Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 11, 2018

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 210730, for oliceridine 1 milligram/milliliter injection, submitted by Trevena, Inc., for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted. The committee discussed the efficacy and safety data and benefit-risk considerations.

These summary minutes for the October 11, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration were approved on December 7, 2018.

I certify that I attended the October 11, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Moon Hee V. Choi, PharmD
Designated Federal Officer, AADPAC

/s/
Kevin Zacharoff, MD, FACIP, FACPE, FAAP
Acting Chairperson, AADPAC

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 11, 2018

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 11, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Trevena Inc. The meeting was called to order by Kevin Zacharoff, MD, FACIP, FACPE, FAAP (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 95 people in attendance. There were 11 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 new drug application (NDA) 210730, for oliceridine 1 milligram/milliliter injection, submitted by Trevena, Inc., for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted. The committee discussed the efficacy and safety data and benefit-risk considerations.

Attendance:
Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Ronald S. Litman, DO, ML; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP (Acting Chairperson); Lonnie Zeltzer, MD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP;

Temporary Members (Voting): John H. Alexander, MD, MHS; Michael Fischer, MD, MS; Jennifer Higgins, PhD (Acting Consumer Representative); Alan Kaye, MD, PhD; Joseph P. O'Brien, MBA (Patient Representative); Marjorie Shaw Phillips, MS, RPh, FASHP, CIP; Steven Solga, MD; Gregory Terman, MD, PhD; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

FDA Participants (Non-Voting): Mary Thanh Hai, MD; Sharon Hertz, MD; Janet Maynard, MD, MHS; Elizabeth Kilgore, MD, MS; David Petullo, MS

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Joseph Answine, MD; Suzanne Griffith, BSN, RN, BBA; Robert Lapidus; Tina Quinn; Tim Beard, MD, FACS; Julie Thornton; Sergio D. Bergese, MD;

Deborah Wagner, PharmD; Savannah Schwerin, BSN, RN; Stephanie Fox-Rawlings, PhD (National Center for Health Research); John V. LeVon, PharmD, PMP, MBA

The agenda was as follows:

Call to Order and Introduction of Committee	**Kevin Zacharoff, MD, FACIP, FACPE, FAAP** Acting Chairperson, AADPAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, AADPAC
FDA Opening Remarks	**Sharon Hertz, MD** Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Trevena, Inc.**
Introduction	**Maxine Gowen, PhD** Founding President and CEO Trevena, Inc.
Efficacy and Safety	**Mark Demitrack, MD** Chief Medical Officer Trevena, Inc.
Special Safety Topics Clinical Interpretation of Hepatic Findings	**Paul Watkins, MD** Professor of Medicine, Toxicology, and Experimental Therapeutics University of North Carolina, Chapel Hill
Special Safety Topics Cardiac Safety	**Robert B Kleiman, MD** Chief Medical Officer Vice President Global Cardiology ERT
Opioid-Related Adverse Events	**Jonathan Violin, PhD** Co-Founder and Senior Vice President of Scientific Affairs Trevena, Inc.
Clinical Perspective	**Gregory Hammer, MD** Professor of Anesthesiology, Pediatric Perioperative and Pain, and Pediatrics Critical Care Stanford University Medical Center

Clarifying Questions

BREAK

FDA PRESENTATIONS

Introduction and Overview	**Elizabeth Kilgore, MD, MS** Medical Officer DAAAP, ODE-II, OND, CDER, FDA
Abuse Potential of Oliceridine	**Katherine Bonson, PhD** Pharmacologist Controlled Substance Staff (CSS) Office of the Center Director (OCD), CDER, FDA
Review of Efficacy	**James Travis, PhD** Statistical Reviewer Division of Biometrics II Office of Biostatistics Office of Translational Sciences (OTS) CDER, FDA
Safety Assessment and Benefit/Risk Considerations	**Elizabeth Kilgore, MD, MS**
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Sharon Hertz, MD**
Questions to the Committee/ Committee Discussion	

BREAK

Questions to the Committee/
Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy of oliceridine and whether the data provide substantial evidence for efficacy of oliceridine for the proposed indication of the management of acute moderate-to-severe pain in adults for whom an intravenous opioid is warranted.

