Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
September 13, 2023

Location: All meeting participants were heard, viewed, captioned, and recorded for this advisory committee meeting via an online teleconferencing and/or video conferencing platform.

Topic: The committee discussed supplemental new drug application (sNDA) 210922-s015, for ONPATTRO (patisiran) lipid complex for injection, submitted by Alnylam Pharmaceuticals, Inc., for the proposed treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults.

These summary minutes for the September 13, 2023 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on November 5, 2023.

I certify that I attended the September 13, 2023 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Frimpong, PharmD	Javed Butler, MD, MPH, MBA
Acting Designated Federal Officer, CRDAC	Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
September 13, 2023

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 13, 2023. 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 Alnylam Pharmaceuticals, 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 Joyce Frimpong, PharmD (Acting Designated Federal Officer). There were approximately 960 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 supplemental new drug application (sNDA) 210922-s015, for ONPATTRO (patisiran) lipid complex for injection, submitted by Alnylam Pharmaceuticals, Inc., for the proposed treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): C. Noel Bairey Merz, MD, MACC, FAHA, FESC; Javed Butler, MD, MPH, MBA (*Chairperson*); Edward K. Kasper, MD, FACC, FAHA; Csaba P. Kovesdy, MD, FASN; David Moliterno, MD; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA; Eric Peterson, MD, MPH; Prabir Roy-Chaudhury, MD, PhD, FRCP; Ravi I. Thadhani, MD, MPH

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting): Thomas D. Cook, PhD, MS, MA

Cardiovascular and Renal Drugs Advisory Committee Member Not Present (Non-Voting): Jerome Rossert, MD, PhD (*Industry Representative)*

Temporary Members (Voting): Rita L. Abernathy, M Arch, AIA Emeritus (*Patient Representative*); David Cella, PhD; Ashley Wilder Smith, PhD, MPH

Industry Representative to the Committee (Non-Voting): David G. Soergel, MD (*Industry Representative)*

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Norman Stockbridge, MD, PhD; Rosalyn Adigun, MD, PharmD

Acting Designated Federal Officer (Non-Voting): Joyce Frimpong, PharmD

Open Public Hearing Speakers: Muriel Finkel (Amyloidosis Support Groups Inc.); Deborah Boedicker (Mackenzie's Mission); Nitasha Sarswat, MD; Ozzie Gigli; Steve Marko; Rebecca Hung, MD; Robert Zimmermann; William Mayweather; Charlie Gerth; Cecelia Beckwith; Josie Cooper (Alliance for Patient Access); Sean Riley; Peter Mallon; David Wolinsky, MD; Isabelle Lousada (Amyloidosis Research Consortium)

The agenda was as follows:

Call to Order	**Javed Butler, MD, MPH, MBA** Chairperson, CRDAC
Introduction of Committee/ Conflict of Interest Statement	**Joyce Frimpong, PharmD** Acting Designated Federal Officer, CRDAC
FDA Opening Remarks	**Norman Stockbridge, MD, PhD** Director Division of Cardiology and Nephrology (DCN) Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Alnylam Pharmaceuticals, Inc.**
Introduction	**Pushkal P. Garg, MD** Chief Medical Officer Alnylam Pharmaceuticals
Unmet Need	**John Berk, MD** Professor of Medicine Clinical Director of Amyloidosis Center Boston University
Efficacy	**John Vest, MD** Senior Vice President, Clinical Research Alnylam Pharmaceuticals
Impact of Patisiran on Patient Health Status	**John Spertus, MD, MPH** Professor, Daniel J. Lauer / Missouri Endowed Chair in Metabolic and Vascular Disease Research University of Missouri-Kansas City
Safety	**Elena Yureneva, MD, MHA** Executive Director, Head of Medical Safety & Risk Management Alnylam Pharmaceuticals
Clinical Perspective	**Ronald Witteles, MD** Professor of Cardiovascular Medicine Co-Director, Stanford Amyloid Center Stanford University School of Medicine
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Patisiran for Transthyretin Amyloidosis (ATTR) Cardiomyopathy	**Rosalyn Adigun, MD, PharmD** Clinical Reviewer DCN, OCHEN, OND, CDER, FDA
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Norman Stockbridge, MD, PhD**
Questions to the Committee/Committee Discussion	

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION**: Discuss the magnitude and clinical meaningfulness of patisiran's treatment effect on 6-minute walk test.

