Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Meeting of the Cardiovascular and Renal Drugs Advisory Committee

October 10, 2024

Location: The FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993-0002. The public also had the option to participate 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 (NDA) 215244, for elamipretide hydrochloride injection, submitted by Stealth BioTherapeutics Inc., for the treatment of Barth Syndrome.

These summary minutes for the October 10, 2024 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on

_March 9, 2025_____.

I certify that I attended the October 10, 2024 meeting of the Cardiovascular and Renal Drugs Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_/s/_	/s/_
LaToya Bonner, PharmD	Javed Butler, MD, MPH, MBA
Designated Federal Officer, CRDAC	Chairperson, CRDAC

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
October 10, 2024

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 10, 2024, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate 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 Stealth BioTherapeutics, Inc. The meeting was called to order by Javed Butler, MD, MPH, MBA (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 140 people in attendance in-person and approximately 397 people online. There were 15 Open Public Hearing (OPH) speaker presentations.

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

Agenda:

The Committee discussed new drug application (NDA) 215244, for elamipretide hydrochloride injection, submitted by Stealth BioTherapeutics Inc., for the treatment of Barth Syndrome.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): Javed Butler, MD, MPH, MBA (*Chairperson)*; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA; Eric Peterson, MD, MPH

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting): Csaba P. Kovesdy, Md, FASN; Prabir Roy-Chaudhury, MD, PhD, FRCP.

Cardiovascular and Renal Drugs Advisory Committee Member Present (Non-Voting): Narimon Honarpour, MD, PhD *(Industry Representative)*

Temporary Members (Voting): G. Caleb Alexander, MD, MS; Gerard T. Berry, MD; Mathew Clark, MD *(Patient Representative)*; Susan S. Ellenberg, PhD; Tobias Gerhard, BSPharm, PhD (*via video conferencing platform*); Jonathan J. Johnson, MD; Michele Jonsson Funk, PhD (*via video conferencing platform);* Priya Kishnani, MD *(via video conferencing platform);* Jean Baptiste Le Pichon, Md, PhD, FAAP; Pamela Shaw, PhD, MS; Devin Shuman, MS, LCGC (*Acting Consumer Representative; via video conferencing platform)*; Jonathan Soslow, MD, MSCI; Carole A. Tucker, PhD.

FDA Participants (Non-Voting): Patrizia Cavazzoni, MD; Peter Stein, MD; Hylton Joffe, MD, MMSc; Charu Gandotra, MD; Ann Punnoose, MD; Steven Bai, PhD.

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

Open Public Hearing Speakers Present: Valerie Bowen (Barth Syndrome Foundation); Lewis Walker Burger; Jamie N. Dubuque; Ibrahim Elsharkwai, MD; Brian Feingold, MD *(via video conferencing platform)*; Amy Goldstein, MD *(via video conferencing platform);* Amie Hall; Nancy Halnon, MD; Ben Holly *(via video conferencing platform)*; Jordan Karle; Benjamin Allen Mann; Jay Randell, DMD; Stacey Reynolds, PhD; Michelle Strawser; Jacob Wilson.

The agenda was as follows:

Call to Order and Introduction of Committee	**Javed Butler, MD, MPH, MBA** Chairperson, CRDAC
Conflict of Interest Statement	**LaToya Bonner, PharmD, MBA** Designated Federal Officer, CRDAC
FDA Introductory Remarks	**Hylton Joffe, MD, MMSc** Director Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Stealth BioTherapeutics Inc.**
Introduction	**Reenie McCarthy** Chief Executive Officer Stealth BioTherapeutics
Urgency of Unmet Need and Benefit:Risk Tolerance	**Kate McCurdy, MBA** Chair, Board of Directors Barth Syndrome Foundation
Disease and Natural History Cohort	**Hilary Vernon, MD, PhD** Professor of Medical Genetics Johns Hopkins University School of Medicine
Safety and Efficacy	**Jim Carr, PharmD** Chief Clinical Development Officer Stealth BioTherapeutics
Statistical Perspectives	**Janet Wittes, PhD** Wittes LLC
Expanded Access Program	**Kathryn Chatfield, MD, PhD** Associate Professor of Pediatrics-Cardiology Director, Cardiac Genetics Clinic Children's Hospital Colorado

Applicant Presentations (cont.)

