Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

June 28, 2023

Location: All meeting participants will be joining this advisory committee meeting via an online teleconferencing platform.

Topic: The Committee discussed new drug application (NDA) 215559, for palovarotene capsules, submitted by Ipsen Biopharmaceuticals, Inc. The proposed indication is the prevention of heterotopic ossification in adults and children (females aged 8 years and above and males 10 years and above) with fibrodysplasia ossificans progressiva.

These summary minutes for June 28, 2023 of the Endocrinologic and Metabolic Drugs Advisory Committee meeting of the Food and Drug Administration were approved on August 10, 2023.

I certify that I attended the June 28, 2023 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/
Cecilia C. Low Wang, MD
Chairperson, EMDAC

Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
June 28, 2023

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on June 28, 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 Ipsen Biopharmaceuticals, Inc. The meeting was called to order by Cecilia Low Wang, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 2891 people online. There was a total of 17 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 will discuss new drug application (NDA) 215559, for palovarotene capsules, submitted by Ipsen Biopharmaceuticals, Inc. The proposed indication is the prevention of heterotopic ossification in adults and children (females aged 8 years and above and males 10 years and above) with fibrodysplasia ossificans progressiva.

Attendance:

EMDAC Members Present (Voting): Cecilia C. Low Wang, MD *(Chairperson);* Elizabeth Chrischilles, PhD, MS; Robert Alan Greevy, Jr., PhD; Thomas Wang, MD; and Jack A. Yanovski, MD, PhD

EMDAC Members Not Present (Voting): Matthew T. Drake MD, PhD; Rita Kalyani, MD, MHS; and Connie Newman, MD

EMDAC Member Present (Non-Voting): Gary Meininger, MD (*Industry Representative*)

Temporary Members (Voting): Kimberly E. Applegate, MD, MS; Marat Chaikhoutdinov, MD (*Patient Representative*); Christopher S. Coffey, PhD; Tobias Gerhard, BS Pharm, PhD; Elizabeth Jones, MD, MPH, MBA; Martha Nason, PhD; Suzanne B. Robotti (*Acting Consumer Representative);* and Thomas J. Weber, MD

FDA Participants (Non-Voting): Lisa Yanoff, MD; Theresa Kehoe, MD; Noreen Cabellon, MS; Alexander Cambon, MD; David Carlson, PhD; Po-Yin Chang, PhD; Lydia Haile, PhD; Wei Hua, PhD; Feng Li, PhD; Li Li, PhD; Yandong Qiang, MD, PhD; Mark Rothmann MD; Shannon Sullivan, MD, PhD; Stephen Voss, MD; and Xiaomeng Xu, PhD.

Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers Present: Megan Olsen; Miriam Rocke; Hope Newport on behalf of Ashley Martucci; Margo Black, RN; Clive Friedman, MD; Erin Danzer; Joseph Suchanek; Karen Kirchhoff, MSPT; Alexis Gonzales; Steve Eichner; Suzanne Hollywood; Charles Levy, MD; Michelle Davis; Rebecca Wallace on behalf of Candace Hixson; Hope Newport on behalf of Suzanne McCloskey; Hope Newport on behalf of Ellen R Elias, MD; and Diana Zuckerman (*National Center for Health Research*).

The agenda was as follows:

Call to Order	**Cecilia Low Wang, MD** Chairperson, EMDAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, PharmD** Designated Federal Officer, EMDAC
FDA Opening Remarks	**Theresa Kehoe, MD** Director Division of General Endocrinology (DGE) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Ipsen Biopharmaceuticals, Inc.**
Introduction	**Howard Mayer, MD** Executive Vice President, Head of Research and Development Ipsen Biopharmaceuticals, Inc.
Unmet Need in Fibrodysplasia Ossificans Progressiva (FOP)	**Matthew Brown, MBBS, MD, FRACP, FAA** Professor of Medicine, King's College London Chief Scientific Officer, Genomics England
Efficacy	**Rose Marino, MD** Vice President, Clinical Development Rare Disease Ipsen Biopharmaceuticals, Inc.
Safety and Risk Management Activities	**Jennifer Schranz, MD** Senior Vice President, Global Head Rare Disease Ipsen Biopharmaceuticals, Inc.
Clinical Perspective	**Edward Hsiao, MD, PhD** Professor of Medicine Division of Endocrinology and Metabolism University of California, San Francisco

Clarifying Questions for Sponsor	
BREAK	
FDA PRESENTATIONS	
Overview of Clinical Studies	**Stephen Voss, MD** Clinical Reviewer DGE, OCHEN, OND, CDER, FDA
Statistical Review	**Alexander Cambon, PhD** Statistical Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Overview of Safety	**Stephen Voss, MD**
Clarifying Questions for FDA	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Discuss the evidence of effectiveness for palovarotene in study 301. In your discussion, consider the following:

    a. The use of post hoc analyses to support a demonstration of efficacy

    b. The interpretability of the results using the external control (Natural History Study)

