram arm, 43 percent. Note that the percentage of patients using rescue within the first 2 hours was 28 percent in the morphine 4-milligram arm.

We also analyzed time to meaningful pain relief at 30 minutes, 1 hour, and 2 hours after first dose of study drug. Time to perceptible and time to meaningful pain relief were evaluated in Studies 102 and 103 using the two stopwatch method.

The two stopwatch method entails giving the patient two stopwatches and asking the patient to click the first stopwatch when he or she feels the first perceptible pain relief, and the second stopwatch when he or she feels meaningful pain relief. The times to perceptible and meaningful pain relief are then documented in minutes.

For both studies, patients who used rescue medications, discontinued early, or never pushed the second stopwatch were censored at 6 hours and not counted as having achieved meaningful pain relief. In the bunionectomy study, the percentage of patients reporting meaningful pain relief within

2 hours was highest in the tramadol 50-milligram arm, followed by the tramadol 25-milligram arm, and then the placebo arm. These findings support the dose-response relationship in analgesic effect with tramadol IV.

In the abdominoplasty study, the percentage of patients who reported meaningful pain relief within 2 hours was highest in the morphine 4-milligram arm, followed by the tramadol 50-milligram arm, and then the placebo arm. Note that the difference in percentage of patients who reported meaningful pain relief within 2 hours between the tramadol 50-milligram arm, 51 percent, and the placebo arm, 48 percent, was only 3 percentage points.

The clinical team concluded that tramadol IV has a delayed onset of analgesia. Tramadol IV's delayed onset of analgesia leads to a theoretical, yet serious, safety concern of additive opioid-related adverse events from opioid stacking. For patients whose pain is not adequately controlled with the first dose of tramadol IV, we

anticipate they will likely receive another immediate-release opioid as rescue analgesia. This will result in opioid stacking and increase the potential for opioid-related adverse events.

The applicant submitted results from three studies in support of the safety of tramadol IV, two placebo-controlled studies that I have discussed in detail, the bunionectomy and abdominoplasty studies, and one uncontrolled study, Avenue 901-104, also referred to as Study 104. Study 104 was a single-arm, open-label study designed to evaluate the safety of tramadol IV, 50 milligrams, for the management of postoperative pain after a variety of elective surgeries. The most common surgery types are listed here.

Overall, tramadol IV's safety profile was consistent with that of Ultram and the typical safety profile of other available opioid products. There were no deaths in the phase 3 program, and there were 6 serious adverse events in total, none of which were opioid complication related. Review of the serious adverse events did not raise any new

safety concerns about tramadol IV.

The most common adverse events reported in Studies 102 and 103 are listed here. You can see that the most common adverse events reported in Study 104 were similar to those reported in Studies 102 and 103.

A review of the respiratory-related safety data in the phase 3 program identified that tramadol IV 50 milligrams was associated with more respiratory impairment events than either morphine IV or placebo. The higher incidence of respiratory impairment events with tramadol IV administration was of clinical concern because respiratory-related adverse events if not treated promptly can result in brain injury and death.

In the bunionectomy study, the applicant collected safety data on any respiratory-related, treatment-emergent adverse events, or TEAEs, across all three treatment arms but did not prespecify a safety assessment of TEAEs related to respiratory impairment.

A review of the adverse event data set

yielded the data presented on the slide. There were 5 AEs of hypoxia defined as an oxygen saturation less than 92 percent in the tramadol 50-milligram arm; one AE of dyspnea in the tramadol 25-milligram arm; and one AE of hypoxia and one AE of dyspnea in the placebo arm.

Overall, tramadol 50 milligrams had a higher incidence of TEAEs related to respiratory impairment than tramadol 25 milligrams or placebo. Additionally, a review of the vital signs data set demonstrated that the tramadol 50-milligram arm had more oxygen desaturation events and larger decreases in oxygen saturation measurements than the tramadol 25-milligram and placebo arms.

In the abdominoplasty study, the applicant prespecified a safety assessment of TEAEs related to respiratory impairment. This allowed for a comparison of the respiratory safety and tolerability of tramadol IV and morphine IV.

The applicant defined respiratory impairment as a clinically relevant worsening in respiratory status based on the safety parameters of

respiratory rate, oxygen saturation, and somnolence or sedation. A respiratory impairment event was documented as an AE with the preferred term of "respiratory disorder." An AE of hypoxia, again defined as an oxygen saturation less than 92 percent, was also considered an AE of respiratory disorder. Any associated events, such as bradypnea, sedation, or somnolence, that led to the respiratory impairment event were also recorded as AEs.

A review of the respiratory impairment events in the abdominoplasty study yielded the data presented on this slide. Thirteen patients had at least one respiratory impairment event, nine in the tramadol 50-milligram arm and four patients in the morphine 4-milligram arm.

For the 9 patients in the tramadol 50-milligram arm, all had AEs of respiratory disorder and hypoxia; two had AEs of sedation; one had an AE of bradypnea; and four discontinued study participation due to the event. For the 4 patients in the morphine 4-milligram arm, all had AEs of

respiratory disorder and hypoxia; one had an AE of sedation; and three discontinued study participation due to the event.

Overall, the incidence of respiratory impairment events was higher for tramadol IV than morphine IV. Additionally, a review of the vital signs data set demonstrated that the tramadol 50-milligram arm had more oxygen desaturation events and larger decreases in oxygen saturation measurements than the morphine 4-milligram arm.

In Study 104, AEs of hypoxia were documented. As you see in this table, 17 patients experienced hypoxia with 16 patients having undergone hernia procedures and one patient having undergone breast augmentation. As Study 104 was an open-label, uncontrolled study, conclusions on safety are limited.

The applicant identified the following adverse events related to abuse potential in the tramadol IV clinical development program: dizziness/dizziness postural; somnolence; sedation; euphoria/euphoric mood; dysphoria; and disturbance

in attention. From the FDA's perspective, adverse events of dizziness, somnolence, and sedation signal that a drug has central nervous system activity but not necessarily abuse potential, while adverse events of euphoria and euphoric mood are more indicative of a drug's abuse potential, as these adverse events signal that a drug has subjective reinforcing effects.

In the bunionectomy study, the most common adverse events related to abuse potential, as defined by the applicant, across all treatment arms were dizziness and somnolence. The incidence of dizziness and somnolence was highest in the tramadol 50-milligram arm. There was only one adverse event of euphoria reported, and it was reported in the tramadol 50-milligram arm.

Similarly, in the abdominoplasty study, the most common adverse events related to abuse potential, as defined by the applicant, across all treatment arms were dizziness, somnolence, and dizziness postural. The incidence of dizziness and dizziness postural was higher in the morphine arm

than in the tramadol arm, whereas the incidence of somnolence and sedation was comparable between the two arms. There were no AES of euphoria reported in any of the treatment arms.

We reviewed the safety data looking for instances of opioid stacking. We defined opioid stacking as use of tramadol IV followed in succession by another opioid, or in other words consecutive use of tramadol IV and another opioid. Very few instances of tramadol IV use followed in succession by another opioid were found.

It was difficult to evaluate for adverse events related to opioid stacking in the phase 3 program because the studies did not allow the use of another opioid as rescue medication. The only allowed rescue medication was ibuprofen in Studies 102 and 103, and non-opioid medication at the discretion of the treating physician in Study 104.

In total, 8 patients were administered tramadol IV followed in succession by another opioid: one patient in the bunionectomy study who

had an AE of hypoxia that was considered unlikely related to consecutive use of tramadol IV and another opioid; 6 patients in the abdominoplasty study; one patient had an AE of nausea; and one patient had an AE of headache. These adverse events were considered possibly related to consecutive use of tramadol IV and another opioid.

One patient had an AE of nausea and vomiting that was considered not related to consecutive use of tramadol IV and another opioid, and 3 patients had no AEs documented. One patient in Study 104 had an AE of nausea that was considered possibly related to consecutive use of tramadol IV and another opioid. Even though opioid stacking rarely occurred in the tramadol IV clinical program, the division remains concerned about the potential for opioid stacking and additive opioid-related adverse events with tramadol IV.

Physicians' behaviors in the clinical study setting are not necessarily reflective of real-world clinical practice. Physicians in clinical practice may offer opioids rather than

non-opioids as rescue analgesia for patients in acute pain that has not been adequately managed with tramadol IV. Physicians in clinical practice may also offer rescue opioid analgesia earlier than one hour after the first dose of tramadol IV.

The clinical team concluded that there was insufficient data in the NDA to determine whether use of tramadol IV followed by another opioid is safe for the intended patient population, particularly given the increased incidence of hypoxia seen with tramadol IV 50 milligrams in the clinical program.

We also evaluated the types of opioids patients transitioned to after completing study drug treatment. Our goal with this analysis was to identify whether patients used tramadol-containing products or Schedule II and III opioids after completing treatment with study drug. The applicant did not include a list of medications prescribed at time of discharge, therefore we focused our analysis on the types of opioids used as, quote/unquote, "new onset concomitant

medications" in all three studies.

Given that opioids were not allowed as rescue medication and few protocol deviations related to opioid usage occurred, almost all of the opioid usage in the phase 3 studies occurred after the last dose of study drug.

Looking at the tramadol 50-milligram arm in the bunionectomy study, approximately 46 percent of patients used opioids after completing study drug. All of these patients used Schedule II and III opioids. There was no documentation of any use of tramadol-containing products after completion of study drug.

Looking at the tramadol 50-milligram arm in the abdominoplasty study, approximately 42 percent of patients used opioids after completing study drug. About half of these patients used tramadol or Ultracet, and the other half used Schedule II and III opioids.

Looking at the morphine 4-milligram arm in the abdominoplasty study, approximately 38 percent of patients used opioids after completing study

drug. Again, about half of these patients used tramadol or Ultracet, and the other half used Schedule II and III opioids.

Lastly, in Study 104, approximately 65 percent of patients used opioids after completing study drug. Only about 11 percent of these patients used tramadol, and the majority used Schedule II and III opioids.

Although this data does not clearly tell us what type of opioid medication patients received at discharge, we can see that a large percentage of patients were administered Schedule II and III opioids in the inpatient setting even after having used tramadol IV for the first 48 hours of pain management.

The applicant conducted a review of the medical literature with the goal of identifying adverse events associated with the use of tramadol hydrochloride for injection. The applicant reviewed 21 controlled studies and 6 case studies that all evaluated tramadol hydrochloride for injection administered for postoperative pain.

Some of the limitations of this data include the following.

The tramadol hydrochloride for injection doses used in these studies were generally higher than the applicant's proposed tramadol IV dose of 50 milligrams. In approximately two-thirds of the controlled studies, tramadol hydrochloride for injection was administered via patient-controlled analgesia rather than using a fixed-dosing regimen as proposed by the applicant for tramadol IV.

Additionally, this data does not involve administration of tramadol hydrochloride for injection followed in succession by another opioid, therefore the data cannot address the division's concern about opioid stacking.

The applicant concluded that rates of adverse events with use of tramadol hydrochloride for injection were comparable to the rates of adverse events with opioid comparators. We agree with the applicant's conclusion. No new or unexpected safety findings for tramadol were identified, however, we are unable to draw any

conclusions about the risk of opioid stacking with intravenous tramadol from review of the published literature.

The applicant also provided a descriptive analysis of VigiBase, an international drug monitoring database established by the World Health Organization. Data from VigiBase has limitations as well.

VigiBase is a spontaneous reporting system that may be subject to underrreporting and reporting biases. The database has no denominator, as we do not know the total number of patients prescribed the drug of interest, therefore, incidence of adverse events cannot be estimated. Any potential safety signals identified may or may not represent adverse events that are truly associated with the drug product of interest, and clinical review of the adverse event report is needed to fully understand the data; but there may be missing, inaccurate, or unsubstantiated data in the report.

Given these limitations, if we look at the

results for the European region, which may have practice patterns most similar to those in the United States, we see that there were approximately 12,600 adverse event reports for oral tramadol and 1,000 adverse event reports for intravenous tramadol. The percentage of adverse event reports of respiratory depression was low relative to all adverse events reported, 0.5 percent with oral tramadol and 1 percent with intravenous tramadol.

The applicant also looked at adverse event reports in which co-use of opioids was documented. Co-use of opioids was defined as any adverse event reports for oral or intravenous tramadol that also reported use of another opioid by any route of administration. The percentage of adverse event reports for oral tramadol in which co-use of opioids was documented was 9 percent. The percentage of adverse event reports for intravenous tramadol in which co-use of opioids was documented was 20 percent. No details were provided on the types of adverse events reported when co-use of opioids was documented.

Conclusions using the available data are limited. We cannot make any comparative statements regarding data in spontaneous reports, however, we can conclude that respiratory depression and co-use of opioids were reported with intravenous tramadol.

We will now hear from Dr. James Tolliver, who will speak about abuse liability considerations for tramadol IV.

FDA Presentation – James Tolliver

DR. TOLLIVER: My name is Dr. James Tolliver. I'm a senior pharmacologist within the Controlled Substance Staff of CDER. I wish to briefly discuss the abuse potential of tramadol IV as used in a supervised medical study.

Under NDA 213231, the applicant proposed that tramadol as a Schedule IV opioid might offer an advantage over intravenous Schedule II opioids administered within a medically supervised setting for treatment of pain by decreasing the risk of subsequent opioid-use disorder. At the same time, the applicant has noted in its AC briefing document that there is no direct evidence to support this

proposal.

Tramadol and other opioids are listed under the Controlled Substances Act, a law intended to mitigate risk of abuse and diversion by regulating the availability and supply of drugs prone to abuse.

There are five possible schedules designated I through V. Schedule I is reserved for drugs having no accepted medical use in the United States. Schedules II through V are for drugs having accepted medical use and have progressively lower abuse and dependence potential. Opioids such as morphine or oxycodone are in Schedule II, indicating a high potential for abuse and in which abuse may lead to severe psychological or physical dependence.

As an opioid in Schedule IV, tramadol is designated as having a lower abuse potential, as well as lower physical and psychological dependence potential than opioids in Schedule III, IV for that matter, and Schedule II.

Tramadol was first approved by FDA in 1995

as Ultram, however, it was first placed into Schedule IV in 2014 in response to petitioner requests and reports of abuse. This action was supported by both a scientific and medical evaluation, as well as a Schedule IV recommendation originating within the FDA, followed by review in concurrence by the National Institute on Drug Abuse, and then sent by the Assistant Secretary of Health to the DEA in 2010.

Information gathered to support Schedule IV control of tramadol included, but not necessarily limited to, the fact that the opioid effects of tramadol are primarily the result of an active metabolite, O-desmethyltramadol, also designated M1, and not to tramadol, which has very limited intrinsic activity at the mu opioid receptor; and also nonclinical and some clinical data coupled with epidemiological data supporting an abuse potential and dependence potential of tramadol similar to that of resisting Schedule IV opioids such as propoxyphene and pentazocine, and less than that of Schedule III and Schedule II opioids.

Tramadol IV is intended for slow intravenous infusion over about 15 minutes for pain in a medically supervised setting and is not intended for take-home use. Opioids in Schedule II are also available for slow intravenous administration to control pain in the supervised medical setting.

Under the strict monitoring and access controls in place within a supervised medical setting, abuse by patients is not likely to occur. Of course, tramadol and Schedule II opioids are available in oral and other dosage forms for take-home use after discharge. At such times, tramadol, as well as Schedule II opioids, may be subject to abuse.

With respect to abuse potential by the intravenous route, two factors are important to consider when comparing tramadol to Schedule II opioids. The first is the relative intrinsic activity at the mu opioid receptor; the other is the rate of intravenous administration.

Due to dependency of tramadol on formation and buildup of an active metabolite, intravenous

injection of tramadol likely will result in delayed lower levels of subjective reinforcing effects. By contrast, intravenous administration of Schedule II opioids having high intrinsic mu receptor activity can produce rapid onset of high levels of subjective reinforcing effects with such descriptions as a rush, high, or euphoria. It should also be noted that intravenous tramadol may carry a higher risk of seizure activity compared to most Schedule II opioids, particularly at higher doses or higher injection rates.

When the speed of intravenous injection of Schedule II opioids is slowed, as recommended for treatment of acute pain in a supervised medical setting, there's a reduced likelihood of subjective reinforcing effects. At sufficiently low injection rates, there may be little or no reinforcing effects detected. Therefore, when factoring in the slow infusion rate as within a supervised medical setting, both tramadol and Schedule II opioids are less likely to produce subjective reinforcing effects. Support for this comes from the clinical

development program for tramadol IV.

Only two incidences of adverse events indicative of subjective reinforcing effects following tramadol IV were documented in the clinical development program for tramadol IV, consisting of three phase 1 and three phase 3 studies.

For both instances, the adverse event was documented as euphoric mood. In the phase 1 study, RVG-12-001, examining the effects of tramadol IV on QT interval, 1 out of 56 subjects receiving a single dose of 200 milligrams of tramadol IV over 15 minutes reported euphoric mood. Euphoric mood was also reported in one subject out of 140 receiving multiple infusions over approximately 48 hours of tramadol IV 50 milligrams in the phase 3 study, 102, in subjects following bunionectomy.

Note that in the phase 3 study, 103, following a abdominoplasty, multiple slow intravenous administrations of tramadol IV 50 in a total of 142 subjects, or 4 milligrams of morphine

in a total of 93 subjects, over durations varying from approximately 2 to 5 days, no adverse events indicative of subjective reinforcing effects were documented.

Keep in mind that on the street, where oral forms of tramadol and Schedule II opioids are available, epidemiological databases indicate that intravenous injection is an important route of abuse for morphine but not for tramadol.

Development of dependence with need to avoid withdrawal can motivate continued drug use, however, the presence of physical dependence does not automatically mean that individuals are abusing or are addicted to opioids. Use of tramadol or Schedule II opioids can be associated with physical dependence development when used at therapeutic and supratherapeutic doses. With longer use, the greater the risk of physical dependence.

There is a lack of understanding of the degree of physical dependence incurred and withdrawal experience following repeated exposure to tramadol or Schedule II opioids within a

supervised medical setting such as for the control of pain postoperatively.

Furthermore, the extent to which a relatively short duration with intravenous administration of tramadol or Schedule II opioids within the medically supervised study for treatment of pain induces individuals to use opioids non-medically, post-discharge, due to dependence or withdrawal symptoms, is not known.

In summary, with any medically supervised setting in which low intravenous infusion of tramadol or Schedule II opioids are administered for pain, there is low likelihood that patients will experience significant subjective reinforcing effects. Conversely, increasing the infusion rates of Schedule II opioids would likely increase differences in reinforcing effects higher for Schedule II opioids relative to IV tramadol.

It is not known the extent to which intravenous administration of tramadol or Schedule II opioids within a medically supervised setting for the treatment of pain results in

subjective reinforcing effects or physical dependence at levels that may induce subsequent non-medical use of opioids.

We're not aware of any direct data to determine that a limited duration of exposure to intravenous Schedule II opioids increases risk of opioid-use disorder that may be prevented or reduced by using intravenous Schedule IV opioids such as tramadol. The impact of inpatient treatment with opioid analgesics, for limited duration, on the risk of opioid use, misuse, or addiction post-discharge is unknown but cannot be ruled out.

Next, Dr. Christina Greene will discuss benefit-risk of intravenous tramadol from the aspect of epidemiologic data and public health considerations. Thank you.

FDA Presentation – Christina Greene

DR. GREENE: Hello. My name is Christina Greene, and I am a senior epidemiologist at the FDA. Today I will be discussing epidemiologic data and public health considerations in evaluating the

benefits and risks of intravenous tramadol.

FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, for some drug classes, including opioid analgesics, FDA explicitly considers the broader public health effects of using these drugs other than as directed and in individuals for which the drug is not intended.

For opioid analgesics, this involves consideration of the risks related to misuse, abuse, opioid-use disorder, accidental exposures, and overdose for both patients and others who may be exposed to the drug, as well as any properties of the drug that may mitigate such risks. In addition, FDA considers the benefits and risks of new opioid analgesics relative to other available therapies intended for the condition.

