Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
May 11, 2023

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 214697, for epinephrine nasal spray, submitted by ARS Pharmaceuticals Inc., for the proposed indication of emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kilograms.

These summary minutes for the May 11, 2023 meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration were approved on July 6, 2023.

I certify that I attended the May 11, 2023 meeting of the PADAC of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Takyiah Stevenson, PharmD	David H. Au, MD, MS
Designated Federal Officer, PADAC	Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
May 11, 2023

The Pulmonary-Allergy Drugs Advisory Committee, Center for Drug Evaluation and Research, met on May 11, 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 ARS Pharmaceuticals Inc. The meeting was called to order by David H. Au, MD, MS. The conflict-of-interest statement was read into the record by Takyiah Stevenson, PharmD (Designated Federal Officer). There were approximately 3499 people viewing the meeting. There was a total of 20 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) 214697, for epinephrine nasal spray, submitted by ARS Pharmaceuticals Inc., for the proposed indication of emergency treatment of allergic reactions (Type I) including anaphylaxis in adults and children ≥ 30 kilograms.

Attendance:

Pulmonary-Allergy Drugs Advisory Committee Members (Voting):
David H. Au, MD, MS (Chairperson); Leonard B. Bacharier, MD; Scott E. Evans, MD, FCCP, ATSF; Fernando Holguin, MD, MPH; John M. Kelso, MD; Janet S. Lee, MD, ATSF; Susanne May, PhD; James M. Tracy, DO

Pulmonary-Allergy Drugs Advisory Committee Member Not Present (Voting):
Emma H. D'Agostino, PhD; Brian T. Garibaldi, MD, PhD; Edwin H. Kim, MD, MS

Pulmonary-Allergy Advisory Committee Member (Non-Voting):
Dawn M. Carlson, MD, MPH (Industry Representative)

Temporary Members (Voting):
Maryann Amirshahi, PharmD, MD, MPH, PhD; Javed Butler, MD, MPH, MBA; Thomas Dowling, PharmD, PhD, FCCP; Mark S. Dykewicz, MD; Paul A. Greenberger, MD; Collin Hovinga, PharmD, MS, FCCP; Bridgette L. Jones, MD, MSc, FAAAAI, FAAP; Jennifer Le, PharmD, MAS; Lewis S. Nelson, MD, MBA; Michael R. Nelson, MD, PhD; David B. Peden, MD, MS, FAAAAI; Karen Schell DHSc, RRT, RRT-RPFT, RRT-SDS, RPSGT, AE-C, CTTS (Acting Consumer Representative); Jennifer Schwartzott, MS (Patient Representative); James Troendle, PhD

FDA Participants (Non-Voting):
Sally Seymour, MD; Kelly Stone, MD, PhD; Jennifer Lan, MD; Miya Paterniti, MD; Yunzhao Ren, MD, PhD; Qianni Wu, PharmD

Designated Federal Officer (Non-Voting): Takyiah Stevenson, PharmD

Open Public Hearing Speakers Present:
Mark Lepore, MD, FAAAAI; Christine Creter; Thomas O'Rourke; Amanda Bee; Lianne Mandelbaum (No Nut Traveler, Inc.); Anne Ellis, MD MSc FRCPC; Nancy DeMore, MD, FACS; Stacey Saiontz and Jared Saiontz; Elani Wiest, PhD; Rachel Richardson; Sung Poblete, PhD, RN (Food Allergy Research & Education); Charmayne Anderson (Allergy & Asthma Network); Kelly Cleary; Priscilla Hernandez and Zacky Muñoz; Ashley Koranteng; Melanie Carver (Asthma and Allergy Foundation of America); Michelle Cades; Talia Day and Zachary Day; Dana Wallace, MD; Ruchi Gupta, MD, MPH

The agenda was as follows:

Call to Order	**David Au, MD, MS** Chairperson, PADAC
Introduction of Committee and Conflict of Interest Statement	**Takyiah Stevenson, PharmD** Designated Federal Officer, PADAC
FDA Introductory Remarks	**Miya Paterniti, MD** Clinical Team Leader Division of Pulmonology, Allergy, and Critical Care (DPACC) Office of Immunology and Inflammation (OII) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**ARS Pharmaceuticals Inc.**
Introduction	**Richard Lowenthal, MSc, MSEL** CEO, President and Co-Founder ARS Pharmaceuticals Inc.
Unmet Need in Use of Epinephrine	**Thomas Casale, MD** Professor of Medicine and Pediatrics Director, Division of Allergy & Immunology University of South Florida
neffy Development Rationale: Pharmacokinetic (PK), Pharmacodynamic (PD) and Safety Data	**Sarina Tanimoto, MD, PhD** ARS Pharmaceuticals Inc. Chief Medical Officer
Clinical Perspective and Conclusion	**John Oppenheimer, MD** Clinical Professor of Medicine Director, Clinical Research Pulmonary & Allergy University of Medicine and Dentistry of New Jersey (UMDNJ) – Rutgers University
Clarifying Questions to the Applicant	
BREAK	