Committee Discussion*: The Committee provided a wide range of input regarding the evidence of effectiveness of palovarotene in study 301. Overall, the members agreed that the pre-specified analyses were flawed and acknowledged the limitations of post-hoc analyses, especially given that they were conducted after unblinding of data. Some of the members*

added that the probability of type I error (false positives) was unknown despite the post-hoc analyses results being statistically significant. Regarding the use of the Natural History Study (NHS) as a control, the members expressed concerns about the differences between the treatment group in Study 301 and the external control, especially those related to age and levels of heterotopic ossification (HO). One member added that the primary reason that post hoc analyses were needed was because the external NHS control and treatment group did not follow the same timing schedule. Another member also expressed their concern with bias being introduced when patients dropped out of the external NHS control to join the Study 301 treatment group. A member added that placebo control trials are possible even for rare diseases such as FOP and should have been conducted as recommended by the FDA. Other members stated that, despite these limitations, the use of post-hoc analyses and external NHS control may have been appropriate given the rarity and the challenges of the disease. These members were reassured by the consistently positive results across the Sponsor's different post hoc analyses as well as the FDA's independent analyses that demonstrated similar findings. On the other hand, other members expressed concerns with the wide confidence intervals and use of whole-body CT scans and HO volume as a surrogate endpoint for functional status. These members argued that the total treatment effect size (e.g. new HO volume mm/year) is less clinically significant than the location of the HO progression, which impacts quality of life (QOL). Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss your view of the flare-up events in subjects treated with the proposed palovarotene dosing regimen and the relevance to benefit-risk considerations. Also comment on whether you have concerns about other safety issues included in the meeting materials and slide presentations or discussed today.

   ***Committee Discussion**: In their discussion of the flare-up events in subjects treated with the proposed dosing regimen and benefit-risk, the Committee highlighted the lack of correlation between flare-ups and HO development. One member hypothesized that the higher number of flare-up events could have stemmed from undercounting in the external NHS control which were monitored every 12 months vs. Study 301 treatment group, which were monitored every 6 months. Another member hypothesized that these flareup events could be a side effect of the palovarotene, which is a retinoid agonist. Overall, the majority of the members agreed that the flareup events were less concerning than other observed safety issues such as premature epiphyseal closure (PCC) in patients under 14 years of age as well as reduced vertebral bone mineral density and subsequent vertebral fractures. Some of the members expressed their concern with aggressive therapy, especially in pediatric population, given the additional safety issues. Members were also concerned with potential rebound HO development during palovarotene treatment interruption. One member highlighted that the mean annualized rate of new HO volume per year was observed to be slightly higher in the Study 301 treatment group during treatment interruption in comparison to the untreated NHS control group. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Does the evidence from Study 301 of palovarotene's treatment effect show the drug is effective in patients with fibrodysplasia ossificans progressiva (FOP)?

   a. Provide the rationale for your vote.

Vote Result: Yes: 10 No: 4 Abstain: 0

Committee Discussion: *The majority of the Committee (10 members) voted "Yes" that the evidence from Study 301 shows palovarotene is effective in patients with FOP. These members stated that, although palovarotene failed to meet its primary endpoint, the post hoc analyses and external control study were consistent and supported evidence of disease management in the treated population. The four members who voted "No" cited insufficient evidence, no symptomatic improvement, statistical design flaws, and inappropriate post-hoc analyses. These members recommended that additional studies be conducted to measure endpoints related to patient function and quality of life. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Do the benefits of palovarotene outweigh its risks for the treatment of patients with FOP?

    a. If you voted yes, provide the rationale for your vote.

    b. If you voted no, provide the rationale for your vote, and provide recommendations for additional data that may support a conclusion that the benefits outweigh the risks.

Vote Result: Yes: 11 No: 3 Abstain: 0

Committee Discussion: *The majority of the Committee (11 members) voted "Yes" that the benefits of palovarotene outweigh its risks for the treatment of patients diagnosed with FOP. These members highlighted the rarity and severe nature of FOP as well as the lack of current treatment alternatives. They added that the risk of delaying treatment, with the drug, in favor of gathering more conclusive evidence is outweighed by the need for palovarotene. The members who voted "Yes", acknowledged that the effectiveness shown by palovarotene was small, but emphasized that these benefits can positively impact the QOL of those affected by this debilitating disorder. They recommended that patient selection criteria be carefully specified to mitigate palovarotene's safety risks, and clear and comprehensive patient/family-provider discussion occur to ensure risks are communicated. They also recommended monitoring bone mineral density in patients, screening for premature epiphyseal closure in pediatric patients, and creation of a patient registry to better understand the patient population and HO volumes. One member suggested additional consideration of alternative imaging modalities to assess disease status and progression. The three members who voted "No" stated that study 301 did not provide enough evidence of effectiveness in patients with FOP. They recommended that the Applicant conduct additional studies to better characterize what specific patient population (e.g., severity of disease and age) might benefit most from palovarotene. One member suggested a study design with a placebo-controlled withdrawal phase. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:24 p.m. ET.