Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Anesthetic and Analgesic Drugs Advisory Committee Meeting
April 19, 2023

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed postmarketing requirement (PMR) 3033-11, issued to application holders of new drug applications (NDAs) for extended-release and long-acting (ER/LA) opioid analgesics to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia. The discussion focused on a clinical trial designed to address these objectives.

These summary minutes for the April 19, 2023 meeting of the Anesthetic and Analgesic Drugs Advisory Committee of the Food and Drug Administration were approved on June 6, 2023.

I certify that I attended the April 19, 2023 meeting of the Anesthetic and Analgesic Drugs Advisory Committee (AADPAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	***/s/***
Rhea Bhatt Acting Designated Federal Officer, AADPAC	Brian T. Bateman, MD, MSc Chairperson, AADPAC

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee
April 19, 2023

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on April 19, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Opioid Postmarketing Requirements Consortium (OPC). The meeting was called to order by Brian T. Bateman, MD, MSc (Chairperson). The conflict of interest statement was read into the record by Rhea Bhatt (Acting Designated Federal Officer). There were approximately 945 people online. There a total of ten Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committee discussed postmarketing requirement (PMR) 3033-11, issued to application holders of new drug applications (NDAs) for extended-release and long-acting (ER/LA) opioid analgesics to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia. The discussion focused on a clinical trial designed to address these objectives.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Brian T. Bateman, MD, MSc (*Chairperson*); Mark Bicket, MD, PhD; Maryam Jowza, MD; Maura S. McAuliffe, PhD, CRNA, FAAN; Mary Ellen McCann, MD, MPH; Timothy Ness, MD, PhD; Abigail B. Shoben, PhD; Michael Sprintz, DO, DFASAM; Sherif Zaafran, MD, FASA

Anesthetic and Analgesic Drug Products Advisory Committee Member Not Present (Voting): Rebecca Richmond, PharmD, BCPS

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (*Industry Representative*)

Temporary Members (Voting): Erica Brittain, PhD; Elizabeth Joniak-Grant, PhD (*Patient Representative*)

FDA Participants (Non-Voting): Rigoberto Roca, MD; CDR Mark Liberatore, PharmD, RAC; Elizabeth Kilgore, MD, MS; Robert Shibuya, MD

Acting Designated Federal Officer (Non-Voting): Rhea Bhatt

Open Public Hearing Speakers Present: Diana Zuckerman, PhD (National Center for Health Research); Andrew Kolodny, MD (Physicians for Responsible Opioid Prescribing); Nancy Connolly, MD, MPH, FACP; G. Caleb Alexander, MD, MS; Edwin R. Thompson (Pharmaceutical Manufacturing Research Services); Jane C. Ballantyne MD, FRCA; Mark D. Sullivan, MD, PhD; Danesh Mazloomdoost, MD; Gary Franklin, MD, MPH (Washington State Department of Labor and Industries); Ravi Gupta, MD (Doctors for America)

The agenda was as follows:

Call to Order	**Brian T. Bateman, MD, MSc** Chairperson, AADPAC
Introduction of Committee and Conflict of Interest Statement	**Rhea Bhatt** Acting Designated Federal Officer, AADPAC
FDA Opening Remarks	**Rigoberto Roca, MD** Director Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
OPIOID PMR CONSORTIUM (OPC) PRESENTATIONS	
Introduction	**Charles E. Argoff, MD** Professor of Neurology, Director Comprehensive Pain Program Albany Medical Center
Overview of Study Design –3033-11	**Charles E. Argoff, MD**
Rationale for Study Design –3033-11	**Nathaniel Katz, MD** President Ein Sof Innovation
Overview of OIH and Its Evaluation	**Martin Angst, MD** Professor, Anesthesiology, Perioperative and Pain Medicine, Vice Chair Strategy and Initiatives Stanford University Medical School
Protocol Considerations	**Sandra Comer, PhD** Professor of Neurobiology (in Psychiatry) Columbia University
Conclusions	**Charles E. Argoff, MD**
Clarifying Questions for OPC	