   ***Committee Discussion*:** *Committee members discussed various viewpoints about the magnitude of the benefit that was seen and whether it was clinically meaningful. Some panel members commented that the treatment duration of the controlled trial was limited to 12 months and that a larger treatment effect may have been observed had the randomized period been longer. Some committee members noted that having a single standard for assessing clinical meaningfulness across the entire spectrum of disease severity was not appropriate, but rather benefit should be considered as a function of disease severity. One committee member commented on the overall literature about the 6-minute walk test, including the variations in what is considered a threshold for clinically meaningful improvement. The committee member suggested that instead of focusing on one specific number for a threshold for clinical benefit, the decision should be based on the totality of evidence, both for benefit and for risk. Please see the transcript for details of the Committee's discussion.*

2. **DISSCUSSION**: Discuss the magnitude and clinical meaningfulness of patisiran's treatment effect on the Kansas City Cardiomyopathy Questionnaire – Overall Summary Score.

***Committee Discussion*:** *Committee members noted that the results were difficult to interpret. Numerical differences were modest, and clinical significance was unclear. However, committee members also mentioned that the numerical differences were consistent with some of the other disease states where the Kansas City Cardiomyopathy Questionnaire was used. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss whether patisiran has other established clinical benefits for the treatment of transthyretin amyloidosis (ATTR) cardiomyopathy.

   ***Committee Discussion*:** *Many of the committee members agreed that it was difficult to assess whether other clinical benefits were established considering the small number of events. Some emphasized that the totality of evidence, biomarker and remodeling data trended favorably for patisiran. Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION:** Discuss whether there is a clinically meaningful benefit of patisiran in patients with ATTR cardiomyopathy who are also receiving tafamidis. Also discuss whether there is a patient population that would benefit from patisiran monotherapy without tafamidis, taking into account that tafamidis is approved for reducing cardiovascular mortality and cardiovascular-related hospitalization in ATTR cardiomyopathy

   ***Committee Discussion*:** *The majority of the committee agreed it was difficult to interpret the clinical results when patients randomized to patisiran were concomitantly treated with tafamidis. It was commented that by limiting the number of patients who can be on baseline tafamidis, it made it difficult to understand how the results would have been without a cap on tafamidis use and how to generalize the results to the clinical population. Committee members emphasized that certain patient populations, such as those with both ATTR-cardiomyopathy and polyneuropathy or those intolerant to tafamidis, may benefit from patisiran. Committee members also noted that the trial was not designed to resolve the question of whether a second agent should be given to patients who were progressing on tafamidis. Please see the transcript for details of the Committee's discussion.*

5. **DISCUSSION:** Discuss whether patisiran has safety issues of concern for the treatment of ATTR cardiomyopathy

   ***Committee Discussion*:** *Committee members generally agreed there were no major safety concerns. Please see the transcript for details of the Committee's discussion.*

6. **VOTE:** Do patisiran's benefits outweigh its risks for the treatment of ATTR cardiomyopathy?

   Provide rationale for your vote.

   If you voted yes, describe the patient population, the clinically meaningful benefit, and how the clinical meaningfulness was established.

   If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment of patisiran for the treatment of ATTR cardiomyopathy

   Vote Result: Yes: 9 No: 3 Abstain: 0

   Committee Discussion*: The panel members voting "Yes" generally noted that the vote was difficult and could not definitively conclude that the benefits were clinically meaningful, but considered the "light wind" for an effect in the context of no serious risks. One panel member also stated that their "Yes" vote was influenced by the rarity of ATTR-cardiomyopathy and its characterization as an unmet medical need despite tafamidis. The panel members voting "No" noted the small treatment effect and concluded that there was a lack of clinical meaningfulness. Many panel members commented that a longer-term study may have produced a more robust treatment effect. Capping the use of tafamidis influenced the no vote as the benefit was largely seen in patients not taking tafamidis. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:20 p.m.