Throughout the briefing document, the applicant argues that intravenous tramadol would confer a public health benefit by reducing reliance on Schedule II opioids to manage postoperative pain in inpatient settings. They state that this could

result in improved safety relative to other currently available intravenous opioids through reducing risks of opioid-related harms.

To consider the risks and benefits in relation to public health, we asked the following question. Would making intravenous tramadol available for use in medically supervised settings reduce the risk of subsequent opioid-related harms such as misuse, abuse, opioid-use disorder, and overdose in patients and others?

In response, we agreed with the applicant that there are no data that directly answer this question, however, to attempt to address these public health considerations, the applicant provided the following: epidemiologic data on misuse and abuse of tramadol in the United States and select non-U.S. countries where intravenous tramadol is approved, as well as published literature on short-term, postoperative opioid exposure and prolonged opioid use in patients.

The applicant provided recent data from various epidemiological sources on the rates of

misuse, abuse, and diversion of tramadol in the community compared to selected Schedule II opioid analgesics in the United States and select international countries.

Generally, tramadol's rates of these outcomes are lower than those observed for opioid comparators, consistent with tramadol Schedule IV status in the United States. It's important to note, however, that these data reflect rates primarily observed for oral tramadol, as this is the predominant formulation used in many locations and the only formulation available in the United States.

Generally, manipulation of oral tramadol for abuse by injection route is uncommon relative to some oral formulations of Schedule II opioids, including morphine. Additionally, documented abuse of tramadol liquid formulation for injection is rare in countries where this product is approved. This is not surprising given that the product is used in medically supervised settings and would not be expected to be very available in the community

where misuse and abuse occur.

The applicant also cited five published articles on postoperative exposure to opioid analgesics in the context of medical or a postoperative setting. One older article from 2013 reported high prevalence of in-hospital postoperative use of opioid analgesics, however, this study did not obtain any information on outpatient opioid use following hospital discharge. A narrative review and an editorial letter were also cited, both cautioning against the liberal use of opioid analgesics in the postoperative setting.

Lastly, two retrospective U.S. cohort studies of outpatient opioid dispensing patterns in opioid-naïve, post-surgical patients were also provided for the purpose of further investigating postoperative opioid analgesic use and subsequent outcomes.

These U.S. cohort studies found that from 6 to 10 percent of opioid-naïve patients with an initial postoperative opioid analgesic developed prolonged opioid use, defined as one or more opioid

fills within 90 to 180 days after surgery. While both studies investigated whether certain patients used opioids for a prolonged period, neither provided any data on the association between intravenous or inpatient opioid use and the type or quantity of opioids dispensed or used after discharge.

Additionally, no clinical information was provided on the reason for subsequent opioid dispensing in these patients. The study by Brummett also found that postoperative opioid-use patterns were influenced by other factors such as the type of surgery, previous substance use, and pre-existing mental health conditions.

Finally, neither study measured whether patients developed physiologic dependence, misuse, abuse, opioid-use disorder, or overdose. Although these are known serious risks of opioid analgesics, receiving additional opioid analgesics in the months after surgery does not equate to development of opioid dependence or abuse or to opioid-use disorder.

To summarize the current epidemiologic evidence, we acknowledge what is known and unknown on this topic. We know that postoperative opioid use is prevalent and that some opioid-naïve surgery patients may continue to receive opioid analgesics four months after surgery. We also know that all outpatient opioid use carries a risk of misuse, abuse, opioid-use disorder, and overdose, and that tramadol abuse rates in the community are generally lower than that observed for Schedule II opioids.

Additionally, we know that manipulation of oral tramadol for abuse by injection route is uncommon relative to many oral formulations of Schedule II opioids. However, we do not know whether the type of intravenous opioid analgesic administered postoperatively predicts the type, amount, or duration of opioid analgesics used in the outpatient setting, or whether there is a difference in the risk of developing opioid misuse, abuse, dependence, or opioid-use disorder following use of intravenous tramadol compared to Schedule II opioid analgesics when administered in an inpatient

setting.

In conclusion, we agree with the applicant that broader public health effects such as misuse, abuse, opioid-use disorder, and related risks are critical considerations in regulatory decisions related to approval of new opioid analgesic products. Based on available epidemiologic evidence, however, it is unknown whether the availability of intravenous tramadol for use in inpatient settings would reduce these risks in patients or the broader community.

This concludes my presentation. Dr. Wiltrout will now return and provide a summary and concluding remarks.

FDA Presentation – Lisa Wiltrout

DR. WILTROUT: In summary, tramadol IV demonstrated efficacy in two adequate and well-controlled phase 3 studies, however, analyses of time to first rescue use and time to meaningful pain relief suggested that tramadol IV has a delayed onset of analgesia. Tramadol IV's delayed onset of analgesia, combined with its inability to

be titrated to effect, poses a theoretical, yet serious, safety concern of additive opioid-related adverse effects.

Tramadol IV's overall safety profile was consistent with the safety profile of Ultram and the typical safety profile of other available opioid products. In Study 103, tramadol IV was associated with more hypoxia events than morphine IV but less dizziness than morphine IV, and comparable rates of somnolence and sedation. No adverse events of euphoria were reported in either the tramadol or morphine treatment arms.

Available published literature and real-world data from VigiBase do not address the division's safety concern of additive opioid-related adverse events from opioid stacking. We know that intravenous tramadol is a Schedule IV opioid that carries less abuse liability than a Schedule II or III opioid, however, we do not know whether patients receiving tramadol IV in the inpatient setting will necessarily be discharged home on oral tramadol, another opioid, or possibly

a non-opioid analgesic.

Looking at the applicant's drug development program and the published epidemiologic literature, no robust conclusions can be made as to whether use of intravenous tramadol in an inpatient setting would lead to any difference in risk of post-discharge misuse, abuse, or opioid-use disorder compared to other currently available opioid analgesics administered intravenously in the same setting.

In conclusion, the division questions whether the minimal benefit from using tramadol IV, given its delayed onset of analgesia, outweighs the potential risk of additive opioid-related adverse effects -- in particular, sedation and respiratory depression -- from opioid stacking.

This concludes our presentation. Thank you for your attention. We will now take questions.

Clarifying Questions for FDA

DR. BATEMAN: Thank you.

We'll now take clarifying questions for FDA. Please use the raised-hand icon to indicate that

you have a question and remember to lower your hand by clicking the raised-hand icon again after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Alright. We'll start with Dr. Zacharoff.

DR. ZACHAROFF: Thank you.

Hi. This is Kevin Zacharoff from Renaissance School of Medicine at Stony Brook University. My question is for Dr. Wiltrout with respect to your presentation, slide number 22.

Dr. Wiltrout, my question is, with respect to the comments made about the safety implication

of tramadol intravenously, this statement was made on slide 22 about opioid stacking increasing the likelihood of additive opioid-related adverse events. And I'm wondering, is there any evidence or any reason for me as an anesthesiologist to think that I should consider there to be increased risk of opioid stacking with the use of intravenous tramadol compared to opioid stacking with any other opioid that might be used for managing acute pain in the postoperative period?

DR. WILTROUT: Dr. Wiltrout, FDA.

I think the question you're asking is should there be additional concern for opioid stacking with tramadol IV as compared to opioid stacking with other opioid analgesics. Is that correct?

DR. ZACHAROFF: That's correct. As an anesthesiologist, I think any time anyone's received an opioid of any kind, and there's a need to provide rescue medication with an opioid, there needs to be consideration of the possibility of inadvertent cumulative overdose.

So I'm wondering, is there any good answer,

anything provided in the documents that would make me think that there is an increased risk other than its delayed onset of action?

DR. WILTROUT: Sure. Additional areas of concern, I think, would be the fact that there is a delayed formation of M1, and we think that there would then be a delayed onset of the mu opioid effects, which would include not only the analgesic properties but the adverse events. The drug also has other mechanisms of actions, the serotonin and the norepinephrine reuptake inhibitor component, which may lead to other drug-drug interactions. The drug also has a longer half-Life, about 6 to 7 hours, which may play a role in terms of interactions with other drugs as well.

DR. ZACHAROFF: So to tack on to that, with respect to the last statement you just made about the half-life, is there any evidence that the FDA has to consider that there should be some delayed period to time of discharge for patients who receive IV tramadol?

DR. WILTROUT: I think that's an excellent

question, but that's something that I don't actually have the answer to.

DR. ZACHAROFF: Right. Thank you very much. That concludes my questions.

DR. WILTROUT: You're welcome.

DR. BATEMAN: Thank you.

Dr. McAuliffe?

(No response.)

DR. McAULIFFE: Can you hear me?

DR. BATEMAN: Yes. Go ahead with your question, please.

DR. McAULIFFE: Thank you. This is for Dr. Wiltrout as well.

Dr. Wiltrout, on your excellent slides -- thank you for your presentation -- slide 29 and 30, you pointed out for us that the AEs of respiratory disorder and/or hypoxia in Study 103 was about 6.3 percent, and in 104 was about 6.8 percent.

I'm wondering if there is any time frame in there. Did you correlate those incidences with the time of the medication delivery? Was it within the

2 hours that we could assume that somebody may be asking for an additional rescue drug, or was there variability in the time of onset to those respiratory events? Thank you.

DR. WILTROUT: Dr. Wiltrout, FDA. There is actually quite a bit of variability as to when the hypoxia events occurred. There were some that occurred in the 4-to-8 hour window, but quite a number that occurred at a later timepoint, so it would not necessarily correlate with receiving rescue at an early timepoint. It could be that the patients were receiving rescue at some later timepoint while still on the fixed dosing of tramadol IV every 4 hours, and the hypoxia would occur at that time.

DR. McAULIFFE: That would be at a time when the patient perhaps is not under the monitoring, strict monitoring, that they would be when they were given this IV. Thank you very much.

DR. WILTROUT: You're welcome.

DR. BATEMAN: Thank you.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. I'm the consumer representative to AADPAC, and I believe this question should be directed to Dr. Wiltrout, but perhaps just to the FDA in general.

You did touch on this, and others have spoken -- Dr. Zacharoff spoke in a similar vein about the stacking issue. We've heard a lot from sponsor about prescribing behaviors in Europe, the European countries, and I'm just wondering if there is any research on the opioid stacking behaviors in the U.S. by prescribers, and I wonder to what extent these may differ from European opioid stacking behaviors.

DR. WILTROUT: This is Dr. Wiltrout.

Could you repeat the question for me just to make sure I understood it properly.

DR. HIGGINS: Sure. I had said that we've heard a lot about opioid stacking behaviors in Europe, European countries, from the sponsor, and I wondered if there's any research on opioid stacking behaviors in the U.S. and how that may differ at all from prescribing behaviors in European

countries. It sounds as though there is scant data on this topic, but I just wondered if you had come across anything.

DR. WILTROUT: Yes. Dr. Wiltrout, FDA. I'm not aware of any data that tells us about opioid stacking behavior in the United States, but I'll defer to my colleagues in case there are any additional comments from anyone from the FDA.

DR. ROCA: Hi. This is Dr. Roca from the FDA as well. I don't think we have any additional information regarding your question, particularly with respect to behavior, so I don't have anything to add to what Dr. Wiltrout said.

DR. HIGGINS: Thank you very much.

DR. BATEMAN: Thank you.

Dr. McCann?

DR. McCANN: Hello. This is Dr. McCann, Harvard Medical School. My question is directed to Dr. Wiltrout. I'm a pediatric anesthesiologist, and we dose everything in milligrams per kilo. So a 50-kilo adult would get half the dose that a 100-kilo adult would get.

Is there any evidence that the negative respiratory events occurred in the small adults in this study? Did anybody try to correlate the size of the patient with respiratory events?

DR. WILTROUT: This is Dr. Wiltrout, FDA. You're asking not about the dose; you're asking about whether the weight of the patient varied in terms of whether there was a hypoxia event?

DR. McCANN: Yes, whether there was an association that the smaller patients were more likely to have respiratory events, and therefore maybe the initial dose of 50 milligrams per kilo globally is just too much for smaller patients.

DR. WILTROUT: Okay. Excellent question. I actually don't have that data, so I don't know the answer to that question.

DR. McCANN: Thank you very much. That was my question.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: Thank you. This is Maryam Jowza from University of North Carolina. This is a

question for Dr. Wiltrout.

Thank you for your presentation. It seems like one of the main points here of concern is the delayed onset of action for tramadol based on the metabolite M1 when it's given in this form. However, in slide 36, when you review the published literature outside of the U.S., you make a point that tramadol is used in an IV PCA format in other countries.

My understanding of IV PCA, as someone who does acute pain service fairly commonly, is the patient has the ability to administer themselves a dose of the medication by pressing a button, and usually for medications that can be fairly quick-acting, you could put it in a PCA format.

So my question is, if you found any data on the dose or the frequency of tramadol to be given in an IV PCA format or the efficacy of it? Because I imagine if they can be used in an IV PCA, that it should have some immediate effect or at least quick onset for analgesia. Thank you.

DR. WILTROUT: Dr. Wiltrout, FDA. I

actually don't have any information to be able to present to you on the dosing that's used in the PCA format when it's used outside of the United States. I can speak to the dosing regimen that's used in European countries, that it's a bit different than the dosing that's planned for the sponsor here, but I can't answer the question in terms of how it's dosed in a PCA, but potentially the sponsor may have information on that.

DR. BATEMAN: Okay. We can ask the sponsor when we go back to them for further clarifying questions.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz from Harvard Chan School of Public Health. I have one question probably for Dr. Greene, and then one for the FDA in general.

For Dr. Greene, regarding the label postoperative, its use, do you have any comment on whether having a Schedule IV available in the hospital may give a sense of safety and actually increase the use of opioids versus other

analgesics?

For FDA overall, a related question; what is the rationale for FDA not to require a non-opioid analgesic reference for the studies? Because it seems to me that we are seeing placebo as a reference for efficacy and then a Schedule II as the reference for abuse. But what I think would inform the current questions on the table is the reference of potential alternative non-opioid analgesics.

What is the rationale for not requiring other analgesics of the reference? Thank you.

DR. GREENE: Yes. This is Dr. Christina Greene. Can you please repeat the first question?

DR. HERNANDEZ-DIAZ: Sure. In the context of the label postoperative opioid analgesics that you were mentioning, if you think that having a Schedule IV available might increase the use of opioids overall in the hospital setting, giving them potentially a sense of safety? Thank you.

DR. GREENE: Yes. Thank you. I am going to defer to my colleague, Dr. Tamra Meyer, to answer

your question.

Tamra?

DR. MEYER: Hi. This is Tamra Meyer, associate director for Nonmedical Drug Use in the Division of Epidemiology. I'll just respond to that by saying that we are not aware of any data that can help support that, and we're also just really looking forward to the committee's discussion on question 3 about the relevance of the opioid analgesic scheduling when administered in an inpatient setting. Thanks.

DR. BATEMAN: Thank you.

And then to the second part of Dr. Hernandez-Diaz's question, Dr. Wiltrout?

DR. WILTROUT: This is Dr. Wiltrout, FDA. Could you have her rephrase the question for me? I don't think I recall it at this point.

DR. HERNANDEZ-DIAZ: Sure. No. Thank you. What is the rationale for not requiring, in the reference group for the randomized trials, the use of active controls, like the non-opioid analgesics?

DR. WILTROUT: So you're asking if we would

run a trial where we compare an opioid to a non-opioid analgesic?

DR. HERNANDEZ-DIAZ: Right. Like in the trials that are presented by the sponsor, we are seeing placebo as the reference for efficacy and the opioid with a Schedule II as the reference for abuse. The question is, how could they compare with other analgesics? I think it would make sense in some settings to have non-opioid analgesics as the reference, but we are not seeing any study that uses that as the reference.

DR. WILTROUT: Okay. The goal in this study from the efficacy perspective is to be compared to placebo, so there's not a requirement to have any comparison to an opioid from the efficacy perspective. We asked for the comparison to an opioid so that we would be able to look at the safety relative to comparator products that are currently being used. So it's just for comparison purposes, no statistical comparison at all.

Then we need to have some sort of a product available to the patients for pain control if the

study drug is not working, so that's the purpose of having the ibuprofen. So we did not ask the sponsor to run a study where there's a comparison to a non-opioid analgesic with tramadol IV.

DR. HERNANDEZ-DIAZ: Thank you.

DR. BATEMAN: Thank you.

Could everyone please lower your hands if your question has already been addressed?

Next, we'll move on to Mr. O'Brien for a short question. We're getting close on time here.

MR. O'BRIEN: Thank you. Yes. Joe O'Brien, patient representative. My question is for Dr. Wiltrout primarily on your benefit-risk profile, slide 39.

Before I ask that question, though, maybe you could answer the question that I think was asked of the applicant but wasn't answered, that I didn't hear. Just what was the placebo that was used in Study 102 and 103?

DR. WILTROUT: Hi. Dr. Wiltrout, FDA. The placebo is saline. It's not any other kind of drug. It's just saline.

MR. O'BRIEN: Straight saline. Okay. Thank you.

My question on your slide 39, it's just the statement that's made, and the second-to-last statement of, "Schedule IV opioid has less abuse liability than a Schedule II or III opioid." I know that's been stated as a matter of fact. I guess my question is, is FDA comfortable, with the level of evidence currently available, that tramadol is appropriately identified as a Schedule IV opioid?

Secondly with that, with the potential theoretical risk of stacking, does that then, therefore, give it to -- actually more than probably -- the risk of a Schedule II opioid?

DR. CHIAPPERINO: Hi. This is Dominic --

DR. WILTROUT: Yes. Sorry. I was going to defer to you, Dr. Chiapperino. Thank you.

DR. CHIAPPERINO: Sorry to cut you off, Dr. Wiltrout. Yes, I thought that was a question for the Controlled Substance Staff.

This is Dominic Chiapperino, FDA's

Controlled Substance Staff, and I understand your question. It's about whether tramadol is appropriately controlled in Schedule IV. We do have a lot of epidemiology data that continues to show a difference [inaudible – audio gap] -- the abuse liability of tramadol that's relative to Schedule [inaudible] -- not to confirm FDA's position on the control status of tramadol, the data continues to appear to support its Schedule IV status.

DR. BATEMAN: Thank you.

Okay. So we're now going to break for lunch. We'll keep track of those of you who have questions for the FDA that have not been addressed, and we'll ask those after the open public hearing.

We'll now break for lunch. We'll reconvene at 2:00 p.m. Eastern time. Panel members, remember that there should be no chatting or discussions of the meeting topics with the other panel members during the lunch break. Additionally, you should plan to rejoin around 1:50 to ensure you are connected before we reconvene at 2 p.m. Thank you.

(Whereupon, at 1:15 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(2:00 p.m.)

Open Public Hearing

DR. BATEMAN: Welcome back. We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is 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 the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in 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 for 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, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is now connected. Will speaker number 1 begin and

introduce yourself? Please state your name and any organization you're representing for the record.

DR. FALTLHAUSER: Good afternoon, Chairman and honorable members of the hearing panel. My name is Dr. Andreas Faltlhauser. I am a practicing anesthesiologist [indiscernible] and intensive care and emergency care physician. I'm currently serving as a director of Eventful Emergency Care Services and the [indiscernible] in Austria.

Up until recently, I also served as the head of [indiscernible], a hospital in [indiscernible], Germany. Both of these institutions -- University [indiscernible] -- are the last teaching hospitals with a strong research acumen. I have no financial relationships with the results in reference to this meeting.

On the topic, I've used intravenous tramadol as a routine medication in various settings for more than 25 years now. Intravenous tramadol is a clinical mainstream medicine in Europe. Physicians use tramadol to treat moderate pain and acute care, as well as [indiscernible] settings and ICU

settings.

I use intravenous tramadol in hundreds of patients every year and truly believe that this is a beneficial drug for my patients. Intravenous tramadol provides very good pain control in the setting of moderate pain, either as a sole medication or in combination as per WHO recommendations. Occasionally, I do also use additional opioids as a breakthrough medication to facilitate the future [indiscernible] of tramadol. Overdosing due to the opioid stacking problem is not a concern in the use of short-acting opioids for this purpose.

