Food and Drug Administration
Center for Drug Evaluation and Research
Final Summary Minutes of the Genetic Metabolic Diseases Advisory Committee (GeMDAC) Meeting
August 2, 2024

Location: FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

Topic: The Committee discussed new drug application 214927, for arimoclomol, submitted by Zevra Denmark A/S, for the treatment of adults and pediatric patients 2 years of age and older with Niemann-Pick disease type C.

These summary minutes for the August 2, 2024 meeting of the Genetic Metabolic Diseases Advisory Committee of the Food and Drug Administration were approved on September 10, 2024.

I certify that I attended the August 2, 2024 meeting of the Genetic Metabolic Diseases Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Robert Alexander, MD
Designated Federal Officer, GeMDAC	Chairperson, GeMDAC

Final Summary Minutes of the Genetic Metabolic Diseases Advisory Committee Meeting
August 2, 2024

The Genetic Metabolic Diseases Advisory Committee (GeMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on August 2, 2024. FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Zevra Denmark A/S. The meeting was called to order by Robert Alexander, MD (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 70 people in attendance in-person and approximately 697 people online. There were 15 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 214927, for arimoclomol, submitted by Zevra Denmark A/S, for the treatment of adults and pediatric patients 2 years of age and older with Niemann-Pick disease type C.

Attendance:

Genetic Metabolic Diseases Advisory Committee Members Present (Voting): Gerard T. Berry, MD; Sarah Chamberlin *(Consumer Representative)*; Wendy K. Chung, MD, PhD; Priya S. Kishnani, MD *(via video conferencing platform)*; Jonathan W. Mink, MD PhD

Genetic Metabolic Diseases Advisory Committee Members Not Present (Voting): None

Genetic Metabolic Diseases Advisory Committee Member Present (Non-Voting): Bradley J. Glasscock, PharmD *(Industry Representative)*

Temporary Members (Voting): Robert C. Alexander, MD *(Acting Chairperson)*; Kiera N. Berggren, MA/CCC-SLP, MS; Cheryl D. Coon, PhD; Susan S. Ellenberg, PhD; Kenneth Fischbeck, MD; Elizabeth Heinze *(Patient Representative);* Walter K. Kraft, MD; Richard J. Kryscio, PhD; Jean Baptiste Le Pichon MD, PhD, FAAP; Andrew Lieberman, MD, PhD; Carole A. Tucker, PhD

FDA Participants (Non-Voting): Patrizia Cavazzoni, MD; Peter Stein, MD; Janet Maynard, MD, MHS *(via video conferencing platform)*; Catherine Pilgrim-Grayson, MD, MPH; Naomi Knoble, PhD; Maura RZ Ruzhnikov, MD, FACMG; Shawna L. Weis, PhD; Wonyul Lee, PhD; Sydney Stern, PhD

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

Open Public Hearing Speakers: Elizabeth Berry-Kravis MD, PhD *(via video conferencing platform)*; Krystal Samuelson; Alexander Kray *(via video conferencing platform)*; David Sellers; Cara Gilmore *(via video conferencing platform)*; Barbara Lazarus; Raymond Wang *(via video conferencing platform)*, MD; Saikat Santra (Birmingham Women's and Children's NHS Foundation Trust) *(via video conferencing platform)*; Anna and Sanjay Kambhatla *(via video conferencing platform)*; Dawn Stites; Amanda Wallace *(via video conferencing platform)*; Justin Hopkin, MD and Joslyn Crowe (National Niemann Pick Disease Foundation); Garland Alvey (AbbyStrong Fights NPC); Toni Mathieson (Niemann-Pick UK) *(via video conferencing platform)*; Caitlin Hahn *(via video conferencing platform)*

The agenda was as follows:

Call to Order and Introduction of Committee	**Robert Alexander, MD** Acting Chairperson, GeMDAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, GeMDAC
FDA Initial Remarks	**Patrizia Cavazzoni, MD** Director CDER, FDA
FDA Opening Remarks	**Catherine Pilgrim-Grayson, MD, MPH** Acting Director Division of Rare Diseases and Medical Genetics (DRDMG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Zevra Therapeutics**
Introduction	**Louise Himmelstrup** Vice President (VP), Regulatory Affairs Zevra Therapeutics
Clinical Background on Niemann-Pick Type C	**Marc Patterson, MD** Professor of Neurology, Pediatrics and Medical Genetics Emeritus Chair Division of Child and Adolescent Neurology Mayo Clinic, Rochester, MN
Pivotal Efficacy	**Dan Gallo, PhD** Senior VP, Medical Affairs and Advocacy Zevra Therapeutics

APPLICANT PRESENTATIONS (CONT.)