FDA PRESENTATIONS

Overview of the Clinical Program	**Jennifer Lan, MD** Medical Officer DPACC, OII, OND, CDER, FDA
Overview of the Clinical Pharmacology Data	**Qianni Wu, PharmD** Clinical Pharmacology Reviewer Division of Inflammation and Immune Pharmacology Office of Clinical Pharmacology Office of Translational Sciences, CDER, FDA
Clinical Considerations and Risk/Benefit	**Jennifer Lan, MD**

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to the FDA

BREAK

Charge to the Committee **Miya Paterniti, MD**

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the pharmacokinetic/pharmacodynamic (PK/PD) approach for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) including anaphylaxis, specifically:

    a. The PK-bracketing approach using approved epinephrine injection products.

    b. The relevant PK/PD parameters to support clinical efficacy for the intended indication, including the significance of the following findings:

        - The diminished PK/PD sustainability in subjects with allergen-induced nasal congestion compared to epinephrine injection products and lack of data from repeat dosing under allergen-induced nasal congestion conditions.

        - The different PK comparisons of single-dose ARS-1 and Adrenalin in the first 10 minutes for Study EPI 15, EPI 16 (without allergen-induced nasal congestion), and EPI 17.

c. The uncertainty of translation of PK/PD results from healthy subjects and subjects with allergen-induced nasal congestion to patients with anaphylaxis, and whether clinical data are needed.

***Committee Discussion**: Overall, the committee members provided a variety of input on whether the PK/PD approach was sufficient for establishing efficacy for ARS-1 (epinephrine nasal spray) for the emergency treatment of Type I allergic reactions, including anaphylaxis. Some members stated that the PD data were compelling as they demonstrated comparable to higher systemic responses for ARS-1 when compared to injectable epinephrine products in healthy subjects, and a similar trend is expected in patients with anaphylaxis. Some members stated that the diminished PK of ARS-1 in allergen induced nasal congestion conditions may be over-interpreted and the systemic epinephrine exposures were still likely within the therapeutic range despite that the PK dropped below the injectable comparator arm after around 20 minutes post-dose. Several members stated that the variable and inconsistent PK profile of ARS-1 in the first 10 minutes of administration decreased their confidence that minimum effective plasma concentrations were reached in a timely manner. Other members expressed concern that the PK/PD data may not translate to clinical outcomes and recommended that clinical data be collected. Members suggested potential clinical trial designs, including studies on patients on oral immunotherapy, patients undergoing food allergy challenges, utilizing injectable epinephrine as backup. Please see the transcript for details of the Committee's discussion.*

2. **VOTE:** Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

    a. If not, what additional data are needed?

Vote Result: Yes: 16 No: 6 Abstain: 0

***Committee Discussion**: The majority (16) of committee members voted "Yes," reflecting agreement that the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of allergic reactions (Type I) and anaphylaxis. These members acknowledged the unmet need of a needle-free delivery system for epinephrine and stated that the in general, PD profile, more so than the PK profile, demonstrated a favorable benefit-risk assessment. They recommended a robust post-marketing surveillance program to further assess benefit-risk in adults. The six members who voted "No" expressed concerns regarding the limitations of translating PK/PD data from healthy subjects to patients with anaphylaxis, the lack of clinical outcomes data, and the inconsistent and lower PK data within the first 10 minutes of ARS-1 administration, especially compared to EpiPen, which is a product that is most commonly used in the community setting. Some of these members also noted that higher doses should be explored and that ARS-1 would be administered in a community setting, so the risks of lack of efficacy were high. These members recommended*

additional studies be conducted to collect clinical outcomes data to better characterize benefit-risk ratio. These members also acknowledged the unmet need of a needle-free delivery device for epinephrine; however, they agreed that epinephrine auto-injectors currently on the market are effective and administration is manageable. Please see the transcript for details of the Committee's discussion.

3. **VOTE:** Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children (<18 years of age) ≥30 kg for the emergency treatment of allergic reactions (Type I) and anaphylaxis?

    a. If not, what additional data are needed?

Vote Result: Yes: 17 No: 5 Abstain: 0

Committee Discussion*: The majority (17) of the committee members voted "Yes" that the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children (<18 years of age) ≥30 kg for the emergency treatment of allergic reactions (Type I) and anaphylaxis. Members again acknowledged the unmet need of a needle-free delivery device for epinephrine and emphasized a greater need in the pediatric population. These members agreed that, if approved, ARS-1 would address the logistical issues that occur with injectable products such as delays, hesitancy, and refusals. These members acknowledged that the low number of pediatric patients enrolled in the study was of concern. As a result, members recommended a robust post-marketing surveillance program to further assess benefit-risk, including risks surrounding inappropriate use and ingestion. The five members who voted "No" stated that the pediatric data were less robust than the adult data and also highlighted the low number of enrolled pediatric patients. These members highlighted that children are a vulnerable population and advised that additional studies be conducted if feasible. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 6:13 p.m. ET on May 11, 2023.