Pain management is well established in Europe and is akin to routine and excellent acute care in all settings I have just mentioned. Thus, undertreatment is a very rare instance, however, upgrading pain management from tramadol to another strong-acting opioid as needed is also of no concern or possible additional effect of theoretical risk and overdosing in the overlap and neglectable due to the specific pharmacological

mode of action of tramadol, and therefore can be easily avoided by using protocols, as they are already in place for opioid change from fentanyl to [indiscernible] or something.

Concerns of provinces today are to the facts [indiscernible] there are a lot of issues in Canada's [indiscernible] practice. These attributes are [indiscernible] for different reasons. Firstly, in the clinical trials that enroll patients for, actually, research purposes, they didn't have to meet certain degrees of pain. This is the official construct. It has never been used in a clinical setting.

In clinical practice, pain medications such as IV tramadol are provided through [indiscernible] to avoid development of pain in the first place. That's a [indiscernible] and provides the patient with a long-acting pain killer already intraoperatively in order to avoid postoperative pain, and ideally the occasion for tramadol.

In the acute setting, we would always choose a fast-acting, short half-life medication that can

be easily gauged to the needs of the patient as a first approach. However, immediately following, you would actually give some more long-acting prescription, which again is tramadol in the setting of moderate pain.

In Germany, as well as most middle European countries, many patients get intravenous tramadol in the hospital, and will be then prescribed oral tramadol, so the change is quite easy. A combination of non-opioid medication will provide them a very good pain relief without the opioid-related risk of abuse and dependency.

In my clinical practice, I have not seen an issue with addiction when patients are prescribed intravenous tramadol and switch to oral tramadol. However, there are episodic cases in the literature of long-term abuse for the use of oral tramadol, as with all pain medications, and most of these relate to poor prescribing practices of general medical colleagues.

Intravenous at-risk cases do not [indiscernible], to my knowledge, due to the lack

of [indiscernible] -- the actual use of dependent people resulting from the mode of action of the drug. Importantly, due to restrictive handling and prescribing of opioids in Germany, we do not have the opioid addiction problem as seen in the U.S. The use of tramadol is to avoid opioid overprescribing. From a socioeconomic point of view, I conceive this as a very huge advantage for using the drug.

A further advantage of intravenous tramadol is seen in perioperative pain management and is related to the fact that tramadol does not cause GI paralysis and related problems like other opioids do. It does not worsen postoperative or paralytic ileus.

In the management of patients who suffer from acute, severe pancreatitis, the use of tramadol provides sufficient pain relief without pharmacologic or constriction of the pancreatic sac as other opioids do; mainly the mu agonists are the mainstay. This aids to reduce the amount of acute complications and fosters recovery in the setting

of perioperative and intensive care pain management.

I'm open for your questions. Thank you very much.

DR. BATEMAN: Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. WOLFE: Dr. Sidney Wolfe, Public Citizen Health Research Group. I have slides that are supposed to start going up now, so the first slide, please?

DR. BATEMAN: Okay. We can see your slides.

DR. WOLFE: I don't see the slides here, so hopefully my 10 minutes won't start.

DR. BATEMAN: We can see them.

(Pause.)

DR. WOLFE: Hello?

DR. BATEMAN: Dr. Wolfe, we can see your slides.

DR. WOLFE: I can't see them. I'm on your

website, and it just says "Open Public Speaker Number 1," and I don't see number 2, and I don't see my slides. Someone just hasn't put the slides up.

Oh, here we go. It says "Speaker Number 2" but, again, there are no slides up yet. So whenever they get up, I can start because I don't have my slides.

DR. BATEMAN: There may be some kind of delay on your end because I can see your slides --

DR. WOLFE: Fine. The first slide is --

DR. BATEMAN: -- or you may be on the wrong link, is what I'm being told.

DR. WOLFE: The slide is up. I'm looking at the first slide, so let me just read the first slide.

The reason the background is up is that four years ago, just confirmed Commissioner Califf, who was then the commissioner, asked the National Academies for a study to formally incorporate the broader public health impact of opioid abuse in future FDA-approval decisions regarding opioids;

and a report came out four and a half years ago from the National Academies, and they recommended a number of specific changes as to what the FDA could do within the existing laws to make things better with opioids.

Next slide, please.

(Pause.)

DR. BATEMAN: The slides have advanced on our view. Are you using the YouTube link? There's a 30-second delay with the YouTube link.

DR. WOLFE: I am using the YouTube link.

DR. BATEMAN: If you have a copy of your slides --

(Crosstalk.)

DR. BATEMAN: -- you can read off of those, and I'll tell you when we've advanced.

So we're on slide 2 right now.

DR. WOLFE: So I can put my own slides up, right? I don't have slide 3 here.

DR. BATEMAN: We can see slide 2. So if you have a copy of slide 2, just read off of that.

DR. WOLFE: Well, I'll just put my slides

up, then. We have the phone connection, so I just need to read my slides, which are going to go up in a second here.

Okay. My slide 2 is -- again, I hope I have the full 10 minutes.

The National Academies recommended that the investigational drug evaluation process has limitations, and one of the limitations, which came about a year after their report, was that the FDA approved Dsuvia, a sublingual version of sufentanil, and didn't do any kind of active comparing, just versus the placebo.

Like the situation with tramadol, we're talking about today, the people who got this drug did not get clinically meaningful pain relief for 54 minutes. And because there was no active comparator, it turned out that the pain relief for the placebo was not significantly different than the pain relief for the drug.

Are you on the third slide or fourth slide?

DR. BATEMAN: Yes. We can see table 1.

DR. WOLFE: Okay, fine. We're working fine.

We're catching up with the 30 seconds.

This is information from three states two years after hydrocodone has been down-coded -- down-scheduled -- from Schedule III, where you could get refills, but Schedule II was tighter. And we can see that all three states -- California, Michigan, and New York -- decreased in hydrocodone in terms of prescriptions per 100 people. The decrease in hydrocodone was almost exactly the same as the increase in all those states -- California, Michigan, and New York -- for tramadol.

So tramadol -- because it was, and still is, unfortunately, Schedule IV -- was taking advantage of less hydrocodone and increasing the amount of prescriptions that were going on in those States.

The next slide has to do with the misuse of various opioids, and as you will see in the slide --

DR. BATEMAN: We can see the high rate of tramadol misuse, is the next slide.

DR. WOLFE: You've got table 2 now?

DR. BATEMAN: Yes, we do. Yes.

DR. WOLFE: I've skipped a slide. I'll read the one that's up, then.

For the interval of 2016 to 2018, the proportion of people using tramadol, who misused the drug, exceeded the corresponding proportion of people who misused Demerol and morphine, both Schedule II drugs, and was approximately two-thirds as high as the corresponding proportions of misuse for fentanyl, hydrocodone, and oxycodone.

Now, the next slide is just a graphic portrayal of that. What you can is with tramadol, if you look at the 2018 column, there were -- because it's thousands -- 1,455,000 people who were misusing tramadol, which was 8 percent of all the people using tramadol. These are figures from the National Institute of Drug Abuse, the NSD rate study, which people are familiar with.

What you can see is that morphine, a couple below, is 7.9. So there's actually a larger proportion of misuse of tramadol than with morphine, and it's up there, two-thirds as high as hydrocodone, oxycodone, and even fentanyl.

Let's go to the next slide now. These are studies done and published in 2019. They're mentioned in the briefing package, but I don't think they have these details. The study was people who had discharge prescriptions after their surgery. The question is there were about a half a million people from administrative databases, observational studies, so people either had a short-acting opioid other than tramadol; or tramadol; or tramadol plus a short-acting; or a long-acting opioid. Those are the four groups, and it was all adjusted for everything possible.

If you go over to the right column, you see what happened to these people over time, over the 180 days after they left the hospital, with a prescription for either tramadol, another short-acting, both, or long-acting.

What you can see is that with the reference being the short-acting/other short-acting, tramadol alone had 1.41 times as many episodes. This is the persistent use of opioids. So it was either more than 90 days after discharge and either more than

10 refills -- because, again, with tramadol, well, you can get opioid refills -- or more than a 120-day supply of opioids. So clearly -- and it was almost as high as someone who had been discharged with a long-acting opioid.

The next slide -- just briefly, because I don't want to abuse the time -- this is a study in the UK looking at patients who had osteoarthritis, who were treated either with tramadol initially or with non-opioid analgesics: naproxen, diclofenac, celecoxib, etoricoxib, or codeine. The finding was that after 12 months of follow-up, the mortality rate was higher for tramadol users than for any of the non-steroidal anti-inflammatory drugs.

There's obviously an issue here because this company, Avenue, when they were checking things out did not really try and use as a comparator anything other than an opioid -- morphine -- and it was actually better than morphine. So again, the finding was the ratio of tramadol use for the people who took naproxen, it was 1.7 times a high mortality rate than naproxen; 1.88 times higher

with tramadol than diclofenac; and 1.7 times higher with tramadol than with celecoxib; and 2.04 with etoricoxib.

The point is that tramadol had a much higher mortality rate on these people, all whom had osteoarthritis, than any of these five non-steroidal anti-inflammatory drugs, and an important point has obviously been raised in the briefing documents that these companies should be trying non-opioid alternatives, not just something like morphine.

The next slide, this is, again, mentioned briefly in the briefing documents. Everyone understands that with P450 2D6 -- CYP2D as it is called euphemistically -- it seems like people have the danger of more rapid metabolizing of tramadol to the active moiety, and obviously they have an increased risk of fatal respiratory depression.

Most people have no idea, when they're taking tramadol, whether they do or do not have the genotype, and in fact, many racial subgroups on this slide point out 3 to 4 percent of African

Americans, 1 to 2 percent of East Asians, and greater than 10 percent of other ethnic groups, including people from North Africa, Middle Eastern, Puerto Rico, and Ashkenazi Jews. So it's just another concern for more tramadol, which has happened since hydrocodone went down, and here's a product, another product, the first parenteral product applying for approval for the FDA.

So we're now at the discussion questions and the vote. Discuss the importance of time to onset of action and risks related to delayed onset of action for intravenous tramadol proposed for the management of moderate to severe -- letting you know the questions.

This is, again, from the FDA's briefing package. It says approximately 50 percent of patients administered tramadol IV did not report meaningful pain relief in 6 hours. I agree with FDA's concern that patients will need additional opioids, severely reducing the efficacy of the IV tramadol and increasing risks such as respiratory depression. The danger is that often

with an outpatient operation, they don't get meaningful pain relief for 6 hours, so it doesn't work out at all.

The second question, discuss the benefits and risks of intravenous tramadol for acute pain management in the inpatient setting considering its metabolism [sic] of analgesia, drug pharmacokinetics, and complex metabolism. Again, I have the same answer as the first question; the additional risk is the Thiels study I showed, which is increased risk of opioid dependence with tramadol, and the risks further outweigh the benefits.

These people may have used, let's say, IV tramadol during the procedure, but afterwards, or even during it -- in the real world as opposed to the clinical trial -- someone may say, "Oh, they don't have any pain relief; we're going to give them another opioid."

Let's go to the next one. Any impact on risk of abuse, misuse, or addiction in the outpatient setting, again, the Thiels study -- the

one that I went through a few minutes ago -- of transitioning from acute to prolonged opioid use in opioid-naïve patients treated with tramadol for postoperative pain clearly showed tramadol with higher long-time dependence than other short-acting opioids. And plus --

DR. BATEMAN: Dr. Wolfe, if you can wrap it up.

DR. WOLFE: What?

DR. BATEMAN: If you could wrap it up. Thank you.

DR. WOLFE: I have about 20 seconds, at the most. Any comparative advantage over currently available Schedule II opioids for the management of pain, the company's study failed to show superiority over morphine and failed to use non-opioid alternatives in a randomized study.

Then the last question, does benefit outweigh the risk? Again, FDA has said in the briefing package, they question whether "the minimal benefits of using tramadol IV, given its delayed onset of analgesia, outweigh the risks of

potential sedation and respiratory depression from opioid stacking," end quote.

Based on the evidence from the agency, as well as the Thiels study showing increased risk of long-term dependence in people that have a discharge prescription for tramadol, the risk-benefit balance argues unequivocally for rejecting its approval.

Thank you for bearing with me with our audio/visual difficulties, more difficult on this first one. And I really would like to commend the FDA because in their review of this, the FDA has incorporated a number of the recommendations made -- now four and a half years ago -- by the National Academies, such as using an active control and really looking at the public health implications, which are clear, for the possibility of putting the first intravenous version of tramadol, which is already misused enough. Thank you very much.

DR. BATEMAN: Thank you, Dr. Wolfe.

Speaker number 3, your audio is now

connected. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. POLLAK: My name is Dr. Richard Pollak. I am a practicing podiatric surgeon and a principal investigator in Avenue's pivotal phase 3 bunionectomy study. I am affiliated with Endeavor Clinical Trials. My comments here today reflect my personal opinion. I am not being compensated for my time or for this presentation.

I saw firsthand that patients received good pain relief in the IV tramadol study and believe that it would be a beneficial drug for our patients. Currently, patients are discharged with Schedule II opioids, such as hydrocodone or oxycodone, after receiving Schedule II intravenous opioids in the perioperative process. It would be desirable to use intravenous tramadol, and if patients respond well, discharge them on oral tramadol.

The availability of IV tramadol makes it more likely that patients can go through the entire

post-surgical process with Schedule IV drugs without ever needing a Schedule II opioid. With the current opioid crisis in our country, I see this as a huge benefit. This drug is a significant IV opioid advancement in decades, and this is the reason this drug should be approved.

I have been in private practice for over 40 years and recently retired from private practice in September of 2020. I have also been in clinical research for well over 25 years. I assume that I have performed over 7,000 bunionectomy procedures in my career. In fact, I believe I have also participated in well over 200 clinical trials in which I was a principal investigator, and well over 20 trials involving pain following the bunionectomy model.

I had the opportunity to be the principal investigator, as well as the primary foot surgeon, in the Avenue 901-102 trial. Endeavor Clinical Trials randomized 148 patients, and 140 of those patients completed this study. The study started in 2016 and completed in 2017. I had the privilege

of not just screening these patients, as well as operating on them, rounding on the patients, and finally seeing the follow-up care of these patients until the surgery was completely healed. In summary, I had the opportunity to follow the patients from screening until 6 weeks following their surgery, therefore, I feel uniquely qualified to lend my impressions of these patients.

Another item worth noting is that I also participated in the IV meloxicam trial, as well as the bunionectomy trial with the IV oliceridine. Once again, I was the surgeon, as well as the principal investigator, and participated in the follow-up care of these patients. In my opinion, all three of these drugs have a place in the immediate postoperative management of patients following elective surgeries.

I am extremely impressed that 370 million doses of IV tramadol have been taken in Europe in the past 10 years. I have a difficult time understanding why this drug has yet to be approved in the United States. As you would expect, the

Avenue IV tramadol study was a double-blind study, and consequently I was not aware of what medication that subject was receiving. Nevertheless, overall, the patients seem to tolerate the IV medications well, and the side effects were less than one would see in the traditional bunionectomy trial that included Schedule II opioids.

With that said, I have found that IV tramadol was well tolerated by the patients, and these findings are similar to my experience and clinical practice when I have prescribed oral tramadol as well. I hope that the panel will approve IV tramadol and allow surgeons to have additional effective modalities to treat patients immediately following the surgeries, whether the procedures are performed in an outpatient setting or at a hospital facility. Thank for your consideration.

DR. BATEMAN: Thank you.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any

organizations you are representing for the record.

MR. DEES: I just wanted to start out by saying hello to all the participants of this meeting, and to thank you for giving me the opportunity to share my experience with the use of the pain medication, tramadol.

My name is Charles Aaron Dees, and I am about 63-and-a-half years old and recently retired. For the record, the information I am providing you today is purely voluntary. I am not getting paid or reimbursed in any way for my testimony here.

At the time of the clinical study, I was 58 years old, 6 foot tall, weighed 220 pounds, and was in reasonably good health, other than being a little overweight for my age and height. After a colonoscopy in early July of 2018, the doctors told me that I had an early form of colon cancer. After discussions with the surgeon, my wife, and obtaining a second opinion, I decided to have colon surgery, and that occurred on July 18th of 2018. The surgeon removed an approximate 12-inch section of my colon, which turned out to be stage 1

malignant. I did not require radiation or chemo treatments, and to my knowledge, I am and have been cancer-free since the surgery.

Before the procedure, I was asked if I would be interested in participating in a clinical trial study regarding the use of tramadol as a pain medication. I was told the trial drug was being tested due to being a potential alternative to more highly addictive Schedule II opioid pain medications that were currently being utilized for patients undergoing this surgical procedure.

After discussions with my wife and my family doctor, I agreed to be a participant primarily for the following reason. There's a history of drug addiction in my family. My mother had chronic back pain most of her entire life, and in early 2001 went through surgery, chemo, and radiation therapy for breast cancer. She had been taking medications and consuming alcohol since I was quite young. She died in 2004 from results of a traffic accident, and I was told she was under the influence of both drugs at the time.

I also have a niece who has been an RN in the Houston, Texas area for approximately eight years. Six years ago, she underwent rehab at a facility that specializes in drug addictions in the medical profession and has been clean and sober since then. She is now a charge nurse at a dialysis hospital facility and is doing quite well.

As for myself, I smoked marijuana when I was young. I am still a light cigarette smoker. I do not want to take the chance of another potential chemical addiction in my life. Additionally, my late wife, who never consumed alcohol or smoked, strongly encouraged me to try this route.

I say all this for my reasoning as to why participating in this clinical trial study appealed to me. I was in the hospital for three days. After the surgery, I had no stomach pain for about 36 hours or so, and then just some light discomfort the last day. I suffered no side effects or withdrawal symptoms from my surgery and release from the hospital, and to the best of my knowledge haven't taken any pain medications, including even

aspirin and such since then.

The only exceptions to this would be that I had to inject my stomach area once a day with some sort of antibiotic for several days after the surgery. The other exception was when they knocked me out for a couple of follow-up colonoscopies. God, I hate needles.

I hope this information is useful to you in your trial studies and for patients who may require pain medications for surgical procedures in the future. Thank you again for allowing me the opportunity to share my story.

DR. BATEMAN: Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? Please state your name and any organizations you are representing for the record.

MR. MATTHEWS: My name is Clint Matthews. Good afternoon. I was a patient in one of the trials you're speaking about. I had a colectomy; part of my colon was removed as well. I'm a teacher and a private tutor, and I'm at the school

right now, and I've got a minute to be on the trial -- phone conversation. I don't have any financial ties to the drug companies or tramadol, and I'm not being paid for my testimony.

I wanted to offer my personal experience for this discussion. I was going in for a colectomy, as I said, and I was approached to take the trial. I've had several surgeries in my life before this colectomy. I've had several knee surgeries, shoulder surgery, hand surgery. I've had some other surgeries when I was younger.

So I've had to take a lot of different pain medications over the years, and I've come out of surgery in a lot of pain sometimes. I've been on morphine and various opioids, and other ones coming off of the surgery, so I was kind of interested to try something new.

Obviously, the intravenous, just going in, my IV was also appealing. I didn't want any extra needles or anything else. I went ahead and took part in the trial, and I was very impressed overall with tramadol IV. My experience was very good. It

gave me a steady pain relief. I remember awake, and when I got up, I wasn't in much pain. I had a steady even keel where I didn't experience ups and downs. I didn't have any bad side effects like I had sometimes. Even with morphine before, I had a highly anxious feeling, and I didn't experience anything like that with tramadol in the IV.

Also before, with my other medications, I would have withdrawals or I'd feel really bad afterwards. I didn't have that experience with tramadol in this case. I was very happy because I didn't get the same kind of ups and downs, and I didn't get the same kind of withdrawal feelings that I had with the other medications I've taken in the past.

After the colectomy, I was worried that it would be very painful, but it wasn't my experience. I don't remember being in serious pain for a long time at all. The tramadol made it a much more pleasant experience. Part of that experience was that I could move around a lot more when I was in the hospital. They wanted me to move around and

start walking a little bit, and I didn't have any sharp pains that kept me from doing that.