Closing Remarks	**Reenie McCarthy**
Clarifying Questions to the Applicant	
BREAK	
FDA PRESENTATIONS	
Efficacy Assessment of Elamipretide for Barth Syndrome	**Ann Punnoose, MD** Clinical Reviewer Division of Cardiology and Nephrology OCHEN, OND, CDER, FDA **Steven Bai, PhD** Biometrics Reviewer Division of Biometrics II Office of Biostatistics Office of Translational Sciences CDER, FDA
Clarifying Questions to the FDA	
LUNCH	
OPEN PUBLIC HEARING	
Clarifying Questions to the Applicant and FDA	
Charge to the Committee	**Hylton Joffe, MD, MMSc**
Questions to the Committee/Committee Discussion	

Questions to the Committee:

1. **DISCUSSION:** Discuss whether SPIBA-201, Part 2 demonstrates that elamipretide is effective for the treatment of Barth syndrome (BTHS). Include in your discussion the interpretability of the single-arm, open label study design and the findings on:

    a. 6-minute walk distance
    b. Other functional outcomes: hand-held dynamometry, 5 times sit-stand-test, SWAY application balance.
    c. Echocardiography
    d. Patient reported outcomes (e.g., BTHS-Symptom Assessment total fatigue score, patient- and caregiver global impression scales)
    e. Monolysocardiolipin (MLCL) to tetralinoleoyl cardiolipin (CL) ratio (MLCL:CL ratio)

***Committee Discussion**: A few committee members noted that the increases in 6-minute walk distance (6MWD) appear large. However, stated concerns included challenges interpreting effort-dependent endpoints in the open-label extension study, uncertainty about how to reconcile the discrepancy between the findings in SPIBA-201 Part 1 and Part 2, and the differences in 6MWD between the screening and baseline (pre-dose Period 1 Part 1) measurements. Other comments noted that the echocardiographic data were difficult to interpret due to changes with body growth, lack of adequate understanding of the natural history of echocardiographic changes in Barth Syndrome, and no awareness of diseases where left ventricular dilatation is beneficial. There were also concerns with merging of the 2-dimensional and 3-dimensional echocardiographic data.*

Some committee members provided comments on SPIBA-001 in response to this question, including concerns with propensity scoring and residual confounding, that a subset of patients identified for the natural history control did not have available efficacy data, and lack of data on the MLCL:CL ratio in the natural history control.

Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss whether SPIBA-001 demonstrates that elamipretide is effective for the treatment of Barth syndrome. Include in your discussion the interpretability of the externally-controlled study design and the findings on:
    a. 6-minute walk distance
    b. Other functional outcomes: hand-held dynamometry, 5 times sit-stand-test, SWAY application balance.
    c. Echocardiography

***Committee Discussion**: Some Committee members noted findings that may be suggestive of a drug effect (e.g., an apparent sustained increase in 6MWD over time, an increase in 6MWD that appears larger than the placebo effect seen in SPIBA-201 Part 1, different endpoints moving in the same direction on forest plots), whereas others noted limitations of the externally-controlled study making interpretation difficult (e.g., effort-dependence of endpoints, variability in the 6MWD from one visit to the next, lack of follow-up for some patients, and issues with the imputation and propensity scoring). Some Committee members said a new randomized study, such as one using a withdrawal design should be considered, but others said there may be challenges with such a study (e.g., statistical powering in a rare disease, willingness of subjects to discontinue study drug, and risk of unblinding due to injection site reactions). See also the discussion related to SPIBA-001 under Discussion Question 1.*

Please see the transcript for details of the Committee's discussion.

3. **DISCUSSION:** Discuss the extent to which other data (e.g., nonclinical data or other clinical study results) support the effectiveness of elamipretide.

***Committee Discussion**: The Committee noted compelling anecdotal testimonies of patients and health care providers during the open public hearing, many of which involved very young patients. However, the Committee was left with uncertainty as to whether these reports reflect a drug effect given that very young patients can have a severe presentation and*

spontaneously recover and there is variability in the natural history of the disease. Other comments included the apparent discrepancy in results between the anecdotal reports and the randomized, controlled trial and whether the young patient population with a dramatic presentation is the more appropriate population to study in a trial rather than the stable older population enrolled in SPIBA-201 and SPIBA-001.

Please see the transcript for details of the Committee's discussion.

4. **VOTE:** Based on available evidence, do you conclude that elamipretide is effective for the treatment of Barth syndrome?

   Provide rationale for your vote.

   If you voted **yes**, specify the evidence of elamipretide's effectiveness.

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

Vote Result:	Yes: 10	No: 6	Abstain: 0

Committee Discussion: *Ten Committee members voted "Yes," and 6 voted "No." Reasons cited for the "Yes" votes included use of regulatory flexibility given the rare disease, anecdotal evidence from the open public hearing, and sizeable effect sizes that appear maintained over time. Other comments among the "Yes" votes noted that the decision was difficult, that there is significant uncertainty of the drug's effect, but it is not clear what can be done to resolve the uncertainty, and that it is not clear there is evidence from an adequate and well-controlled trial.*

Reasons cited for the "No" votes included that there are too many uncertainties even with regulatory flexibility, that the randomized, placebo controlled trial (SPIBA-201 Part 1) did not show a treatment effect and Part 2 and SPIBA-001 are not adequate for establishing effectiveness, that one cannot reliably rely upon anecdotal data, and that more systematic evidence should and could be generated.

Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:45 p.m. ET.