Confirmatory Evidence of Effectiveness	**Travis Mickle, PhD** Co-Founder, Senior Advisor Zevra Therapeutic
Safety	**Christine í Dali, MD** VP, Group Clinical Science Zevra Therapeutics
Clinical Perspective	**Kristina Julich, MD** Assistant Professor Department of Neurology Chief, Pediatric Neurogenetics Center University of Texas at Austin

Clarifying Questions to the Applicant

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FDA PRESENTATIONS

Overview of the Clinical Program	**Maura RZ Ruzhnikov, MD, FACMG** Clinical Reviewer DRDMG, ORPURM, OND, CDER, FDA
Primary Efficacy Results in Pivotal Trial	**Wonyul Lee, PhD** Senior Staff Fellow Division of Biometrics IV Office of Biostatistics Office of Translational Sciences (OTS) CDER, FDA
NPCCSS: Measurement Considerations	**Naomi Knoble, PhD** Associate Director Division of Clinical Outcome Assessment Office of Drug Evaluation Sciences OND, CDER, FDA
Additional Data: Nonclinical	**Shawna L. Weis, PhD** Lead Pharmacologist (Acting) Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine ORPURM, OND, CDER, FDA

FDA PRESENTATIONS (CONT.)

Additional Data: Clinical Pharmacology	**Sydney Stern, PhD** Pharmacokineticist Division of Translational and Precision Medicine Office of Clinical Pharmacology OTS, CDER, FDA
Additional Clinical Data and Summary	**Maura RZ Ruzhnikov, MD, FACMG**
Clarifying Questions to the FDA	

BREAK

OPEN PUBLIC HEARING

Charge to the Committee	**Catherine Pilgrim-Grayson, MD, MPH**
Questions to the Committee/Committee Discussion	

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss your assessment of the efficacy results of trial CT-ORZY-NPC-002 (NPC-002). In your discussion, please comment on:

    a. The 5-domain Niemann-Pick disease type C Clinical Severity Scale (5DNPCCSS) and the rescored 4-domain Niemann-Pick disease type C Clinical Severity Scale (R4DNPCCSS).

    Committee Discussion*: The general consensus on the Committee's assessment of the efficacy results of trial CT-ORZY-NPC-002 in regard to the 5DNPCCSS and the R4DNPCCSS was that both scales could be improved, adding that although imperfect, probably they are adequate to the task of measuring improvement in the trial. Please see the transcript for details of the Committee's discussion.*

    b. Your assessment of whether the trial results demonstrate a treatment effect of arimoclomol on the treatment of Niemann-Pick disease type C (NPC).

    Committee Discussion*: The consensus of the Committee members was that the study showed a treatment effect. There were differences of opinion on the importance and reliability of the treatment effect given that it was a small study with a lot of*

variability. The treatment effect was described as small or really small. Some Committee members commented that the improvements observed in a number of patients may seem small; however, given the number of patients enrolled in a rare disease trial, the trial results suggested a treatment effect of arimoclomol. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss your assessment of other data (specifically the additional clinical and nonclinical data) with respect to support for the effectiveness of arimoclomol.

   ***Committee Discussion**: Overall, the Committee members agreed the additional clinical data was consistent with the data from the trial. For the non-clinical data, the Committee members expressed concerns with the apparent lack of randomization and blinding, and the lack of pharmacokinetic (PK) data, given that the drug was administered in the drinking water, and agreed the data did not support treatment effectiveness. One committee member noted the mice studies may have been more compelling if treatment was initiated after disease manifestation. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do the results of trial NPC-002 in concert with the other data (clinical and nonclinical in particular) support a conclusion that arimoclomol is effective in the treatment of patients with NPC? Provide a rationale for your vote.

   Vote Result: Yes: 11 No: 5 Abstain: 0

   a. If you voted no, provide recommendations for additional data that may support a conclusion that arimoclomol is effective.

   ***Committee Discussion**: The majority of the Committee members agreed that the results of trial NPC-002 in concert with the other clinical data support a conclusion that arimoclomol is effective in the treatment of patients with NPC. These Committee members noted: 1) there was a clinical unmet need; 2) arimoclomol displayed a good safety profile; and 3) there was consistency in the clinical efficacy data. The Committee members who voted "No" noted, both the clinical and nonclinical data had problems and did not meet evidentiary standards for approval. These Committee members provided the following recommendations for additional data that may support a conclusion that arimoclomol is effective: 1) an additional study with a prospective statistical analysis plan and 2) additional animal studies and studies on the mechanism of action. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:59 p.m.