I was able to comply with everything the doctor wanted me to do because I wasn't in pain. I was able to do the activities, and I didn't have a lot of soreness later. I kept waiting for things to feel like they wore off, and then I'd be in serious pain, but that didn't happen because I had just a steady feeling of comfort with a slight discomfort and soreness.

The bottom line is that I've had many surgeries, and because of my experience with tramadol IV, if I had another surgery and they gave me a choice, I would choose this IV tramadol over anything else I've taken before, if my doctor said it was appropriate. Thank you for allowing me to speak.

DR. BATEMAN: Thank you.

Speaker number 6, your audio is connected now. Will speaker number 6 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ZUCKERMAN: Thank you. Can you hear me?

DR. BATEMAN: We can.

DR. ZUCKERMAN: Yes. Thank you.

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our center is a non-profit think tank that scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products.

My expertise is based on postdoctoral training in epidemiology and public health, and as a faculty member, a former faculty member, and researcher at Yale and Harvard. I've also worked at HHS, and the White House, and I'm on the board of the non-profit, Alliance for a Stronger FDA, which educates Congress about the need to support the work of the FDA.

As we all know, the FDA and physicians are under pressure to find ways to reduce the opioid epidemic, and that makes today's meeting especially important. The big question is whether IV tramadol will have benefits that outweigh the risks, not

just for individuals but also for public health, so I'll focus my remarks on the scientific evidence.

Recent studies have shown that for patients who were not already using opioids, over-the-counter pain relievers can be as effective as an opioid. So why was IV tramadol compared to placebo and compared to morphine, but not compared to effective over-the-counter pain medication?

If the risk of addiction can be avoided by giving non-addictive medications, that should always be studied instead of, or in addition to, a comparison with a placebo. That wasn't required by FDA, we've heard, but it should have been, and that's a fatal flaw in the data provided.

The research indicates that IV tramadol has a delayed onset, as you know. Patients given tramadol took a median of 64 more minutes to experience pain relief, and they were more likely than those given morphine to use a rescue medication within 2 hours of being given the initial drug.

The sponsor has suggested that in clinical

practice, there is no major delay in pain relief, but that could be due to a placebo effect. That's why FDA depends on clinical trials for unbiased results when those data are available. The data in this case clearly indicated small differences between placebo and IV tramadol in the first hour after administration, and only moderate differences even after 2 hours.

We agree with FDA scientists that the slow action of the drug may lead to a faster-acting opioid being given to patients in addition to the IV tramadol. Data from Europe has shown that IV tramadol is twice as likely to have a co-use with other opioids compared to the oral version of the drug.

The sponsor argues that opioid stacking can be avoided by supplementing with a non-opioid medication such as ibuprofen. However, as one of the advisory committee members pointed out, if patients' pain can be adequately managed with a non-opioid OTC medication, then why is an opioid needed? This is a clear acknowledgment of the

issue I've been raising. If an over-the-counter medication can be as effective as an opioid, there is no documented need to be given IV tramadol.

The sponsor asserted that opioid stacking is standard practice in the hospital setting, and I hope you'll all agree that that's not a reasonable justification for approving an opioid that could increase the risk of opioid stacking. The World Health Organization has noted that the oral version of tramadol has the potential for abuse and/or dependence. Research is needed to determine under what conditions IV tramadol carries those risks, however, the sponsor did not develop any formal evaluation regarding the drug's abuse potential.

Concerns about postoperative use after leaving the hospital are a legitimate concern despite the unknowns that have been described. Although lower than some opioids, what is the safety and efficacy of this drug compared to over-the-counter medications? And that's a big issue.

Lastly, the proposed indication is broader

than what is typical for other immediate-release opioids. According to the FDA, the typical indication for an immediate-release opioid analgesic is, quote, "management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate," unquote.

The applicant's proposal to use tramadol IV for moderate to moderately severe pain suggests a broader use than the typical immediate-release opioid indication, and this would be a very dangerous problem --

DR. BATEMAN: If I could ask you to finish up, please.

DR. ZUCKERMAN: -- yes -- of opioid use that absolutely should be avoided. Thank you for the opportunity to speak today, and please consider these issues when you vote. Thank you.

DR. BATEMAN: Thank you.

Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? Please state your name and any organizations you are representing for the record.

DR. LEIMAN: Hi. This is Dr. David Leiman. I am a board certified practicing anesthesiologist, and I'm an assistant clinical professor at University of Texas, Houston. In my 11 years of practice, I've consulted for and served as an investigator for a number of different pharmaceutical companies. I'm here to share my experience as an investigator in the IV tramadol phase 3 study being considered today. Please know that I've not been compensated for this testimony, and I have no financial stake in the outcome of this meeting.

First, as an investigator, I was impressed that no patients withdrew from the open-label safety study after painful procedures that are usually treated with Schedule II opioids. Patients were satisfied with the treatment and provided very high ratings. After seeing the patients' response firsthand, I truly believe that IV tramadol is a beneficial drug for my patients.

Based on the clinical trial experience, instead of Schedule II opioids, I could use a less

abusable opioid, and patients would still be satisfied with the post-surgical pain management. Given the fact that there's no way for me to predict which of my patients will develop an addiction or dependence problems down the road, I try to manage their pain with drugs with lower abuse potential before having to use a higher abuse-potential drug. IV tramadol also makes it easier for physicians and surgeons to transition and send a patient home with oral tramadol, which also has a lower abuse potential.

Second, I'd like to point out that FDA's safety concern is a theoretical one, which is not supported by real-world evidence from decades of data and experience with use in Europe. As the clinicians on the panel know, the use of multiple opioids is routine in the inpatient setting.

Patients have different responses to analgesics. If a patient does not have the optimal response to a given opioid, we may have to rescue them with another opioid. When patients are on IV opioids, we always continuously assess patients

with regular monitoring of their pain levels, respiratory rate, oxygen saturation, and cognition. Healthcare professionals are trained to monitor for the clinical signs and symptoms of opioid-related side effects. Proper monitoring for IV opioid therapy is mandatory in every hospital and ambulatory surgical center.

There are also protocols in place with dosing instructions to optimize safe administration of opioids based on real-time evaluation of an individual patient. Importantly, healthcare professionals, not patients, administer opioids in this setting, and the healthcare professionals are trained to hold doses and notify physicians if patients are showing any signs or symptoms of an adverse reaction.

Lastly, the onset of action is measured by the stopwatch as an artificial construct of a clinical trial, which requires patients to have moderate-to-severe pain before they can get randomized into the trial. In clinical practice, we attempt to control patients' pain prior to them

needing more analgesics, and we start the patients' post-surgical pain meds immediately after surgery or during surgery.

This is different in the clinical trial setting where patients must reach a certain panel before dosing, therefore, the onset of an analgesic in the post-surgical setting is not as relevant because we will treat those patients with medications that will bridge to effect.

We already have opioids that can titrate to effect such as IV fentanyl. We don't necessarily need more of those. On the other hand, IV tramadol with its fixed regimen can provide sustained pain relief without analgesic gaps or breakthrough pain, with a lower abuse potential than what's available today. It would be a beneficial drug to have as an option for my patients, and I hope it will be approved today. Thank you very much for your time.

DR. BATEMAN: Thank you.

Speaker number 8, your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any

organizations you're representing for the record.

MR. BACCUS: Greetings, committee members, ladies and gentlemen, and I want to thank the FDA for giving me time to speak to all of you today. My name is Jim Baccus. I live in Houston with my trophy wife of 48 years, Linda, and my children and grandchildren. I was a full right knee replacement patient treated with IV tramadol for a clinical trial here in the U.S. in August of 2018. I'm happy to speak to you about my experience. I am not receiving any financial compensation for my testimony today. I'm here only as a volunteer.

I was invited to the trial prior to surgery. I was aware of tramadol as a pill, but not aware that it was also available intravenously. Since pain is pain, and pain management is very important, I didn't mind having it administered for this surgery. IV tramadol provided excellent pain management during the recovery phase, and although it did not completely eliminate the pain, it did provide comfort. I had no nausea or other noticeable side effects.

What makes my story a little unique is that following February of 2020, I had surgery on my left knee, my other knee. This time the pain drug administered in recovery was Demerol. My left knee was a mess. I had injured it in high school sports, had surgery, and injured it again when I was in the Marine Corps and had surgery courtesy of the Navy at Balboa Hospital in San Diego, and another surgery. I re-injured it several more times through skiing, hiking, or other sports over the years.

When I compare both surgical experiences in my head, I will say the recovery experiences were different. Considering my left knee surgery, the one with the traditional pain management, it was much more difficult. As a full disclosure, as I mentioned before, my left knee had been abused and injured so many times over the years, where on the other hand, I had no issues with the right knee until bone met bone. So the comparison is not perfect, but when I focus on my experiences with pain, I will say that I needed more pain

medications after the left knee surgery.

Those pain medications were the more traditional opioids. As a result, I had side effects from the doses of Demerol and hydrocodone, mainly constipation and a sluggish hangover feeling. However, I had no noticeable side effects after the surgery with the tramadol.

As soon as possible, after knee surgery, medical staff wants a patient to ambulate. It is a painful but a necessary exercise toward full recovery. In comparing the tramadol and the Demerol, my assessment is that both drugs did their job, but the tramadol gave me a few less issues.

I have no more knees to repair, but if I had to have another surgery requiring a general anesthetic and IV tramadol were offered to me, I would certainly take it. It made be comfortable in terms of pain relief without side effects, and that's what was important to me. Thank you for your time.

DR. BATEMAN: Thank you.

Speaker number 9, your audio is connected

now. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. FUGH-BERMAN: Good afternoon. I'm Adriane Fugh-Berman. I'm director of PharmedOut, a Georgetown University Medical Center project that fosters rational prescribing. My conflict of interest statement is that I'm a paid expert witness on behalf of plaintiffs in litigation regarding pharmaceutical marketing practices, including the marketing of opioids.

Tramadol is an inferior, unpredictable opioid. Because tramadol is far more potent orally than parenterally, intravenous tramadol is an inferior, unpredictable opioid administered via a route that makes it worse.

Tramadol will have almost no analgesic effect in people with a deficiency of CYP2D6 and, conversely, a super potent effect on people who are rapid metabolizers. Poor metabolizers will have little analgesic effect. Rapid metabolizers will gain the fastest effects that are also most likely

to be the population most at risk of addiction.

According to the WHO, the prevalence of ultra-rapid metabolizers varies widely, and this is not just a problem in Africa and Southeast Asia. In southern Europe, 7 to 10 percent of the Spanish population and 10 percent of Sicilians are ultra metabolizers. One in 15 African Americans are ultra metabolizers. Sure, that's lower than in Africa or Southeast Asia, but that's hardly insignificant.

Avenue Therapeutics appears to be arguing that because tramadol is a Schedule II drug, it is less harmful than other opioids, but that's not true. In fact, tramadol may be associated with long-term use more often than other short-acting opioids, and tramadol addiction is a major problem in many countries.

Tramadol manufacturers have downplayed tramadol's addictiveness for decades. When tramadol was first approved, it was unscheduled. One reason that the FDA was persuaded into approving an opioid as an unscheduled drug is that

data submitted by the manufacturer was on intravenous administration, which gives a far weaker effect. Intravenous administration of tramadol is only about half as potent as oral administration. Avenue Therapeutics presents this weaker effect as an advantage, but in the setting of pain, weak analgesia is not an advantage; and in any case, individual results vary too widely for this to be a useful drug clinically.

Tramadol has zero advantages over morphine, which is more effective and faster, whether it's administered via oral, sublingual, intramuscular, or intravenous routes. But never mind morphine; tramadol's no better than over-the-counter NSAIDs, against which it has failed to show superiority in numerous clinical trials.

Several committee members asked about this. There are many studies of the efficacy of oral and parenteral NSAIDs for post-surgical pain, including bunionectomies. A systematic review and meta-analysis found tramadol less effective for analgesia after third-molar surgery than NSAIDs.

Tramadol, the more effective oral form, was barely better than placebo for osteoarthritis, according to a Cochrane systematic review of 22 placebo-controlled RCTs.

The concept of using an NSAID as a rescue medication for an opioid post-surgically is backwards. NSAIDs should be used first, and opioids as rescue medication, not the other way around. And when opioids are used, they should be predictable and effective opioids. That leaves tramadol out.

Tramadol should be a Schedule II opioid, and it should be used only rarely orally -- and when it is used, it should be used orally. Besides having all the adverse effects of opioids, including addiction, respiratory depression, and death, tramadol adds unique side effects, including serotonin syndrome. Well, that one's not unique, but it also will cause serious seizures.

One study found that 1 in 13 of all drug-related seizures were related to tramadol.

DR. BATEMAN: If I could ask you to finish

up, please.

DR. FUGH-BERMAN: Yes.

Tramadol's no more effective than NSAIDs and no safer than other opioids. It's unpredictable, addictive, and it's already overprescribed by clinicians who believe it to be a week opioid. Please don't support approval of IV tramadol. Thank you.

Clarifying Questions to Applicant (continued)

DR. BATEMAN: Okay. Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. Before we start our discussion, though, we will continue with clarifying questions, initially for the sponsor, and then FDA.

For questions for the sponsor, we'll go to Dr. Hernandez-Diaz.

(No response.)

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: I think I was double-muted, but my question was answered.

Thank you, Dr. Bateman.

DR. BATEMAN: Okay. Thank you.

We'll now go to Dr. Huybrechts for a clarifying question for the sponsor.

(No response.)

DR. BATEMAN: You're on mute.

DR. HUYBRECHTS: Thank you.

Am I on mute now?

DR. BATEMAN: We can hear you now.

DR. HERNANDEZ-DIAZ: Okay. Thanks.

This is Krista Huybrechts, Harvard Medical School. A lot of this hinges on time to onset of action, so I just had a clarifying question with respect to the time to use of rescue medication, and specifically how to reconcile data presented in slide 34 and slide 41. But I can summarize these; we don't have the slides up anymore.

This relates to Study 103, and for the median time to rescue medication, it was listed as

22.9 hours. Thank you. Then on slide 41, it was indicated that 42.6 percent of patients actually required rescue within 2 hours. I just wanted to understand how the two can be reconciled.

My interpretation is that for the 22.9 hours, that is on the patients overall and not on the patients requiring rescue medication. But I just wanted to clarify that, given that 42.6 percent will have less than 2 hours as time to need for rescue.

DR. LU: If I cannot answer that question adequately, I will ask Dr. Neil Singla to jump in. But both tramadol, and placebo, and morphine patients, most of the rescue happened early. So overall, approximately 52.5 percent of IV tramadol patients needed rescue in this entire study. And as you saw on this slide, 42.6 percent actually needed it within the first 2 hours.

The same pattern, actually, was observed for the morphine IV 4-milligram dose as well, in the sense that approximately close to 40 percent of morphine patients needed rescue over the entire

treatment period, and obviously 28 percent of that actually happened within the first 2 hours. So if patients needed rescue, they needed it early; but the average dose was low in both active arms.

DR. HUYBRECHTS: Right. But that's exactly my question, that the median time to rescue is still listed as 22.9 hours, so that is just because those additional 7 to 8 percent of patients that didn't need it in the first 2 hours then really only requested it much later, correct?

DR. LU: That's correct.

DR. HUYBRECHTS: Okay. Thank you.

DR. BATEMAN: Okay. Thank you.

DR. HUYBRECHTS: And one follow-up question or additional question.

DR. BATEMAN: Sure.

DR. HUYBRECHTS: Okay.

My other question was for Dr. Iwanicki, which she presented basically the epidemiological data on non-medical use from various countries. It's clearly illustrated that the data differ a lot by country, so there's a lot of variability. And

actually, tramadol did not always have the lowest, at least, point estimate across the different opioids considered in the various countries.

I was just interested in your thoughts about applicability of the data from those various countries that show a lot of variability to the U.S., where we know there's a very different approach to treatment with opioids.

DR. LU: Dr. Iwanicki?

DR. IWANICKI: Yes. This is Dr. Iwanicki. You know, it's very interesting looking at the data from Europe because while I do think we see some variability from country to country, and when we compare back to the U.S. as well, I think the thing that really remains striking is how similar the trends are, actually.

Even though each of these countries had some differences in, in particular, drug availability, as well as their practices as far as prescribing goes, we still see pretty remarkable similarities across each of these countries. And in every country, we see that tramadol non-medical use is

amongst the lowest and that intravenous use is also very low.

So I think that's really the take-home point here, is that looking at multiple data sources from multiple countries, we see those similarities across the board, and that's probably the thing that's most relevant for us to keep in mind.

DR. HUYBRECHTS: Thank you.

Clarifying Questions to FDA (continued)

DR. BATEMAN: Okay. We'll now finish up clarifying questions to the FDA.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thanks. Sherif Zaafran.

I wanted to ask and get a little bit of clarification around this whole concept of opioid stacking. I'm wondering if there's a different definition that the FDA has between opioid stacking versus appropriate opioid escalation of medications for pain relief. There was a remark made about tramadol being used as a monotherapy, but obviously with any narcotic, whether it's fentanyl or morphine, if it's not working, we obviously

escalate to something more than that, at least at the practice of most of us anesthesiologists.

Was there a comparison made between escalation of tramadol to another narcotic, and that narcotic use being lower than what it would have been had tramadol not been used? Again, I'm trying to understand the definition of opioid stacking versus appropriate opioid escalation.

DR. WILTROUT: This is Dr. Wiltrout, FDA. The definition of opioid stacking is one that we use in terms of not to try to talk about dose escalation per se. It was to talk about delayed onset of effect, and then a need for additional medication to address the pain. I don't know if that clarifies your question in terms of asking about opioid stacking.

The second question asked about whether we saw a difference in the need to escalate to other narcotics in the studies, and we really weren't able to evaluate that because there was no use of opioids as rescue. Only very minimally were patients discontinued from the study due to that

lack of efficacy, and then were given another opioid at that time.

DR. ZAAFRAN: Thanks for that, but what I was really asking, from the standpoint of opioid stacking versus opioid escalation, is that we routinely use stronger narcotics when the initial narcotic given has not worked, and we typically call that escalation of the use of the medication in trying to control pain.

Are you defining that the same way as stacking? Because that's a very common practice out there and fairly routine. So I'm just wondering if we're kind of confusing the two.

DR. WILTROUT: I'm not intending to confuse the two. I agree that in medical practice there's going to be use of dose escalation. We're just looking at what was available in the trials and trying to see whether there was use of opioid as rescue. But no, we're not considering opioid stacking and your description of opioid dose escalation to be the same.

I'll defer to my colleagues if anyone else

has something to add on that. Thank you.

DR. BATEMAN: Thank you.

Dr. Horrow, a clarifying question for the FDA?

DR. HORROW: Yes. Thank you, Dr. Bateman. This is Jay Horrow. I'm an anesthesiologist and the non-voting industry representative from Bristol-Myers Squibb.

Dr. Zaafran addressed the ambiguity in the definition of opioid stacking. I'd like to address something related to the stopwatch metric and its use and conclusions about onset time. There appears to be clear ambiguity in how to treat the second stop in the stopwatch with respect to rescue medications. The applicant apparently chose a reasonable but, much to their disadvantage, conservative way of defining or treating this particular metric.

The FDA does review clinical study protocols prior to the enrollment of the first patient, so the question to the agency is, did the agency notice, comment, or otherwise communicate with the

applicant regarding their particular analysis choice or their treatment of stopwatch data when the applicant submitted their protocol?

DR. WILTROUT: This is Dr. Wiltrout. I'll have Dr. Rigo Roca answer that question, please.

(No response.)

DR. BATEMAN: Dr. Roca, I'm not sure if you're on mute. We can't hear you.

DR. ROCA: Okay. Are you able to hear me now?

DR. BATEMAN: I can. Yes. Thanks.

DR. ROCA: Great.

Yes, we certainly do look at the phase 3 protocols and the way the applicant wishes to analyze their data. Therefore, in answer to your question, yes, we did look at what the different applicants proposed.