BREAK

SPEAKER PRESENTATION

Enriched Enrollment Randomized Withdrawal Design for Studies in Chronic Pain	**John T. Farrar, MD, PhD** Professor of Epidemiology, Anesthesiology, and Critical Care Hospital of the University of Pennsylvania

Clarifying questions for Dr. Farrar

LUNCH

FDA PRESENTATION

FDA's Perspective on the Proposed Protocol Intended to Fulfill Postmarketing Requirement (PMR) 3033-11	**Elizabeth Kilgore, MD** Medical Officer DAAP, ON, OND, CDER, FDA

Clarifying Questions for FDA

OPEN PUBLIC HEARING

Charge to the Committee — **Rigoberto Roca, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION**: Discuss the advantages and limitations of using the enriched enrollment randomized withdrawal (EERW) design to assess long-term effectiveness; discuss the advantages and limitations of using a placebo-controlled design to assess long term effectiveness.
    a. Include in your discussion the likelihood of maintaining sufficient patients in the randomized treatment period in each of these study designs to assure an adequate assessment of effectiveness at the end of the double-blind treatment period.

Committee Discussion*: The committee members noted that the principal advantage of this trial design is that it is feasible, which may not be the case for other designs. Members expressed that it is likely that patients will be able to enroll in the trial and retained until the*

point of randomization. It was also mentioned that the study design addresses clinically relevant questions for patients who respond to opioids (i.e., for whom opioids have some efficacy): In these patients, what is the impact of withdrawing treatment and whether continuing on extended-release and long-acting (ER/LA) opioids is beneficial. This may provide a general sense of which patients will benefit from long-term opioid therapy.

For limitations, the committee members noted the design did not address the broader question related to what proportion of the population is likely to respond in a sustained way. The committee members discussed concerns around blinding, specifically whether the withdrawal of treatment and use of placebo would result in bias towards the treatment arm. Some committee members noted limitations with the enrollment criteria regarding heterogeneity of the population, particularly the inclusion of patients with neuropathic pain. Some suggestions included capping certain indications and planning analyses of subsets of patients to see if there is variation in effect based on the underlying indication. Regarding the discussion around dropout prior to randomization, the committee members mentioned that dropout could be controlled, and an adequate number of patients can be enrolled to ensure there are enough patients to the randomization point. The committee members further emphasized the importance of setting expectations in order for the study to be able to retain patients through the post-randomization period. In addition, the committee members mentioned the importance of understanding dropouts, suggesting that the endpoint should incorporate capturing patients that drop out because they are doing poorly, and those who drop out for other reasons could be handled in a non-informative censoring approach. That may be something that could be handled in the statistical analysis plan. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION**: Discuss the proposed protocol for PMR 3033-11 (EERW). Include in your discussion the following:
    a. Is 42 to 52 weeks an adequate duration to assess the long-term effectiveness of opioids?

    Committee Discussion: *Several committee members agreed that 42 to 52 weeks is an adequate duration, but there was some concern that duration of taper may be too rapid, particularly for patients on higher doses of opioids. One member expressed that there should be consultation with addiction specialists and other experts who may be able to provide insight regarding whether that period is too brief. Some committee members expressed concerns that a longer follow-up period after the opioids are tapered off is needed to fully assess the patient, after all of the potential withdrawal symptoms have resolved. Please see the transcript for details of the Committee's discussion.*

    b. What degree of dropout is expected in a study in this patient population? Will enough patients be expected to complete this study in order for the results to be interpretable?

Committee Discussion: *Some committee members expressed that while there would be some dropout, with adequate enrollment, enough patients could get to the point of randomization. It was further commented that after randomization, the basis for dropout could inform the primary endpoint if it is because the patients are not doing well; and could be incorporated into the endpoint being assessed. Please see the transcript for details of the Committee's discussion.*

c. Is the time-to-treatment-failure endpoint informative? If yes, should use of rescue above a prespecified threshold be added as a treatment failure criterion? If no, why not?