   Committee Discussion*: Overall, the committee was in agreement that oliceridine showed efficacy compared to placebo in relatively healthy individuals. However, the committee members also agreed that the controlled Phase 3 post-operative study populations were not indicative of complex populations that may have multiple drug interactions and comorbidities, and therefore agreed that the efficacy of oliceridine is not clear compared to an active comparator. Several committee members expressed concern that the dosing recommendations are unclear and there was agreement that there would be challenges treating patients with different conditions and with dose titration in real- world situations. Some committee members stated that there was not substantial evidence of the efficacy of the 0.1 mg dose based on the data presented. Other committee members noted their appreciation of the rapid onset of efficacy. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss the safety profile of oliceridine and whether the safety profile of oliceridine is adequate to support approval of oliceridine for the proposed indication of the management of moderate-to-severe acute pain in adults for whom an intravenous opioid is warranted. Provide comment on the following issues:

   a. Safety database
   b. Hepatic safety
   c. Respiratory safety
   d. QT prolongation

   Committee Discussion*: The committee's general consensus was that oliceridine is relatively safe overall. Some committee members noted that the agonist-bias that was displayed appeared to have potential benefits, as providers are looking for new ways to find a tailored approach to treatment of acute pain. Several members of the committee expressed concerns of possible safety signals that could arise with higher doses, comorbid conditions, multimodal therapy, and use of concomitant medications, including other opioids, in real- world situations. One committee member noted that the decreased incidence of vomiting compared to morphine was notable. In regards to hepatic safety, overall, the committee was in agreement that there wasn't much concern for a hepatic safety signal. In terms of respiratory safety, some committee members made note that the hypercapnic testing that was performed in young healthy volunteers does not indicate a lower risk of respiratory depression compared to morphine. One member noted the decreased β-arrestin activation shown in animal models is suggestive of decreased respiratory depression, but other members noted limitations in the available clinical data. Some committee members noted there was insufficient data on QT prolongation and agreed more ECG data were needed. Other committee members agreed that real world*

implications were unclear, as there was a disconnect between pharmacokinetic and QT effects. One committee member added that although there were modest effects on QT prolongation used in the thorough QT study, the effects of the 40 mg per day in the proposed labeling is unknown. Several committee members expressed concerns regarding the available safety database that doesn't appear to represent what will be used in terms of doses in practice or the types of patients who are anticipated to receive the drug. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Considering the abuse potential of oliceridine, and its proposed use for acute pain in adults for whom an intravenous opioid is warranted, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

   ***Committee Discussion**: Overall, the committee found no superiority for abuse deterrence and considered Schedule II appropriate for oliceridine. Some committee members agreed that people may presume that oliceridine is a safer medication, which may increase its abuse potential. One committee member added that healthcare professionals managing patients with opioid use disorders may improperly perceive oliceridine as safer, which could limit vigilance and amplify public health concern. Another committee member added that abuse of oliceridine may lead to unforeseen adverse effects with respiratory depression, hepatic pathology, and QT prolongation. Please see the transcript for details of the committee discussion.*

4. **VOTE:** Do you recommend approval of the proposed dose of oliceridine for the proposed indication of the management of moderate- to-severe acute pain in adults for whom an intravenous opioid is warranted. If not, what data are needed?

   Vote Result: Yes: 7 No: 8 Abstain: 0

   ***Committee Discussion**: The committee did not reach a general consensus on the approval of the proposed dose of oliceridine for the proposed indication of the management of moderate- to-severe acute pain in adults for whom an intravenous opioid is warranted. Committee members who voted "Yes" recommended inclusion of "not safer than traditional opioids" on the label and that further studies be required. Considerations in favor of recommending approval included a potentially favorable PK data, no active metabolites, decreased β-arrestin activation, and positive GI profile with decreased nausea and vomiting. Committee members who voted "No" stated that the benefit/risk profile was not favorable enough, with a need for more data regarding demographic variability, including patients with comorbidities, drug interactions, and real-world dosing. Some members voiced concerns that the perception of oliceridine being safer may lead to increased abuse and downstream problems. Several committee members discussed the need for additional data. One member suggested a study showing decrease in length of hospital stay (time to discharge) as possible compelling data for approval. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:54 p.m.