As was previously mentioned, there are different ways that an applicant can choose to analyze their data, and if an applicant wishes to analyze their results in a certain manner, unless there's some particular objection that we can see

with respect to perhaps the way that they're analyzing may be inappropriate from a statistical methodology standpoint or some other issues, we usually do not require for them to do it in one way or another.

So beyond that, I don't think I can, unfortunately, get into a lot of details with respect to the way other companies may have been analyzing their data because the specifics to the program may be particular to their program, and I don't think I'll be able to address that to any great detail in this forum.

DR. HORROW: Thank you.

In follow-up, might the agency have an opinion, then, about the alternative analysis of the stopwatch data in Studies 102 and 103 that the applicant presented in there slide 31?

DR. ROCA: As you may have noticed, I believe that was the one that they mentioned that they have not submitted to us for an analysis. Actually, I think they mentioned that they did not submit that, so I really cannot offer an opinion at

this point.

DR. HORROW: Okay. Thank you.

In follow-up, does that indicate an invitation to the applicant to submit such data to the NDA?

DR. ROCA: I think applicants are always entitled to submit any additional data to the NDA that they wish. That's our usual position. We do not prevent them from submitting any additional data. So it's not necessarily an invitation, but it's not necessarily something that we would say, no, you cannot.

You may want to go back and look at the numbers that they achieved with their analysis, and I must say, as I mentioned, we did not review it. We cannot make any comment as to its adequacy. But see what the analyses provide as far as whether it improved it significantly enough to make a difference. But again, I cannot comment on anything with respect to whether we concur or not because we did not review it.

DR. HORROW: Thank you very much, and that's

all for my questions.

DR. BATEMAN: Alright. Thank you.

So a final clarifying question from Dr. Huybrechts for FDA.

DR. HUYBRECHTS: This is Krista Huybrechts. My question is very closely related to the previous one, and it relates to the strength of the evidence regarding the delayed onset of action. There's been a lot of discussion about the results of the stopwatch metric, where I think the consensus is that there's no clear uniform standard. But there are other ways in which delayed onset of action is evaluated, being the pain intensity difference, time to rescue medication, and patient perception.

I believe the applicant's view is that, in essence, these other three measures do not really support the delayed onset of action, and it's really more based on the stopwatch metric. And I was just interested in FDA's view as to how much weight they put into results of the stopwatch metric analysis versus these other three ways of evaluating delayed onset of action.

DR. ROCA: This is Dr. Roca again. That is a very good question, because I think one of the things that was presented in the context is that you can look at the, quote, "totality of the data." You can look at the stopwatch method. I think it was verbalized as being somewhat of an outlier with respect to the other results.

So you do integrate it all when you do make an assessment. And in reality, not to sound a little bit cheeky about this, but in a way, that's sort of why we would be very much interested in hearing what the committee members think about the importance of one particular parameter that seems to not behave the way you would have expected it to.

In a sense, I guess my response to you is I will be very much interested in hearing the panel's opinion regarding that particular point that you are raising.

DR. HUYBRECHTS: Thank you.

DR. BATEMAN: Okay. Thank you.

We'll now move ahead and proceed with the

charge to the committee from Dr. Roca.

Dr. Roca?

DR. ROCA: Okay.

DR. LU: Dr. Bateman? Hi.

Dr. Bateman, I'm sorry to apologize, to interrupt, but we have a couple of questions, that during the lunch we gathered additional data that we wanted to share with the committee in response to some earlier questions.

Is that okay?

DR. BATEMAN: If you can do it in just a couple of minutes because we're a bit behind schedule.

DR. LU: Absolutely.

I'd like to go back to the hypoxia question, as well as the discharge medication, as we gathered additional data.

Go ahead, Dr. Langford.

DR. LANGFORD: Yes, Dr. Langford speaking. I'll be extremely brief. There was a question about any relationship between the hypoxemias and body weight. Essentially, there was no clear

correlation, and the range of weights was in the range of 55 to 89 kilograms, so none of the patients were particularly on the small side.

However, extremely briefly, I think it's terribly important to understand the perspective of the hypoxemia data. It sounds alarming, but in fact we're talking about patients who deliberately -- because of the protocol design in order to show any difference between the two groups, the patients were breathing room air from the time of their surgery.

This is unusual. We usually give oxygen after surgery or very frequently, so that was desensitized. These were all investigator-reported adverse events labeled as hypoxemia, but in fact the levels of hypoxemia were not very great. No patients had a respiratory rate less than 10, none were heavily sedated, and most importantly -- and I'm sure will resonate with those of us that work in this area -- no patient required naloxone rescue.

So per protocol, the other very vital

feature is that the discontinuations were not because of alarming levels of hypoxemia. They were patients who were unable to maintain saturations above 92 percent without oxygen. So all of the patients we're talking about were corrected with simple oxygen therapy, which in normal clinical practice would be what we do.

Finally, none of these recorded hypoxemic events were anything beyond mild and would not have been remotely predictive or a cause of any serious outcome.

DR. LU: Thank you, Dr. Langford.

Just a very quick comment, we found some interesting information to share with the committee that we believe would be helpful. One of the things is, in Study 102-103, the efficacy studies, obviously surgeons prescribed whatever they felt comfortable with sending patients home. In Study 104, patients were also discharged on their current protocol, and as you saw all of that, approximately 11 percent we were sending home with oral tramadol

Just during the break, we actually found some interesting data. A group of researchers surveyed patients aged between 16 and 64, with four medium-risk procedures, and they looked at what patients went home with in the U.S. and in Sweden. The reason they picked Sweden is because they had a great national database that really had a lot of detail.

What they found was, in the U.S. -- whether one day we'll have these patients -- is 3.5 percent of patients were going home with oral tramadol Schedule IV; the rest were hydrocodone and oxycodone Schedule II. In Sweden, of patients that had the same age, same procedures, 29 percent actually went home with oral tramadol.

So that is interesting information, and I do want to just ask Dr. Minkowitz to quickly put this in clinical perspective.

DR. MINKOWITZ: Thank you very much, Dr. Lu.

Dr. Minkowitz. As I said, in the clinical trials, it was very protocolized, and the surgeons would send the patients home as per the standard of

care. But having tramadol available would allow U.S. physicians to move from their current regimens that only include C2 opioids to one where our patients would never be exposed to a C2 opioid.

So I think physicians need to see that acute postoperative pain can be managed with a C4 opioid. Once they see that their patients can be controlled on IV tramadol, then they will be confident and transition their patients to oral agents with a similar or lower abuse potential.

DR. BATEMAN: Okay. Thank you.

We need to move on. We're now going to proceed with the charge to the committee from Dr. Roca.

Dr. Roca, please.

Charge to the Committee – Rigoberto Roca

DR. ROCA: Hi. This is Dr. Roca again. If you can put up the questions and the points for discussion? And when they pull them up, you will see that, basically, it is sort of a bookend to the comments I made at the very beginning of the meeting this morning.

There are three discussion questions that I would like you to consider. The first one, as you know, is related to what we were just discussing a few minutes ago regarding the importance of the time to onset of action and the risks of the delayed onset of action, and obviously, you have started some of that discussion as well already.

The second one has to do with the benefits and the risks of intravenous tramadol when you take into consideration the mechanism of the analgesia, and you have started discussion about that as well, including the drug pharmacokinetics and the complex metabolism and how they contribute to the benefits and risks of IV tramadol.

The third one, also the third discussion point, was also touched upon in some of the clarification questions. It has to do with the abuse potential as a Schedule IV and what impact does that have regarding the subsequent risk of abuse, misuse, or the development of opioid-use disorder. And again, you have started discussing some of that, and the corollary to that is any

comparative advantage over currently available Schedule II intravenous opioids.

There's only one voting question, and that would be the fourth item. As you know, when an application comes in, questions come up, and additional information and additional data may be submitted to the application.

What I would like you to consider is whether the information that has been submitted to the application -- some of which has been summarized and the salient points discussed by both presentations today -- is whether there's enough information, adequate information at this point, to support a favorable risk-benefit ratio.

Do the benefits of IV tramadol outweigh the risks for the management of the acute pain severe enough to require an opioid analgesic in an inpatient setting? And it would be specific to acute pain severe enough to require an opioid.

As before, if you vote yes, it will be very helpful for us to hear your discussion as to the rationale of why you voted in that way and also

whether there's any need, if the product ends up being approved, as to whether any post-approval studies should be required.

Similarly, on the flip side, if you decide to vote no that the benefit-risk ratio is not favorable, again, the rationale for your vote will be very helpful for us as we take your advice and discuss it internally, and also whether you feel that any additional data are needed for approval and what that data would be.

So I will stop there and see if you have any questions; otherwise, I'll turn it back to you, Dr. Bateman.

Questions to the Committee and Discussion

DR. BATEMAN: Thank you, Dr. Roca.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and the panel discussions. I would like to remind public observers that while this

meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording, then we'll open the question to discussion.

We'll start with discussion question number 1, if we could pull that up.

Discuss the importance of time to onset of action and risks related to the delayed onset of action for intravenous tramadol proposed for the management of moderate-to-severe acute pain in the inpatient setting, such as postoperative or acute severe injury setting.

Are there any questions regarding the wording of the question, anything that needs clarification before we start our discussion?

Dr. Sprintz, clarification?

DR. SPRINTZ: Yes. Hi. Actually, this is a question that I want to be clear, really, for all four.

Each one of these are describing everything

that is narrowed down to the inpatient setting, but I was under the impression that the labeling request is for in a medically supervised setting, a medically supervised healthcare setting, which can be an ASC or an ER, and those are not inpatient settings.

So I have a concern about the way I'm going to be answering these questions. It's not congruent with what actually the labeling request is, and I think that's important to clarify that.

DR. BATEMAN: Okay. Thanks for that question.

Dr. Roca, can you comment on that?

DR. ROCA: Sure. This is Dr. Roca.

That is true, and sometimes what happens is when an indication is proposed by an applicant, as the information is reviewed, and the application and the data are reviewed and presented, et cetera, different questions come up exactly like what was just voiced.

To that end, one of the things that would be helpful is to see if you have any comments

regarding your interpretation; for example, if you were to have a certain thought of concern about inpatient -- and what would that mean -- versus what you may feel is a different setting where somebody could end up using the product but it's not necessarily inpatient, and what implications that might mean.

Definitely, I think you hit it on the nose in the context of trying to define the setting. And if the indication, which obviously has not been finalized yet, has a possibility to be impacted by the definition of those settings, I would love to hear your thoughts on that and the difference between the settings, because that can certainly impact what final indication, if any, gets approved.

I don't think that answered the question, but basically saying, yes, let us know what you think about the two different settings and any thoughts you may have.

DR. SPRINTZ: Thank you. I definitely will.

DR. ROCA: Thank you. Okay.

DR. BATEMAN: Any other clarifying questions regarding the question?

Dr. Zacharoff, you had a clarifying question?

DR. ZACHAROFF: Yes, I do. Thank you.

Kevin Zacharoff. I guess, Dr. Roca, this would be along the same lines as Dr. Sprintz's question with respect to acute severe injury setting. Am I to interpret that that means an emergency department?

DR. BATEMAN: Dr. Roca?

DR. ROCA: Not necessarily. And actually, Dr. Zacharoff, you sort of motioned to acute severe injury setting, and that's what's on the screen, is acute pain, acute severe pain. It's sort of like a gemish of severe pain that's acute as opposed to chronic, and it's usually due to -- an example would be like an acute severe injury.

It could be an emergency room, but not necessarily. And again, that's per the previous question, if you have any thoughts regarding the importance of making a distinction between those

two settings, that would be important for us to hear.

DR. ZACHAROFF: So I guess, based on what you're saying, instead of acute severe injury setting, it would be acute pain treatment setting.

Is that correct?

DR. ROCA: Yes, I think that that's probably a little bit better. I think what we're trying to do is differentiate between surgical and perhaps other types of acute severe pain, and that's why we put it as "such as" postoperative -- that would be surgical -- or acute severe injury, which would be, for example, trauma, emergency room, et cetera. But again, any thoughts you have regarding the importance of making a distinction between the settings, we would like to hear, too.

DR. ZACHAROFF: Thank you.

DR. BATEMAN: Okay. Any further clarifying questions?

Dr. Ruha?

DR. RUHA: Yes. I was just going to add on to that. I do think that if this had an indication

of acute pain in a medically supervised setting, it could easily be used in emergency departments, in trauma bay.

During our discussions, we've talked about how well the delayed onset of action may not be that important in the perioperative setting because they're getting meds in the OR, or the surgeon could be instructed to administer it prior to the end of surgery. But that has very different implications for patients receiving it on arrival to a trauma bay or in the emergency department for acute pain. They're not going to be able to get it before the onset of pain. So I do think there's a distinction.

DR. BATEMAN: Thank you.

Okay. Any other clarifying questions? And if not, we can begin our discussion.

Again, we want to focus here on the importance of time to onset and specifically risks related to delayed onset of action for IV tramadol.

(No response.)

DR. BATEMAN: Okay. We'll start with

Dr. Robotti, please.

(No response.)

DR. BATEMAN: I think you're on mute.

MS. ROBOTTI: Okay, many mutes to turn off.

Well, in reading through the package, it was clear that from the very first teleconference that the FDA had with the applicant, the FDA was clear that an IV analgesic drug product should have a quick effective pain relief. The applicant never fully responded to that or never gave a solution to that, that it involved their own drug. It involved layering other drugs on top of it.

Using a drug that take 2 hours to become effective means that doctors have to anticipate what the pain level of their patients will be 2 hours into the future. The patient has no ability to know what their actual pain rate is and if it actually does need to be managed, or managed so heavily.

All drugs should be given at the lowest effective dosage for the shortest period of time possible. The process that is in place for this

drug, or is proposed in place for this drug, and perhaps through the industry -- I don't know; I'm not actually a doctor, despite the honorary title I just got a moment ago -- is this process takes the patient's involvement in their own pain management away. It doesn't take into account their own values or their own choices that they may want to make.

Tramadol has also a unique pathway affecting two complementary and synergistic mechanisms, the opioid receptors and the reuptake inhibitors for the norepinephrine and serotonin systems. This puts patients at risk for all the usual side effects of opioids, and on top of that, the side effects for SSRIs and SSNIs. And that's all I have to say on this question.

DR. BATEMAN: Okay. Thank you.

Other comments, please?

Dr. Zacharoff?

DR. ZACHAROFF: Thank you. Kevin Zacharoff, Stony Brook Medicine. I guess in the spirit of hearing Dr. Roca's desire to have us address this,

I think that pertaining to this discussion point, there are a variety of different answers that might be appropriate.

The importance of time to onset in an inpatient setting, taking into account what I said earlier, what Dr. Zaafran said earlier, I think is significantly less important because I think that timing of management of pain and the utilization of a variety of different treatments available act in concert with one another.

On the flip side, I think that as we heard Dr. Ruha mention, and I brought up, in terms of trying to get a clearer sense of this particular discussion point, I think it would be an entirely different answer in an emergency department setting; for example, or as Dr. Sprintz mentioned, in an ambulatory surgical setting where the desire is to just achieve a certain degree of pain relief to achieve discharge, and then send the patient home on some medication that will get them through the discharge period.

That being said, I think in the variety of

different potential settings that this medication could be used, its effectiveness and its ability to achieve pain management in the time needed in the desired medical setting is going to dictate itself. I think that with respect to this discussion point, I don't consider the onset of action to be a danger per se, or a risk, but I think it will be something that will dictate its use based on the timing and what is going to ultimately happen to the patient after this medication is administered. Thank you.

DR. BATEMAN: Okay. Thank you.

I think it would be really important to have additional comments on the risks, potential risks, associated with opioid stacking. That's one of the FDA's major concerns; that because of the delayed onset, that patients will get additional doses of other opioids that could potentially be the respiratory depression associated with terminal or other adverse effects of opioids. So if people could please comment on that.

DR. ZACHAROFF: Brian, before I end my time, then, if I could just address that because I think

that is a critical piece. I think that opioid stacking, or whatever we would call it in clinical practice, happens all the time where people basically may give a medication that is part of an order set, and then treat breakthrough pain or lack of pain control as needed with a variety of different medications.

I don't particularly consider this to pose any greater risk than giving someone fentanyl, for example, who's already had Dilaudid, or morphine, or some combination of opioid medications intraoperatively, and then some combination of medications in the postoperative setting.

So from a risk perspective and with this phrase of stacking, I think as Dr. Zaafran said, I would have to agree that this happens all the time in clinical practice, and this is part of why these medications are being administered in a controlled setting. Thank you.

DR. BATEMAN: Thank you.

My own comment, just in response, is I think what makes this different is because of the delay

in onset, there's concern that the patients will get many more doses of opioids, fentanyl or other short-acting opioids, waiting for the tramadol to peak in its effect, which may be less relevant for other opioids that have faster onset.

Dr. McAuliffe?

DR. McAULIFFE: Yes. Maura McAuliffe, East Carolina University. I do want to address this onset of action, and from the perspective of the PACU after surgery. I think patients, when they arrive in the PACU and they are in discomfort, they can't wait. They have a sympathetic nervous system response to pain, which has physical and psychological sequelae for those patients.

In addition, I don't think we can always say that the medications we give intraoperatively are contributing to their postoperative analgesia. In fact, some of the drugs we give actually cause hyperalgesia. So patients when they get there -- and that's the patient I'm focusing on right now -- need to have an immediate onset-of-action drug. We're talking about

escalating dose, and we're talking about stacking, but really what we do in the PACU is we titrate the hydromorphone or morphine with immediate onset until we get to the effect that we're looking for, which is the analgesia that the patient needs with minimal respiratory depression.

This drug, on the other hand, with a 2-hour potential onset to action, would cause us to have to utilize the immediate onset drug while we're waiting for that to work, and I really do see a potential problem there. Thank you.

DR. BATEMAN: Thank you.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thanks. I'd just like to address a couple of things.

Number one, I think this drug is a little bit different from the typical drugs that we would typically look at over here as an advisory panel, from the standpoint that we have some history in its use in Europe with hundreds of millions of doses being given and a little bit understanding of what it looks like practically as opposed to

theoretically. That's why I'm really concerned about the use of the term "theoretical opioid stacking."

For context, when I asked about stacking earlier, I had, actually, a very specific drug in mind, and that is intrathecal morphine, which peaks about 6 to 7 hours after its given, and the concern there of a patient being at home, and possibly taking other opioids, and having multiple medications peak down the road. That is the one medication where I can see a concern. I don't see that practically here, either in the studies that were done or in the practical sense of what's been observed in Europe.

Relating to the question that was talked about in PACU, there are two things that we do in PACU. There's one where we give the medication to have an immediate onset of pain control, but we're also giving a medication that when that short duration of action of a narcotic wears off, you have another medication that is starting to kick in and take effect.

Now, we all know that fentanyl doesn't last very long. You may utilize it and titrate it in to get pain under control very quickly. But you might be using something like another narcotic, whether it be morphine, or hydromorphone, or in this case, tramadol, to take effect as the fentanyl is wearing off. So you're not having to give fentanyl right when you're trying to get that patient discharged at the last minute.

Again, from a practical standpoint, I think it does have a practical use, and the duration of action and the concern about its onset of action is something that myself as an anesthesiologist would actually use to my advantage as I'm giving medication to get a patient's pain level under control.

From a practical standpoint, what would this mean as far as in an ASC setting or in an outpatient setting -- well, not outpatient, in an emergency room setting, I think it would be helpful for the FDA to put criteria as to how long a patient needs to be monitored prior to discharge.

I mean, typically, we usually wait anywhere from 45 minutes to an hour after we give the last dose of an IV narcotic before discharging a patient from PACU to home. Maybe there needs to be a recommendation for that to be a little bit longer with IV tramadol in a setting where they may be going into an unmonitored setting.

So those are the caveats that I would put specifically as far as this question is concerned.

DR. BATEMAN: Thank you.

I think you raise an important point about the European experience, and it would be good to have other people weigh in on whether we should be reassured by the pharmacovigilance data from Europe. I think the perspective of the FDA is that that data does not necessarily provide robust reassurance of safety, but it'd be good to hear other perspectives.