Committee Discussion: *The committee members generally agreed the time-to-treatment-failure endpoint is a reasonable analytic approach, although not a particularly intuitive one. One member suggested methods to preserve the power for time-to-event analysis. Some committee members agreed it is important to present the results in a way that is more clinically meaningful and more intuitive. Other members mentioned that the use of rescue above a pre-specified threshold should be part of the treatment failure criterion because we are trying to capture whether chronic opioid therapy confers benefit in this population of responders. Please see the transcript for details of the Committee's discussion.*

d. Given that the pain scores could be variable, are there measures that could be employed to assure that the threshold for increase in pain is clinically meaningful and does not represent short-term variability?

Committee Discussion: *Several committee members raised concerns about the 7-day period being too brief since it may only reflect variability associated with life events and not changes associated with treatment. Committee members further mentioned the desire to incorporate functional measures in addition to disease-specific measures for patients. Please see the transcript for details of the Committee's discussion.*

e. Does the proposed tapering scheme adequately mitigate concerns about unblinding?

Committee Discussion: *It was noted that this question was addressed in earlier discussion and that it was a general agreement that the proposed tapering scheme does adequately mitigate concerns about unblinding. One committee member recommended that when the study has ended to not only send information to the health care practitioners, but also inform the patients of what worked or did not work. Please see the transcript for details of the Committee's discussion.*

f. Is the proposed definition of opioid-induced hyperalgesia (OIH) and surveillance for development of the condition appropriate?

Committee Discussion: *Most committee members agreed that the definition of opioid-induced hyperalgesia (OIH) was appropriate. One member expressed that the definition is vague as there is overlap with different pain conditions and expressed concern of how, for example, withdrawal effects vs. fibromyalgia and other variables would be differentiated. Most committee members agreed that surveillance timepoints are appropriate as well. Please see the transcript for details of the Committee's discussion.*

g. To better characterize, OIH, should patients diagnosed with OIH undergo a diagnostic/therapeutic opioid taper?

Committee Discussion: *Many of committee members mentioned they were comfortable with OIH. The committee members further commented that patients should undergo a diagnostic or therapeutic opioid taper when diagnosed with this condition, which is in alignment with the protocol. Please see the transcript for details of the Committee's discussion.*

h. Is the design fit-for-purpose to appropriately answer the question as to whether patients who appear to be responders to (and tolerating) opioids are really benefitting over 52 weeks, or do you think that the confounders we heard about will make the results not interpretable?

Committee Discussion: *The committee members expressed concern about the pace of the taper and whether blinding could be maintained. One member mentioned that one main concern of the proposed design is the underestimation of the potential risks and further, another member noted that they would have preferred to see a risk-benefit analysis of long-term opioids assessing other risks such as dependency, tolerance, CNS, and gastrointestinal risks; not just OIH. Another committee member noted that while internal validity would be strong, there are issues with external validity for generalizability because of difficulty in interpretation of the data, which may not provide clinically relevant information. Several members agreed that the design is fit-for-purpose, though acknowledging that the trial is addressing a very narrow question for a narrow patient population, which may not be extrapolated to chronic pain in general. One committee member mentioned that the EERW design only assesses whether opioids are effective for the treatment of chronic pain and tolerated for the first 42 weeks, and for those patients for whom it was effective and tolerable, what happens when you taper that. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION**: Discuss other designs that should be considered in the assessment of long-term effectiveness of opioids.

Committee Discussion*: The committee members expressed interest in approaches that compared opioids to either pharmacologic or nonpharmacologic opioid alternatives, recognizing the limitations associated with some of those designs. The committee members*

acknowledged that randomizing a patient to placebo vs. an opioid will be challenging. The committee members were in favor of innovative approaches to randomization including sequential randomization, or other innovative approaches to address questions in a way that would make it possible to recruit and retain patients in the trial. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:36 p.m. ET.