Dr. Sprintz, you're next.

(No response.)

DR. BATEMAN: I think you're on mute, Dr. Sprintz.

DR. SPRINTZ: Hi. This is Michael Sprintz, and I appreciated everyone's input. I guess for myself, again, the clarifications are really important on the type of setting, where I see a few problems with the onset of action.

I'm concerned, one, that there seems to be the general idea of when we give something IV, we get an immediate response, and when we don't, the concept of titration. So that means there would be an important amount of education and re-education that would have to be done with staff on the administration of this drug because of the assumptions of when we give an opioid, we're going to see a relatively immediate response, and then we titrate. And that would be the first question that I would have.

I appreciated Dr. Zaafran's response about leveraging the pharmacokinetic as an advantage in terms of time you're discharged. In an ambulatory surgery center, that could be also positive in that sense, where they've got a little bit on board, but it also can be negative, where if they discharge

someone prior to the onset of action of this, along with other medications, we could have that problem of what we're calling opioid stacking, if you will. It depends on where the patient is and what their previous experiences are with medication, et cetera, and their experience with opioids prior to this issue.

I have less of an issue with the onset of action in an inpatient setting because they're going to be monitored and they can be addressed accordingly, but I think I've got a lot more concerns when it comes to an outpatient or ambulatory surgery center.

DR. BATEMAN: If everyone can remember to put your hand down after you've asked your question.

Dr. Shoben, please?

DR. SHOBEN: Abby Shoben. One of the advantages of, I guess, having -- so I'm not a medical doctor, but having been on this advisory committee for a long time, there was an advisory committee several years ago now where there was

this concern about a delayed onset for an extended-release opioid, sort of the concern that people at home taking this drug as a long-term thing wouldn't get appropriate relief, and that they would therefore take more.

Then you'd have this stacking, true stacking I think, leading to potential opioid overdose like in the setting of your house. So I appreciate the concern, and the FDA appropriately raised a concern there, and we talked about it.

Here, I think it's less -- I'm less convinced that it's a major safety issue, in part because this is an inpatient setting. Presumably the patient's not like the ones that are readily giving themselves more opioid. This would be in consultation with a physician who has read this data.

I also think this perspective that there's this delayed onset, it depends on what you're expecting out of this particular IV opioid. If you look at the data, you're seeing differences in the pain scores at 30 minutes and an hour later

compared to placebo in those pivotal trials. So just making sure that that is clear to physicians doing the prescribing that it doesn't work as quickly as fentanyl or something like that, I think would allay a lot of these potential safety concerns. Thanks.

DR. BATEMAN: Mr. O'Brien?

MR. O'BRIEN: Yes. Thank you. Joe O'Brien, National Scoliosis Foundation, and patient representative. Just speaking in that role, I would guess, perhaps anecdotally, I've had 21 surgeries as an adult, including 6 spinal fusions and a subpartial colectomy for diverticulitis. I've also been hospitalized twice for bowel obstruction.

I would say that the importance of the onset of action is extremely important in certain circumstances, and others perhaps not as much, which I guess brings up the issue to me that there's clearly variability that exists within whatever the procedures may be.

I guess the biggest risk would be the poor

nurse that's taking care of me because I'd drive her crazy if I had to wait 2 hours now to get it, and in some cases after spinal fusion, I would probably jump out a window. So those would be the relevant risks.

But I think part of the problem that I have with it is while I looked at it, I didn't have enough information, really, even though I think there was plenty of data to show that they met the criterion that was asked for them. But I still don't know. I mean, we said that they agreed to -- we look at management of moderate-to-severe acute pain, but then we had discussion that they agreed to opioid labeling, which says for which non-opioid medication is not adequate.

I don't know if we have the answer to that as I go through this. I don't know whether or not, in the particular situations that are given, an IV non-opioid, or other NSAID, or non-opioid medication may in fact resolve this pain.

When I was listening to the patients, it just brought up a lot of questions in terms of what

this setting was in terms of how this particular drug was evaluated versus, quote, "the real-world situation" that exists out there, and that is the fixed dose versus the variable dose.

There's a lot of patient satisfaction. I think there's quite a bit of bias that I heard in terms of the patients' views towards needles, and addiction, et cetera, that all plays an impact in terms of how they would rate something going forward. So I don't think it's quite clear to me in terms of the setting that's there.

Particularly, the question I also had with it is that I don't know the effect of tramadol before the M1 takes effect, and how that relates to an non-opioid medication and what I was seeing in terms of some of the results that were coming towards that. So to me, it's still a little bit unclear in terms of the advantage. To stacking itself, I think there's always a problem with that. As I said, the biggest risk, though, would be to the nurses taking care of them.

DR. BATEMAN: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, Harvard Chan School of Public Health. I think that the delayed time of onset I would say is not a benefit because I can see two big groups of situations, one where the non-opioid analgesics may be enough, and with the delay, we will not be able to observe that, so we have the rescue backwards, as it had been said.

With analgesics, if non-opioid analgesics aren't enough, we won't be able to give the optimal strategy, and if the opioids have necessary delays, it will not help the patient and can potentially lead to other opioids being given anyway.

Related to stacking, I think with the evidence from the controlled trials presented, we cannot tell because they were not designed to answer that question. The opioids were not allowed, and the severity of the patients included in the study population probably was lower than what we might see in real life.

Based on the results from the placebo, over

60 percent didn't need any analgesia, actually, and recovered with only the placebo. So probably that's why we are not seeing many rescues or trying to rescue with other analgesics or with opioids. But lacking that formal evidence, based on what the clinicians are discussing with us, they are going to be giving other opioids while waiting for the tramadol IV to kick in.

I think this stacking, at least theoretically, is possible. I agree with Dr. Shoben in that probably if this is really kept in the inpatient setting, the situation will be not as bad as if it was an outpatient. Thank you.

DR. BATEMAN: Okay.

Any additional -- Dr. Hertig?

DR. HERTIG: Yes. John Hertig, faculty at Butler University. In listening to the discussion, I do want to just emphasize a few key points from a medication safety perspective.

First, I do appreciate the concerns that were raised by the FDA with regards to opioid stacking. I for one am a little reassured by the

pharmacovigilance data from Europe but feel that there needs to be some clear guardrails, and setting is one of those.

The inpatient setting I feel much more comfortable with. When you look at outpatient or even the emergency room, with so many handoffs and points of communication risks, I can see a circumstance where someone starts this and gets transferred, and the patient's not under control, so additional opioids get added.

You couple that with the somewhat counterintuitive nature of this, where the oral works quicker than the IV -- and I think that point was made by Dr. Sprintz -- that's going to require some significant education, and those guardrails I think are essential for us to be comfortable. But in general, the time to onset of action is not a great concern if we very much focus this on the inpatient setting alone. Thank you.

DR. BATEMAN: Thank you.

Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from

the NIH, and I just wanted to echo some of the comments that we've heard earlier with regards to the delayed onset of action. I think that is actually, clearly, a liability for this drug.

There are a number of limitations with this drug that are really due to the inherent properties of the drug itself and in the context of the proposed indication, so I think, clearly, a delayed onset of action is not ideal. Can it be skillfully managed? In the right hands, of course. But again, as has been pointed out, in a real-world setting, that may not be handled optimally.

I also think that the fact that you can't titrate this drug, a single dosage level, is going to be problematic in that setting as well. The unpredictability of the response with this drug, the potential for differences in metabolism, and so forth, there are a number of issues that I think are inherent in the drug itself in the context of the proposed use. So I do think that there are some potential liabilities there and concerns. Thank you.

DR. BATEMAN: Thank you.

I think it would be good to hear from others on this issue of titratability. This is proposed as a single-dose infusion, and unlike many of the other opioids that we use, this can't be titrated, so if others can comment on that.

Dr. Griffin?

(No response.)

DR. BATEMAN: Dr. Griffin, I think you're on mute.

DR. GRIFFIN: Okay. Sorry. Marie Griffin from Vanderbilt. Yes, I do think the timing of onset is a problem. I think we expect an IV drug to work -- the patients do -- and we're talking about the doctors will need to be educated. Yes, some of them will understand this, but we have a lot of variability in medical care.

I think that that delay is a problem. In this situation in the trial, people were not allowed to get opioids, but we don't know what will happen in the real world, so I think that is a concern. The fact that so many of these patients

did fine, maybe they would have done fine with non-opioid analgesia, and I think that's a concern, that we're using opioids in situations where they are not necessarily required.

So I don't necessarily feel great about using the European experience to feel comfort that stacking would not occur here. That's all. Thank you.

DR. BATEMAN: Can you comment a bit more about why you feel like the issues around stacking were not observed in Europe but would be more relevant here. I think you made that point again, but if you could just say a bit more.

(Crosstalk.)

DR. GRIFFIN: Yes. I'm just not sure that the right studies were done, and I don't know if -- I think they have to be specifically addressed, and in the pharmacovigilance studies it wasn't reported. But I'm not sure the methods to study this -- I think it's difficult to study, and I'd like to see a really good study comparing the use of a short-acting opioid with tramadol to

answer some of these questions.

DR. BATEMAN: Okay. Thank you.

Dr. Jowza?

DR. JOWZA: Thank you. Maryam Jowza from UNC. I'm going to be a minority voice here, and part of it is that I'm having a really hard time with the onset of action data that was presented at face value, especially in light of the decades of use for tramadol in Europe for acute postoperative pain, for IV, PCAs, and inpatient settings.

I think that part of it is that the metric used to determine the onset of action, I think it's misleading. It's very hard to put the 2-hour delay in onset with a drug that's been used for acute pain in 30-plus years. And I know one of the committee members here has said that they've practiced in three continents and has had experience of use of IV tramadol, and I'd be curious to get his perspective on this. But having said [inaudible] -- is a delay, a 2-hour delay to the onset of action.

I do think that we can leverage the

pharmacokinetics and use it to our advantage. I don't particularly see a great use for it in emergency rooms or acute care settings where you're going to be sending the patient out, but I think in the postoperative setting and inpatient, I think that we are monitoring the patient, and I think that it can be used.

There are many instances where you don't quite want to give an opioid, but the patient can't take PO, let's say, so your IV acetaminophen and IV NSAID isn't enough, and you might need a little bit more. So I do see instances where it can be used and would be helpful. Thank you.

DR. BATEMAN: Dr. Lo Re?

(No response.)

DR. BATEMAN: You're on mute, Dr. Lo Re.

DR. LO RE: Can you hear me now?

DR. BATEMAN: We can. Thanks.

DR. LO RE: Vincent Lo Re from the University of Pennsylvania. I also think that the delayed onset of this drug is a liability. We heard from some of the panelists that clinically

stacking seems to be happening all the time, though sometimes with some drugs but not with others. But I don't know necessarily that we should accept that this is potentially ok. We don't know the real-world data on the frequency of stacking with IV tramadol, and I think that these data really are needed, particularly in this country.

While the indication is for IV tramadol to be administered in a medically supervised setting, I think there's a major question about what happens after patients are discharged, and is stacking going to lead to an increased risk of abuse or misuse afterwards.

I know there were some questions about the European data. I appreciate that there are decades of use of tramadol IV in Europe, but the racial and ethnic composition of the U.S. is quite different from that of many European countries, and the approach to opioids is not necessarily the same in the U.S. compared to Europe.

Moreover, these existing drug monitoring databases like VigiBase, they're not constructed to

ascertain opioid stacking or abuse/misuse after IV tramadol; they're merely collecting adverse effects that are reported, and as we heard, they have a whole number of limitations. I think more real-world data specifically examining the incidence of opioid stacking with IV tramadol and subsequent risk of abuse/misuse after discharge for medically supervised settings is warranted. Thanks.

DR. BATEMAN: Okay. Thank you.

We're now going to take a 10-minute break. Panel members, please remember that there will be no chatting or discussion of the meeting topics with other panel members during the break, and we will plan to reconvene at 4:10 p.m. Eastern time.

(Whereupon, at 4:00 p.m., a recess was taken.)

DR. BATEMAN: Okay. I think we can resume now. The next comment from Dr. Ruha, please.

DR. RUHA: Hi. This is Michelle Ruha. You had asked for more thoughts on titratability, so I just want to add that I do have concerns about the

lack of titratability. I'm actually not concerned about stacking, and I agree with other comments that multiple opioids are often used simultaneously.

But I think that one of the things is patients have different pain medication requirements and opioids are titratable. Sometimes people use different opioids; sometimes they add more. But with the tramadol not being titratable, I actually worry more about undertreatment because it's a fixed dose, and the order will be written, and I do have concerns that other opioids might not get added on, if needed because of the fact that, well, they're already on and opioid, and it's a fixed dose, and that's the dose. And I just worry about, actually, undertreated pain because of the untitratability.

DR. BATEMAN: Thank you for that comment.

Dr. Horrow?

DR. HORROW: Yes. Thank you, Dr. Bateman. I'm going to make a comment not as an industry representative but as a practicing anesthesiologist

for 45 years, and then this is with respect to onset time.

As anesthesiologists, we give many pain medicines and a variety of onset times. Modern perioperative analgesia utilizes a multimodal approach, so I'll give oral Tylenol and oral gabapentin to my patients pre-op, knowing that an hour and a half, 2 hours later, it will be on board and present when they wake up. Likewise, I'll give a variety of intravenous medications. NSAIDs are opioids with varying onset times, intraoperatively, the purpose of which is, in a combination, to achieve a smooth transition of analgesia from the intra-op to the post-op period.

Now, I appreciate the positive role of paternalism in the quest to improve safety, but perfect safety is just not achievable, and each restriction that we make has a cost in terms of limiting our options. We all eventually will encounter the patient who claims allergy to dozens of effective drugs, especially opioids. And for me, a modestly prolonged onset time is not a

concern; it's actually a potential tool to use in dealing with the spectrum of patients that I treat. Thank you.

DR. BATEMAN: Thank you.

Okay. I'm going to try to summarize the opinions of the committee with respect to discussion question 1, and then we'll move on to discussion question 2.

I think there was variation in terms of the opinion of the committee as to whether the delayed onset of action was problematic and increased the risk. Some of the panel members pointed out that this could be incorporated into practice and skillful hands. This could be really part of an anesthetic plan where the medication would be given early and expected to peak later, and that could be effectively managed. Other people were concerned that with an IV opioid, the expectation is that patients will obtain immediate relief, and if that doesn't occur, then it's very likely that additional opioids would be administered that could increase the risk for respiratory depression or

other adverse effects of opioids as the tramadol peaks.

I think many people, even if they expressed the perspective that the delay could be managed, felt like there needed to be guardrails in terms of where the medication was administered and that it would be not appropriate for an outpatient surgery center or a setting where patients would be discharged to home after receiving a dose of IV tramadol, but rather, patients needed to be in a setting where they could be very closely monitored. I think some people said there would need to be extensive education and clear labeling around the delay of onset in order for this to be effectively managed.

Some on the committee voiced concern about how this would impact on the use of NSAIDs, and the idea that NSAIDs would be the rescue medication for tramadol really inverted the paradigm that we've been working with around opioids, where we expect patients first to be treated with NSAIDs and other non-opioid analgesics before progressing to

opioids, and here the paradigm being proposed is starting with tramadol, and then using NSAIDs as a rescue medication.

There was some discussion about titratability. I think people had concerns that this could even lead to undertreatment. So if patient got a single fixed dose of IV toradol, and there was concern around prescribing additional opioids, that this could lead to pain that went untreated. I think other concerns were that the best practices with opioid administration are to start at the lowest possible dose and titrate up, and that's not possible with this drug as proposed.

Several people pointed to the European data, and I think there's heterogeneity of opinion in terms of how reassuring those data are. Some people pointed out that with many millions of administrations of toradol [sic] and lack of a signal for harms associated with opioid stacking coming from Europe, that we can feel reassured about this medication. Others pointed out the limitations of this kind of pharmacovigilance data

and the fact that opioids are approached in a different way in Europe, so there may not be the same kind of practice of stacking that we might observe in the U.S.

There was a comment that the trials that have been performed really provide no insight because opioids were not allowed as a rescue medication and provide no insight into the safety of opioid stacking.

Anything that people would like to add to my summary?

(No response.)

DR. BATEMAN: Okay. If not, I think we can move on to discussion question 2.

Discuss the benefits and risks of intravenous tramadol for acute pain management in the inpatient setting considering its mechanism of analgesia, drug pharmacokinetics, and complex metabolism.

Any clarifying questions on question 2?

(No response.)

DR. BATEMAN: Okay. If not, Dr. Zacharoff?

DR. ZACHAROFF: Yes. Thanks.

Just for sake of this discussion point, the next discussion point, and ultimately the vote, could we make sure we clearly understand what the words "inpatient setting" in this discussion point is referring to?

DR. BATEMAN: I think we should just take it at face value, and if you want to make additional comments, that you feel like there's a different role for this medication in the inpatient versus ambulatory setting, I think we would just make that comment.

DR. ZACHAROFF: Okay. Fair enough. Thank you.

DR. BATEMAN: Dr. Griffin?

DR. GRIFFIN: Sorry. I didn't put my hand down.

DR. BATEMAN: Dr. Lo Re?

DR. LO RE: Yes. I just wanted to ask the FDA and the committee, from reading the briefing document and hearing the presentation by the agency, I got the sense that opioid stacking is a

major concern, but I'm hearing from various members of the committee that it happens all the time and they're not concerned by it.

So as a person who is an infectious disease physician and a pharmacoepidemiologist, and doesn't stack opioids, I'm curious why there is a disconnect here and how to resolve that. I'm just wondering if the agency or members of the panel could help me to try to understand that, because I was under the impression that the opioid stacking is a concern. And we didn't really hear what are the outcomes, long term, of stacking. I think that would have been helpful for me. So any way to disentangle that would be helpful and appreciated. Thank you.

DR. BATEMAN: Dr. Roca, I don't know if you want to comment before we continue the discussion.

DR. ROCA: Sure. I think what might help is to make sure that we're using the terminology in the same way. I did hear people say, "Oh, we do opioid stacking all the time," and I think the way they're using it is to indicate that they use

multiple different opioids, either simultaneously or rapidly, consecutively, et cetera, so that potentially, from a pharmacodynamic effect, they're both on board at the same time.

The way we're using the terminology, with respect to the concern about opioid stacking, is with respect to adverse events when the opioids are used simultaneously. So there's not a distinction in the context when people say, "Oh, we see opioid stacking all the time." I don't think what they're meaning is that they're seeing adverse events all the time, but its meaning is they're seeing people use it all the time. I am not sure whether that clarifies it, but it's specifically adverse events that we're concerned about.

Does that help?

DR. LO RE: It helps. Thanks.

DR. BATEMAN: Dr. Zaafran?

DR. ZAAFRAN: Yes. Thanks. Sherif Zaafran.

First of all, I would say that when I used the term, I said escalation of opioids as opposed to opioid stacking, and that is a very, actually,

deliberate way for providing pain control and being able to get there, as opposed to I think what is intended by stacking here; that because there's a delayed period of onset, that potentially another opioid is given 2 hours, and that it may be additive. But my understanding from what I heard is that it's a theoretical risk and not something that was observed to have any significant adverse events.

As related to this question, we do acute pain management in several of our hospital systems all the time, and it is multimodal. We're clinicians. We consider ourselves to be halfway smart. We understand the medications that we're giving have different mechanisms of actions, have different onsets of action, and we tailor the medications that we give based on that.

As somebody said earlier, in many instances, time to medication that you give may be preoperatively so that by the time the operation's ended and an hour and a half has gone by, the medication is going to be effective at that point.

The biggest thing I would say as far as acute pain management, though, is that we don't have an opioid out there as an option IV that is Schedule IV. I mean, we obviously have tramadol PO as a Schedule IV, but from the standpoint of you're going from multimodal use of non-steroidals, gaba-noid [ph], IV acetaminophen, or whatever it might be for a patient who can't tolerate PO, the only option that you have to go beyond that is a Schedule II opioid.

I think given the education that physicians would need and could appropriately intake, having an option for an opioid that is a Schedule IV that is not as potent is something that we really need to have. It's a gap, we don't have it, and in a multimodal approach to giving medications, it would be very advantageous to have that as an option in our toolbox.

DR. BATEMAN: Okay. Thank you.

Perhaps we can table the discussion of the benefits of it being Schedule IV until the next question just for subsequent panel members that are

commenting on question 2, because there we're going to explicitly take up the question of its Schedule IV status.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. The studies as they're designed and presented are problematic for me. Earlier on, I asked the applicant if there's a study comparing IV tramadol to ibuprofen, or other non-opioids, and the applicant stated something about the severity of the operation made an opioid necessary, implying it'd be cruel not to give them an opioid, and yet the placebo in the study, people were given saline. That's saline; that's nothing.

So the fact that those in the placebo arm didn't drop out on that when given nothing for pain medication, and added to the fact that the rescue drug was ibuprofen, reinforces my interest in knowing a lot more about how effective ibuprofen is as compared to opioids in many different circumstances and are we over medicating our patients. The use of ibuprofen as a placebo in

these studies would have given us much more information and been much more useful.

Also, the studies did not allow the doctors an option on the rescue drugs. If they did have that option, it might have given us some slight insight as to what doctors would have offered in the real world. Frankly, faced with a patient in acute pain, who's 30 minutes past an IV tramadol and demanding more pain relief, I think the doctor might feel fairly pressured to give him or her some quick pain relief and go to the fast-acting, short-term opioid.

The European, the EU, experience has been brought up, so I just want to add my thought on that. I would suggest that Europe's experience with IV tramadol is of interest, but it's not comparable. The health community in the EU has a different attitude and a different use pattern of opioids for pain, as demonstrated by the fact that 5 million people misuse prescription opioids in the U.S. according to the 2016 National Survey on Drug Use and Health, and the total U.S. population in

2016 was 323 million people. In the same year, there were 1.3 million high-risk opioid users in the European Union, and they have 511 million people. So the drug abuse levels are very different. It would have been more interesting to see how many doses of all opioids were used in the EU compared to the U.S., but I didn't have the time to track that number down.

Also, we also weren't given an idea of the comparative use of IV tramadol in Europe. I believe that the number given was 390 million doses over the course of 10 years per patient. Does that actually come down to 10 million people being given IV tramadol over 10 years? My numbers may be way wrong, but this is what I recall reading. So 10 million people in 10 years doesn't sound like an overwhelming amount of use for a drug that the European doctors seem to say they like. That is what I wanted to say. Thank you.

DR. BATEMAN: Okay. Thank you.

Alright. Any other comments about question 2? I recognize that the content is fairly

close to question 1, and we covered a lot of this ground already, I think. So if there are no further comments, then I think we can move on to question 3, where I think there should be a lot to discuss. So let's move on to question 3.

Question 3, discuss the relevance of tramadol's abuse potential as a Schedule IV substance in the context of the proposed use for the management of acute pain in an inpatient setting with consideration of the following issues: any impact on a patient's subsequent risk of abuse, misuse, or development of opioid-use disorder in the outpatient setting; and B, any comparative advantage over currently available Schedule II intravenous opioids approved for the management of acute pain in the inpatient setting.

So let's go ahead and get started with this. Any clarifying questions on question 3?

(No response.)

DR. BATEMAN: Okay. No clarifying questions?

(No response.)

DR. BATEMAN: Then let's go ahead, and people can offer their thoughts. Is it relevant that this is a Schedule IV substance? And if people in their responses can comment on both A and B at the same time, that would be great.

Dr. McAuliffe?

(No response.)

DR. BATEMAN: I think you're on mute.

DR. McAULIFFE: Yes, I am.

Maura McAuliffe, East Carolina University.

One thing we didn't discuss, and that is the potential theoretical risk of a drug that is being scheduled to be delivered every 4 or every 6 hours versus PRN; so patients theoretically could be getting a dose of an analgesic that they don't need if people aren't assessing their pain level and then treating pain as they are assessed. That sort of contributes to the potential risk of abuse of a drug that a patient's getting that doesn't particularly need at that point in time. Thank you.

DR. BATEMAN: Okay. Thank you.

Dr. Sprintz?

DR. SPRINTZ: Thank you. This is Michael Sprintz. I think the big thing is I don't believe that any reliable conclusions can be shown on the IV use of tramadol in a medically supervised setting. And again, when we talk about that, that it would lead to any difference in risk from a post-discharge misuse, abuse, or OUD, compared to other currently available opioid analgesics administered in the same setting. My background is I'm a pain doc. I'm an addiction doc. I've actually been in recovery myself for over 21 years, so I understand this issue on multiple levels.

The other important point is the implication that addiction is directly related to DEA scheduling is really a simplistic view point, and it's an incorrect assumption that's ignoring the other factors such as biological, genetic, and environmental factors that relate to the development of addictive disease and influence that risk.

That's something that has not been shown in

any way here; that just because it's a Schedule IV drug, that that's any less of a risk for abuse because a drug itself has abuse potential and can be habit-forming, but addiction occurs in the brain, not in the drug, and that's an important factor. So I don't believe there's any reliable conclusions that can be drawn at this point on the impact of that.

Any comparative advantage over currently available Schedule II opioids approved for the management of acute pain in an inpatient setting, in terms of abuse potential, no. I think tramadol is not as -- as they quoted, "the likability." I don't think it's as likable as IV Dilaudid, but is that going to have any impact on the opioid crisis long term?

If we're talking an inpatient setting, not ambulatory setting, or discharge setting, but just in an impatient, I don't believe that will. And I certainly hadn't seen any evidence other than the claim that it's a Schedule IV. Just the fact that it's a Schedule IV drug really is not an

appropriate correlation for overall, real-world development of risk potential for abuse.

If I'm an addict and I have addictive disease, I will use whatever I have that's available. If the only thing I have is tramadol, heck yeah, I'll take tramadol. But if I have Dilaudid and tramadol, yeah, sure, I'll choose Dilaudid. But it doesn't mean I'm not going to choose tramadol or abuse tramadol, because I have addictive disease. So you're still going to be tickling those mu receptors even if you have someone who's only at risk, so I don't think that any conclusions can be really drawn at this point. Thanks.

DR. BATEMAN: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, Harvard Chan School of Public Health. I would like to offer a thought that was mentioned this morning to clarify that not being the abused opioid is not enough. I believe that the question is, is the new option going to increase the number of patients,

unnecessarily introduced to opioids?

I think that Schedule IV is better than a Schedule II, but it is still an opioid, and maybe just because it has the name of Schedule II is going to give a false sense of safety. We have heard that today in the discussion, to avoid an opioid, and it is an opioid.

So I think it's hard to say, based on the available evidence, if having this option in the U.S. would make the opioid epidemic better or worse. But I think the European data doesn't support that one way or another in the sense, as Ms. Robotti said, that the use of opioids in Europe overall is very different. So whether the proportion of IV tramadol is different, I don't think that can be used as an argument one way or another in the U.S. because the patterns of use are very different. Thank you.

DR. BATEMAN: Thank you.

Dr. Huybrechts?

(No response.)

DR. BATEMAN: I think you're on mute.

DR. HUYBRECHTS: Krista Huybrechts, Harvard Medical School. I'm struggling with the risk-benefit trade-off here. In terms of risk, I think we have had extensive discussion as to whether the delayed onset is a problem or not, and I think the consensus seems to be that in some circumstances it may be; in others it may not.

The major benefit, as presented by the applicant and as has been discussed, is that because of its mechanism of action, because it's a Schedule IV, there should be less abuse potential like post-discharge. I think, as one of the other committee members have mentioned, there's really no evidence at this point demonstrating that IV tramadol used in a medically supervised setting will result in less misuse or abuse after discharge when we compare it to the use of Schedule II opioids in that same setting; so there's no evidence available there right now.

Then secondly, it's been discussed extensively that the expectation is that a large number or a certain proportion of patients will

actually be using it together with other Schedule II opioids because of the delayed onset of action. While such opioid stacking is considered common, it sort of raises the question, then, where does it leave us in terms of the benefit?

So it seems that there's going to be a large or substantial proportion of patients where Schedule II opioids can be avoided in that setting because it will be used as a rescue or it's expected to be common to be used in combination. So in that sense it's not obvious to me debating whether the risk is a real risk or not, but on the benefits side, the benefit side is really not clear to me in terms of what the advantage is over just starting with a Schedule II opioid. Thank you.

DR. BATEMAN: Great. Thank you.

As a reminder, please lower your hands if you've already asked your question.

I think one thing that would be good to hear our panelists comment on is the applicant's claim that the use of IV tramadol is more likely to result in patients being discharged on tramadol,

which may have less abuse liability than other oral Schedule II opioids, that connection between inpatient and outpatient prescriptions. So if people have thoughts on that, please offer those.

Mr. O'Brien?

MR. O'BRIEN: Actually to that point, though, I'll begin with that we did clearly see, as we heard from Dr. Langford, it is very common to prescribe oral tramadol for his patients after he's used it with IV tramadol, so I think that is what we accept as happening there.

We do have some studies that indicate -- and even WHO giving warnings -- that we do have long-term use and, clearly, there are studies that show that that's where we get into a problem. Once we get into long-term use of an opioid, then we have potential issues that go along with that.

It just seems to me that when I looked at the data, even after the applicant had massaged the data for the methodology back on slide 31, there was still only a 9-minute differential between the meaningful benefit of relief of tramadol versus the

placebo. So to me, at first I was very concerned as I went through the data and did my research about do we have a proper scheduling; is this really a Schedule IV drug? But I came to listen to the applicant, and the FDA who said that they accept that data that shows us that it is a Schedule IV, and it is less than a Schedule II.

Even when I accept that, the difference is, though, I don't want to be introducing -- I would hate to see -- and we don't make it any safer if we're introducing patients into the drug that otherwise don't have to have it, which still leads me back to without having an active non-opioid comparator, it becomes very difficult to say.

When I look at the amount of people, I get satisfied with the placebo and small differential between the meaningful pain relief, and are we really going to be introducing people in these particular circumstances, 102 and 103 -- did we introduce them into an opioid no matter what?

We don't know what happened after the fact that they left the hospital, but we provide the

potential for a problem no matter what schedule you call it going forward, and I think that's a potential problem we have to see, and it would be great to have that data.

DR. BATEMAN: Thank you.

Dr. McCann?

DR. McCANN: Hi. This is Mary Ellen McCann from Harvard Medical School

You read my mind, Mr. O'Brien. I specifically wanted to mention that, logically, if a patient is well managed with tramadol as an inpatient, the surgeons would be more likely to prescribe tramadol postoperatively for discharge, and that obviously would be a great boon for the company, but it might be a boon for Americans in general.

Specifically to point A, I think that if you believe if drugs make you less euphoric, you're less likely to abuse, misuse, or develop an opioid-use disorder, I think the company did demonstrate that you have less euphoria with this drug, so I think there probably is less risk for

this abuse and misuse. To B, I don't think that there's any comparative advantage for relieving acute pain of this drug over Schedule II drugs. I think the only possible advantage is that in many settings, it would be enough for pain relief, and you could avoid using a Schedule II drug and avoid sending patients home with a Schedule II drug. That's all I need to say. Thank you.

DR. BATEMAN: Alright. Thank you.

Dr. Ruha?

DR. RUHA: Hi. Michelle Ruha here. I also do think that this would increase the prescriptions of oral tramadol on an outpatient basis. I actually think that could be a bad thing for a few reasons. One, there will be less control over prescribing for a Schedule IV and people probably will be on it longer, and then I do believe that we will see more abuse of tramadol because it does get abused.

I also am really concerned about the drug interactions and the problems that could result from increased use of outpatient oral tramadol,

including seizures and serotonin syndrome. Although those were a very small percentage of adverse events here, they do happen; and if it starts to be prescribed more indiscriminately.

Use of other SSRIs is not a contraindication. Seizure disorder I don't believe is a contraindication. People will be prescribed these. Years ago, I used to see a lot of those side effects, or adverse effects, in people on tramadol. For some reason in recent years, I haven't been seeing it very much, but I think if the prescribing increased, we'd start seeing more again.

DR. BATEMAN: Thank you.

Dr. Hovinga?

DR. HOVINGA: Colin Hovinga, UT Austin, College of Pharmacy, I-ACT for Children. I wanted to add to that. I think to really understand the risk, it's also a question of what are you switching it out for?

In my impression, if someone's going home on an NSAID versus a C2, it's very, very different.

The adult colleagues, please correct me if I'm wrong. I perceive that the use of longer-term opioids has been actually decreasing and that there's been a switch to alternative therapies like gabapentin and non-steroidals. So by transitioning patients to Ultram, I think the risk-benefit might actually be negative because you have a drug that maybe carries a little bit more baggage, and side effects, and whatnot. Thank you.

DR. BATEMAN: Thank you.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thanks. Sherif Zaafran here. I'm worried that we're limiting our options because of a lot of theoretical and a lot of secondary concerns, increasing the amount of PO tramadol because we're going to allow IV tramadol.

The bottom line, though, is that we don't have any options, for a patient who cannot take PO, for an IV narcotic that had low potential for abuse. If I can only give an IV narcotic because a patient cannot tolerate PO, and I'm already giving

all the multimodal medications, my options are really only morphine, or hydromorphone, or meperidine. I don't have an option for a weaker narcotic. Even from the standpoint of giving PO, your only options are essentially oxycodone or hydrocodone.

So I just worry that we're limiting ourselves for a lot of potential concerns, when from a practical concern, myself as an anesthesiologist doing acute pain management, my only option is something that is maybe too strong for what the patient needs in that kind of setting. So you can put whatever guardrails you think is appropriate, but to not consider it as an option I think is a disservice to patients and forces us to use something that is stronger than may be necessary. Thank you.

(Pause.)

DR. BATEMAN: Sorry. I got disconnected for a minute.

Ms. Robotti?

MS. ROBOTTI: Hi. Thank you. Suzanne

Robotti. The applicant is proposing a drug that will likely need a supplemental drug, so where is the data to show what is the best way to do that or that it is safe? If they know that in most cases you'll need a rescue drug or a supplemental drug, shouldn't that have been part of the testing?

Just because doctors do stack opioids now, or drugs now, or analgesics now, that doesn't mean that doctors shouldn't have good guidance on how IV tramadol interacts with other drugs. The time to effectiveness for IV tramadol is highly variable, so I think it's only appropriate that doctors have an idea of what the safety windows are. You already know how long opioids last and how long it takes for them to kick in. Tramadol, you don't have that sort of guidance, and that's pretty much what I wanted to say. Thanks.

DR. BATEMAN: Thank you.

Okay. Any other comments on question 3 before I summarize?

(No response.)

DR. BATEMAN: Okay.

I think there was some heterogeneity of opinion amongst the panel members with respect to the question of whether tramadol's abuse potential is different than Schedule II opioids. Some panelists pointed out the fact that there are really no data, suggesting that IV tramadol compared to other Schedule II narcotics impacts on abuse, misuse, or the development of an opioid-use disorder. One panelist did point out that there may be data that the euphoric effects of IV tramadol are less than Schedule II medications, so there is perhaps a theoretical benefit in that regard.

One of the panelists pointed out that we expect that IV tramadol will frequently be used in combination with Schedule II opioids, and thus any potential benefit of IV tramadol would be negated by the fact that patients are co-exposed to other opioids.

One panelist made a comment that the fact that IV tramadol is supposed to be given on a scheduled basis every 4 to 6 hours, or whatever the

interval is, could actually increase its abuse liability because patients would be receiving doses even if they didn't necessarily need them and may have more exposure than an opioid that would be titrated to effect or given on a PRN basis.

One panelist pointed out that the Schedule IV nature of tramadol may give a false sense of security, and perhaps more opioids will be prescribed because of that, when in fact it may not be safer.

A few panelists commented on the potential that the use of IV tramadol would increase the discharge prescriptions for PO tramadol, and some noted that that may have benefits if there is a lower abuse liability to PO tramadol compared to other opioids. But others pointed out some of the problems with tramadol, including extensive drug-drug interactions and seizures that can occur with tramadol that may be problematic if we did see more PO tramadol prescriptions.

Anyone want to add to my summary or clarify any of the points?

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Yes. Sonia Hernandez-Diaz. You mentioned that Schedule IV is safer than Schedule II but not safer than placebo or other non-opioid analgesics, so not safe but safer than others.

DR. BATEMAN: Okay. Great. Thank you for that clarification.

Okay. I think we're ready to move on now to the voting question. The voting question is, has the applicant submitted adequate information to support the position that the benefits of their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient setting?

Then if you vote yes, please discuss the rationale for your vote and specify whether any post-approval studies should be required; and then if you vote no, please discuss the rationale for your vote and what additional data are needed for approval.

Are there any clarifications about the

wording of the question?

Dr. Zacharoff?

DR. ZACHAROFF: Yes. Hi. This is Kevin Zacharoff. So we're here at the vote, and my question is that "inpatient setting" is not the same wording as "medically supervised setting." So before I cast my vote, I'd like to have clarity about whether inpatient setting is a proxy for medically supervised setting or inpatient setting refers to hospital inpatients, patients that are in ambulatory surgical settings, emergency departments, et cetera.

DR. BATEMAN: Dr. Roca, do you want to weigh in here?

DR. ROCA: Sure. This is Dr. Roca.

I certainly understand how that will impact how you answer with respect to yes or no. Based on the discussion that I've been hearing, one way to look at it would be if you felt that there might be some inpatient setting or -- let me say this; one setting where you think you could say that the risk-benefit ratio was favorable, then I think that

would be fine, and then in your rationale, it will be key that you talk specifically about the setting that you're talking about. Similarly, if you feel that no way, no how, I can't think of any setting where it would be used, then, in a sense, it doesn't matter what the inpatient setting definition would be.

Dr. Zacharoff, I think what you would end up doing is voting whether you think the risk-benefit ratio is favorable and adding in your rationale caveat as to what setting you're talking about and what specific use it is that you're voting for. And similarly if you vote no, then you could explain what setting you think it would not be a favorable benefit.

Does that help?

DR. ZACHAROFF: Yes, absolutely. Thanks very much.

DR. BATEMAN: Any other clarifying questions?

(No response.)

DR. BATEMAN: Okay. In that case, we'll now

move on to the voting question. Dr. Moon Hee Choi will provide instructions for the voting.

DR. CHOI: Question 4 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you'll be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting

members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. BATEMAN: Okay. If there are no questions, then I'm going to read the question into the record.

Has the applicant submitted adequate information to support the position that the benefits of their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient

setting?

If there are no questions or comments concerning the wording of the question, we will now begin the voting on question 4.

DR. CHOI: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. CHOI: The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. CHOI: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting question, if any.

For the record, we have 8 yes, 14 no, and zero abstentions.

DR. BATEMAN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to. We'll start with Dr. Griffin.

DR. GRIFFIN: Yes. Marie Griffin. I voted no. I think given the current opioid crisis in the U.S., we should have strong evidence that this new opioid would provide benefits over what's currently available, and I didn't see that evidence. We should also have strong evidence that there would not be unintended consequences that would actually be harmful. That completes my remarks.

DR. BATEMAN: Thank you.

Dr. Shoben?

DR. SHOBEN: Sure. Abby Shoben. I voted yes. It's a tough call for me, but I was persuaded that they had demonstrated benefit in terms of pain management versus placebo from the pivotal trials, and I was persuaded by some of the comments of the physician members that this would serve a need

that's currently unmet in certain patient populations. I was somewhat less convinced by the argument of this theoretical risk of opioid stacking presented by the FDA, so that persuaded me that probably the benefits do outweigh the risks.

The future studies, I think it'd be really important to look for the potential unintended consequences, particularly if you start seeing more IV opioid use altogether, where people are using this drug potentially because they think it's safer when it might not be, and some of the other risks brought up by the committee members, the theoretical risks that could be addressed once it's actually used in clinical practice. Thank you.

DR. BATEMAN: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no regarding the adequate information because I don't think the trials that were presented evaluated the strategies that would be proposed in the label, and that became apparent in the discussion today.

I think we have been discussing that fine

line or room between taking non-opioid analgesics and taking a Schedule II. I believe that it will be great to reduce the use of the Schedule II opioids, but we will not agree if this new option will take the market from the use of analgesics.

I easily went thinking that if the patients need opioids, they will end up adding opioids anyway by waiting for the general effect. I was convinced in the discussion today that there may be a group of inpatient patients that cannot tolerate PO; for example, that can benefit from a weaker narcotic.

In that case, to the question of what would be additional data, I think it would have been useful to have a study with the population that is proposed for this use and with comparisons that are informative, meaning either a non-opioid analgesic with greater benefit, and of course a greater benefit than placebo, and/or a Schedule II analgesic; so an equivalent type of benefit for pain control. Thank you.

DR. BATEMAN: Thank you.

Dr. Richmond?

DR. RICHMOND: Rebecca Richmond. I voted no. The applicant has not presented adequate information to support benefits outweigh risks. There's a lack of evidence from the sponsor for safety when given concomitant opioids or other sedating analgesics given the pharmacokinetics, half-life, time to Tmax, and delayed onset of action, especially when patients are transferred to a lower-level care unit without continuous monitoring or discharge time. Thank you.

DR. BATEMAN: Thank you.

Dr. DeMarco?

DR. McADAMS DeMARCO: Hi. This is Dr. Mara McAdams DeMarco. I voted no, and agree with the previous comments of those who voted no. I would just emphasize that I think there needs to be stronger evidence of a benefit over the existing Schedule II opioids rather than just a placebo, and it should be really done in an inpatient study population, as is indicated by the labeling.

DR. BATEMAN: Thank you.

Dr. Zaafran?

DR. ZAAFRAN: Yes. Thanks. I voted yes. I think that we are boxing ourselves in, unfortunately, and limiting ourselves to opioids that are on the market that are strong. Options that are coming out and not being approved are limiting clinicians' ability to treat patients in ways that are not necessarily as heavy-handed as what we have available out there.

I think the concerns that I heard about the potential use of more of these being prescribed in an outpatient setting because it gives people a false sense of comfort, I'm a regulator. I sit on a medical board. That's my job, to put out rules to make sure that physicians are using the medications that are approved in an appropriate fashion.

I think our job as an FDA advisory panel is to look at the efficacy and look at the ability to use the drug in a proper way. All the potentials that are out there is the job of regulators to make sure that physicians are using it appropriately and

in a specified manner.

We don't have any IV Schedule IV opioids out there to utilize in our toolbox when it's appropriate. Again, as I said before, we're smart enough to understand the mechanism of action, the onset of action, and to be able to use these medications appropriately, at the right time, and the right circumstance, and the right setting.

I just think we're really handicapping ourselves by limiting our options, and moving forward, I would just really hope that we think very hard about the unintended consequences of only limiting our patients with opioids that are too strong. We're already using multimodals out there, and we've got to have some of these opioids out there as an addition to what we're using in our toolbox, and we shouldn't be limiting ourselves and handicapping ourselves. So that's what I have to say.

DR. BATEMAN: Thank you. Could you just state your name for the record and your vote?

DR. ZAAFRAN: Sherif Zaafran. It was a yes

vote.

DR. BATEMAN: Alright. Thank you.

Dr. Higgins?

DR. HIGGINS: Yes. Jennifer Higgins. I voted no. My concerns are consistent with what I already expressed, that the opioid stacking was of concern to me, particularly when we don't really have comparisons between EU and U.S. data in that area. I was also concerned about the onset of analgesia being delayed in the trial.

I don't really believe this product has additive value to what's already on the market. And with respect to what I would suggest going forward, it's much consistent with what other people have already said, and maybe using rescue meds, and analgesics, and diverse populations. We can't limit ourselves to just EU data only.

DR. BATEMAN: Dr. Zacharoff?

DR. ZACHAROFF: Hi. This is Kevin Zacharoff. I voted yes, and I voted yes because the vote was a question about acute pain severe enough to require an opioid analgesic. That does

not mean pain that did not respond to other treatment; it just means, to me, that there is a determination that it's severe enough to require an opioid analgesic.

Also, my definition of inpatient setting for my vote of yes is a setting that is an inpatient setting, and that means that the patient is not going to be discharged to home. So that would not include an emergency department setting. It would not include an ambulatory surgical care setting. It would be truly what my definition of an inpatient setting is.

With respect to the term "opioid stacking" and the theoretical nature of it, as Dr. Zaafran mentioned, if we look at it from the perspective that it's adverse events related to inadvertent cumulative opioid-induced respiratory depression, I would venture to say that unless there's ever a situation where there's only one medication that is a central nervous system depressant that's administered to the patient, the risk of that inadvertent cumulative effect is always there, and

I don't consider it to be any more likely, based on the information provided today from a risk-benefit perspective, with this medication. Thank you.

DR. BATEMAN: Thank you.

Dr. Calis?

(No response.)

DR. BATEMAN: Dr. Calis, you might be on mute.

(No response.)

DR. BATEMAN: We still can't hear you.

DR. CALIS: Hi there. I'm sorry. I got disconnected suddenly.

I'm Karim Calis from the NIH, and I voted no. To my mind, I think that the data that was provided by the sponsor is limited. There are limitations in the design, the narrow population, and I also believe that it will not translate well in the real-world setting. I'm also not really impressed by the largely anecdotal European data, and I think that there are also a number of limitations that I alluded to earlier that are due to the inherent properties of the drug itself for

the proposed indications.

I respectfully disagree with some of my colleagues that are implying somehow that these are only theoretical concerns that we've raised and the FDA has raised, but I don't believe they are. I think we should not approve a drug just so we can have another analgesic option. Our patients really deserve better options.

Can we make something work? Can we force it to work? Sure, but again, that's not really ideal. What are the characteristics of an ideal analgesic for acute pain management? We all know those very well, and I don't think that this particular drug stacks up well.

I think IV tramadol is a suboptimal analgesic. It has modest efficacy at best. But more importantly, it has a number of limitations that we've addressed. The atypical pharmacologic activity; the delayed onset; the fact that it's not titratable; the unpredictable kinetics and dynamics; and the potential for interactions and additive adverse effects really make it a very not

ideal agent for us to use, and that's the rationale for my vote. Thank you.

DR. BATEMAN: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. This is Dr. Michael Sprintz, and I voted no. I appreciated everyone's comments on both sides. I think for myself, I was not convinced by the evidence that the sponsor really put a clear use case together in which this would be beneficial. I definitely do not believe the implication that this will have an impact or decrease the overall risk, abuse, or addiction rates in the population, and is going to change it all. I don't believe they showed any evidence of that.

Given the pharmacokinetics and the issues, I'm still struggling to see how this is better than some of the products on the market already, including oral tramadol. So overall, there would have to be a lot more specificity and a narrow-use case with better data to support the benefits over the risks for me to feel differently. Thanks.

DR. BATEMAN: Thank you.

This is Brian Bateman. I voted no. I think the delayed onset and the unpredictable pharmacokinetics of this drug, coupled with the inability to titrate the drug, make this quite a problematic formulation. I think there are risks to opioid stacking, and these have not been evaluated in the trials that have been performed. I think we need trials that better reflect the type of setting where this drug would be administered, where opioids would be able to be used for continued pain or breakthrough pain.

I think the risks around undertreated pain are a real concern with the delayed onset, coupled with people perhaps being concerned about opioid stacking and avoiding giving opioids if patients had poorly-controlled pain prior to tramadol's effect peaking.

I also think the paradigm that's put forward that this medication should be given and should be rescued by non-steroidals is really problematic and not reflective of best practices around opioids,

where they're used as rescue medications if non-opioid analgesics that have a better side effect profile and less abuse liability are ineffective.

Then finally, I would say there's no compelling evidence presented that there's less abuse liability with this formulation compared to Schedule II opioids. We really have no data that suggest that the use of inpatient IV opioids and the differences between them could impact on long-term misuse, abuse, or development of opioid-use disorder.

Dr. Huybrechts?

DR. HUYBRECHTS: This is Krista Huybrechts. I voted no, and the rationale for my vote was that although the delayed onset of action can possibly be managed in certain circumstances, it is unclear what the implications are for the need of Schedule II opioid rescue medications. It is also unclear what the implications could be in terms of increased use of opioids in patients who could potentially be managed successfully with non-opioid

analgesics. In terms of the public health benefits, the fact that it will lead to lower risk of non-medical use remains to be demonstrated, in my view. In terms of additional data, that would be needed.

I'm very much in line with what other committee members have mentioned, so I think stronger evidence on the use of rescue medication in the context of where both opioids and non-opioid analgesics are allowed would be important in the U.S. setting; comparison of the efficacy to non-opioid analgesic medications; and then stronger evidence than the anecdotal data from Europe that has been presented in terms of risk of non-medical use following IV administration of tramadol versus other opioids in the medically supervised setting. Thank you.

DR. BATEMAN: Thank you.

Dr. McAuliffe?

DR. McAULIFFE: Yes?

DR. BATEMAN: Go ahead.

DR. McAULIFFE: Maura McAuliffe, East

Carolina University. I voted no. Although it may have theoretical advantages, I don't think that the data presented in Studies 102, 3, or 4 were convincing on their own. The international data I think is very informative, but again, I don't think that that data is collected in the same manner. I think that practices differ in different countries, and the population expectations in different countries are certainly there.

My concern about delayed onset and subsequent hypoxic events once the patient is outside of the monitored unit is a real concern, and some data that I would like to see in the future would be some data that showed the combination of IV tramadol and an opioid, or the comparison of IV tramadol and IV, perhaps, non-steroidals. So that's my rationale for now. Thank you.

DR. BATEMAN: Thank you.

Dr. Lo Re?

DR. LO RE: Yes. Vincent Lo Re. I voted no. I appreciated the need for alternative forms

of analgesic therapy that offer freedom from Schedule II opioids, but to me, the delayed onset of analgesia, combined with its inability to be titrated to effect, just raised too many concerns for me.

Notably, I think the data from Study 103 that showed that 43 percent of patients who received 50 milligrams of IV tramadol after abdominoplasty, receiving rescue therapy within 2 hours, and that only 51 percent recorded meaningful relief within 2 hours of initiating the first dose versus 48 percent with placebo, was telling. I think these data raised concerns for me that such frequent need for rescue therapy may lead to subsequent greater use of shorter-acting opioid therapy, either in the inpatient setting or possibly after discharge from a supervised setting.

From a safety standpoint, the applicant provided no new clinical data in response to the agency's safety concerns. Dr. Roca asked us to address whether there's enough information to address safety. To me, the lack of available

published literature and real-world data with IV tramadol do not address the safety concerns about either opioid stacking or its attendant adverse effects, or subsequent risk of abuse, misuse, or opioid-use disorder after IV tramadol therapy. The absence of data, to me, does not imply an absence of safety signals, only a lack of evidence.

The absence of European safety concerns was really because existing systems like VigiBase weren't designed to assess either opioid stacking or abuse-misuse after IV tramadol. More real-world data I think specifically examining the safety concerns after discharge from medically supervised settings is warranted.

Based on the absence of impaired pharmacoepi data with IV tramadol use, I don't think any conclusions can really be made with respect to whether IV use of tramadol in a medically supervised healthcare setting will confer a public health benefit relative to the risks.

Finally, just given the ongoing opioid

epidemic in this country, its subsequent effects on incidence of hepatitis C, HIV, and a variety of different infections of the skin, bone, joint, bloodstream, I think it is very important to acquire additional information to address the safety concerns that were raised by the agency. Thank you.

DR. BATEMAN: Thank you.

Dr. Jowza?

DR. JOWZA: Maryam Jowza. I voted yes for many of the reasons that other panelists had voted. I think the data for the efficacy was there. With respect to the risk, it was largely that related to opioid stacking, and I think that that's something that can be mitigated with proper use and education.

DR. BATEMAN: Thank you.

Dr. Hertig?

DR. HERTIG: Yes. John Hertig. I voted yes. I understand and appreciate the concerns that the FDA has articulated prior to and during the meeting. That said, I think in the overall context

of the data presented, the various discussion points raised, and the available pharmacovigilance data, I do believe there is a role for IV tramadol and practice here in the United States.

This niche role, however, is likely limited to very specific supervised settings -- for example, we talked about inpatient perioperative or procedural use -- and fills a gap in those patients who require pain control above and beyond non-opioid analgesics but may not need or benefit from Schedule II opioids.

Further, and we didn't discuss this in great detail, there is a patient population with an intolerance or documented sensitivity to NSAIDs that may benefit from IV tramadol, again, avoiding the need for administration of Schedule II opioids.

As for additional needs from the applicant, clearly more information and clarification around labeling, risk evaluation and mitigation strategies, and educational requirements must be vetted and incorporated into any proposed plan worthy of final approval. Monitoring parameters,

including guidance on appropriate monitoring time prior to discharge, is also likely essential. Thank you for the opportunity to participate in this valuable process.

DR. BATEMAN: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Yes. Joe O'Brien, and I voted yes. I probably won't sleep tonight. I firmly believed I was going to vote no for this, but at the end of the day I did listen to some of the colleagues in terms of the expressed need to have a Schedule IV and the FDA's confirmation that it is legitimately a viable Schedule II medication.

I looked at the fact that, overall, we still have 70,000 people that are overdosing in this country. We have an epidemic. We have a patient community that is taking two-plus years -- an outpatient community -- of oxycodone and other Schedule II opioids that are stuck in there, and if we can do something to move that needle forward by giving them a Schedule IV instead, I think that is something that at the end of the day is worthwhile.

I think the applicant did provide the data. The FDA readily admitted that they provided the data and accepted what was submitted in Studies 101, 102, 103, and 104. Although, as I indicated in my previous comments, I am very concerned that we are introducing patients to opioid analgesics who do not need this based on these studies. I do not see a very high-risk reward in the benefit ratio here, and I wish the FDA had required a non-opioid comparator instead of a placebo.

DR. BATEMAN: Thank you.

Dr. Ruha?

DR. RUHA: Yes. This is Michelle Ruha. I voted no. I thought the applicant put together an excellent presentation, and I can appreciate that there may be patients that might benefit from this, but, overall, I just wasn't convinced of the benefits.

For one thing, we really don't have any evidence that short-term IV tramadol will ultimately impact the opioid epidemic at all. Then

I was also concerned that the adverse effects in the study that compared it to morphine were actually not on the equal, but a little greater than that with morphine, yet I wasn't really convinced that IV tramadol was even better than NSAIDs. We didn't have it as a comparator, but with NSAID rescue, I wasn't convinced of its efficacy. So to me, the benefits just did not outweigh the risks.

DR. BATEMAN: Thank you.

Dr. Goudra?

(No response.)

DR. BATEMAN: Dr. Goudra, I think you're on mute.

DR. GOUDRA: Yes. Can you hear me now? Sorry about that. Can you hear me?

DR. BATEMAN: We can hear you now.

DR. GOUDRA: Okay. Basavana Goudra. I voted yes, and I think Dr. Zacharoff and Dr. Zaafran made an excellent point for voting yes. Just to add to that, yes; even if it is 30 million usages in Europe and the rest of the world, that's

a big number in terms of safety concerns, so I'm not concerned about the safety issues, and the efficacy is certainly known.

Unfortunately, historically, there have been instances with the FDA where drugs that are being used in Europe for decades are delayed, and metformin comes to my mind. Sugammadex was also delayed and TCA still not approved, target-controlled infusions. So I really don't know what more the manufacturer, the company, can do to convince us.

Yes, decreased risk of euphoria is a good reason. Stacking, as many panel members who voted yes mentioned, I wouldn't say it's a non-issue but a significantly smaller issue. Having worked in England, I've used it, and even yesterday, I spoke to some of the people who are using it, and people who actually have been using tramadol, many of them use just exclusively tramadol other than short-acting opioids. So they're pretty happy with the tramadol.

So I personally feel that we are denying an

opportunity both to physicians to use this drug and also to the American people. Hopefully, one day it will be approved. Thank you.

DR. BATEMAN: Thank you.

Dr. McCann?

(No response.)

DR. BATEMAN: Dr. McCann, I think you're on mute.

DR. McCANN: Can you hear me now?

DR. BATEMAN: I can.

DR. McCANN: You can hear me now?

DR. BATEMAN: Yes.

DR. McCANN: Yes?

DR. BATEMAN: Yes.

DR. McCANN: Okay. Sorry about that.

I voted yes for the reasons that Dr. Goudra, and Dr. Zacharoff, and Dr. Zaafran were so eloquent about. I think there is a prescribing gap. I think that drug euphoria is -- I'm concerned about patients that are already addicted, but I'm particularly concerned, and it was my pediatric background, about adolescents and young adults who

are exposed to the euphoric effects of opioids, and that is a gateway to going on to abusing and misusing these drugs. I think that probably was the most important factor for me.

In terms of safety, I think that it should be, initially at least, prescribed in perioperative or ICU settings, not in the emergency room. So for labeling, I would think about that. Then I think the FDA needs to have clear tracking over the effects of different ethnic groups. I don't know for a fact, but I believe that the United States may be more ethnically diverse than Europe, so we can't completely rely upon the European experience to determine whether it's safe for us. I think we need to be tracking that post-approval, and that's it. Thank you.

DR. BATEMAN: Thank you.

Dr. Hovinga?

DR. HOVINGA: Hello. This is Collin Hovinga. I voted no, largely for many of the reasons others said, very eloquently. I think there were benefits demonstrated in the clinical

trial. I think those are relatively still mild compared to the risks that we don't know and potentially that were reported in the studies. As for the data, answering that question, no is my response. Thank you.

DR. BATEMAN: Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. I voted no. I don't agree with what some of the other committee members said. The applicant did not fulfill the requirements set out by the FDA. The FDA was very clear. The quick action and not delayed action for acute pain was what was required, and the applicant was not able to put together a plan on how their drug could address the immediate need for pain relief when their drug takes, sometimes, up to 2 hours to manage pain. It's not that that is impossible to show; it's just that they didn't do it. The FDA also identified stacking as a risk, and it was another opportunity for the applicant to address and show evidence of how rescuing supplemental pain drugs could have

worked in tandem with IV tramadol, but they didn't do it.

I don't think that we are pushing doctors to use stronger drugs as a previous committee member suggested. I would hope this would encourage a much closer look at a non-opioid category, which has been gathering studies for years showing comparative effectiveness, and much lower side effects, and much lower risk of addiction.

I would encourage the FDA to consider increasing the indications for NSAIDs to higher pain levels. I believe that the patient's assessment of pain should guide the analgesia, not give them a shot every 4 hours for a day or two. Thank you.

DR. BATEMAN: Thank you.

Before we adjourn, are there any last comments from the FDA?

Excuse me. Dr. Horrow has his hand up.

Dr. Horrow?

DR. HORROW: Thank you so much, Dr. Bateman. Jay Horrow, industry representatives from

Bristol-Myers Squibb. I appreciate the opportunity to just take 30 seconds to provide some comment to the agency. As you know, I don't have the option to vote.

I believe it's unfortunate that both the committee and the agency, for whatever reason, had to review data from clinically irrelevant milieu, and I believe you underscored that, Dr. Bateman. I'm hopeful that there is a way forward, and it might perhaps include the following three items: first, submission to the FDA of more appropriate analyses of the stopwatch data; second, the collection of safety data of IV tramadol when given in clinically relevant context, perhaps in a controlled study; and third, indication language that can reflect that clinically relevant use. Thank you.

DR. BATEMAN: Thank you.

Okay. Any last comments from the FDA before we adjourn?

DR. ROCA: Hi. This is Dr. Roca. I just want to say thank you to all the panel members. It

was very evident that you guys really had a lot of thought into this and had a very thoughtful discussion, and I certainly do appreciate all the comments that you have said and the hard work that you put in for today. Thank you all.

Adjournment

DR. BATEMAN: Okay. Thank you.

Thanks to all the panelists. We will now adjourn the meeting. Have a good afternoon, everyone.

(Whereupon, at 5:36 p.m., the meeting was adjourned.)