FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) MEETING

Virtual Meeting

Thursday, May 11, 2023

9:00 a.m. to 6:13 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, PharmD
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. AU: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email is displayed.

My name is Dr. David Au. I will be chairing this meeting. I will now call the May 11, 2023 Pulmonary Allergy Drug Advisory Committee meeting to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting, and will begin with the introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am the designated federal officer for this meeting. When I call your name, please turn on your camera, unmute, and introduce yourself by stating your name and affiliation, for the record. We will first start with the standing committee members.

Dr. Au?

DR. AU: Hi. I'm David Au. I am a pulmonary critical care doc from the University of Washington and the VA Puget Sound Health Care System.

DR. STEVENSON: Dr. Bacharier?

DR. BACHARIER: Hello. Dr. Leonard Bacharier, pediatric allergy and immunology, Vanderbilt University Medical Center, Nashville.

DR. STEVENSON: Dr. Evans?

DR. EVANS: Good morning. My name is Scott Evans. I am a professor and chair at MD Anderson Cancer Center in Houston, Texas and the Department of Pulmonary Medicine.

DR. STEVENSON: Dr. Holguin?

DR. HOLGUIN: Good morning. Fernando Holguin, pulmonary critical care, professor of medicine, University of Colorado, Denver.

DR. STEVENSON: Dr. Kelso?

DR. KELSO: Yes. I'm Dr. John Kelso. I'm an allergist at Scripps Clinic in San Diego.

DR. STEVENSON: Dr. Lee? Dr. Janet Lee?

DR. LEE: This is Janet Lee. I'm a pulmonary critical care physician at Washington University in St. Louis.

DR. STEVENSON: Dr. May?

DR. MAY: Good morning. Susanne May. I'm a professor of biostatistics at the University of Washington in Seattle, and also the director of the Clinical Trials Center.

DR. STEVENSON: Dr. Tracy?

DR. TRACY: Good morning. My name is Jim Tracy. I'm an allergist/immunologist from Omaha, Nebraska, and I'm professor of pediatrics at the University of Nebraska.

DR. STEVENSON: Dr. Carlson?

DR. CARLSON: Hi. I'm Dawn Carlson, pulmonary critical care. I'm the industry representative from AbbVie in North Chicago, Illinois.

DR. STEVENSON: I will now introduce the temporary voting members.

Dr. Amirshahi?

DR. AMIRSHAHI: Hi. Maryann Amirshahi. I'm

an emergency medicine physician, toxicologist, and clinical pharmacologist at Washington Hospital Center. I also work at the National Capital Poison Center, and I'm a professor of emergency medicine at Georgetown University School of Medicine.

DR. STEVENSON: Dr. Butler?

DR. BUTLER: Hi. Javed Butler. I'm a cardiologist at Baylor Scott and White Health in Dallas, Texas, and professor of medicine at University of Mississippi in Jackson.

DR. STEVENSON: Dr. Dowling?

DR. DOWLING: Hi there. Thomas Dowling. I'm a professor of pharmaceutical sciences in the College of Pharmacy at Ferris State University in Michigan.

DR. STEVENSON: Dr. Dykewicz?

DR. DYKEWICZ: Good morning. Mark Dykewicz. I am chief of the adult allergy and immunology and professor of internal medicine at Saint Louis University School of Medicine, in St. Louis.

DR. STEVENSON: Dr. Greenberger?

DR. GREENBERGER: Good morning, everyone.

I'm an allergist/immunologist in the Department of Medicine, Division of Allergy and Immunology at Northwestern University in Chicago. I'm professor of medicine emeritus.

DR. STEVENSON: Dr. Hovinga?

DR. HOVINGA: Hello. I'm Collin Hovinga. I am a clinical pharmacologist and epidemiologist by training. I am a clinical associate professor at University of Texas at Austin, and I'm vice president for Rare and Orphan Diseases at Critical Path Institute.

DR. STEVENSON: Dr. Jones?

DR. JONES: Good morning. I am Bridgette Jones. I am a professor of pediatrics. I'm an allergist and pediatric clinical pharmacologist at University of Missouri, Kansas City School of Medicine and Children's Mercy Hospital.

DR. STEVENSON: Dr. Jennifer Le?

DR. LE: Good morning. My name is Dr. Jennifer Le. I'm with the University of California San Diego, professor of clinical pharmacy, as well as infectious diseases.

DR. STEVENSON: Dr. Lewis Nelson?

DR. L. NELSON: Good morning. I'm Lewis Nelson. I'm a medical toxicologist and emergency physician. I am professor and chair of the Department of Emergency Medicine at Rutgers New Jersey Medical School in Newark, New Jersey.

DR. STEVENSON: Dr. Michael Nelson?

DR. M. NELSON: Hi. I'm Dr. Michael Nelson, allergist/immunologist. I'm professor and division chief at the University of Virginia in Charlottesville, Virginia, and president of the American Board of Allergy and Immunology.

DR. STEVENSON: Dr. Peden?

DR. PEDEN: Good morning. I'm Dave Peden. I'm a professor of pediatrics and senior associate dean for translational research at the University of North Carolina in Chapel Hill, North Carolina. My specialty is allergy and immunology.

DR. STEVENSON: Ms. Schell?

MS. SCHELL: Hello? Can you hear me?

DR. STEVENSON: Yes.

MS. SCHELL: Good morning. This is Karen

Schell. I'm sorry. Can you hear me?

DR. STEVENSON: Yes, we can hear you. I don't see your camera on, though. Could you please turn on your camera?

MS. SCHELL: Fine. Thank you.

Hi. I'm Karen Schell. I'm retired as a professor in respiratory therapy at the University of Kansas Medical Center in Kansas City, Kansas, and I have been a clinical practitioner for over 40 years.

DR. STEVENSON: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: Hi. I'm Jennifer Schwartzott. I am your patient representative. I'm also a patient representative for the NIH and, unfortunately, I have a lot of experience on this topic.

DR. STEVENSON: Dr. Troendle?

DR. TROENDLE: Hello. I'm James Troendle. I'm a statistician and the deputy director of the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute of the National

Institutes of Health.

DR. STEVENSON: I will now move on to the FDA participants.

Dr. Seymour?

DR. SEYMOUR: Good morning. My name is Sally Seymour. I'm the director of the Division of Pulmonology, Allergy, and Critical Care in the Office of Immunology and Inflammation, in the FDA.

DR. STEVENSON: Dr. Stone?

DR. STONE: Good morning. This is Kelly Stone, Associate Director for Therapeutic Review, Division of Pulmonology, Allergy, and Critical Care, and I'm trained as a pediatrician and allergist/immunologist.

DR. STEVENSON: Dr. Lan?

DR. LAN: Hi. I'm Jennifer Lan. I am a medical officer in the Division of Pulmonology, Allergy, and Critical Care, and I'm a practicing allergist/immunologist.

DR. STEVENSON: Dr. Paterniti?

DR. PATERNITI: Hello. This is Miya Paterniti, Division of Pulmonology, Allergy, and

Critical Care, and I'm the clinical team leader.

DR. STEVENSON: Dr. Ren?

DR. REN: Hi. This is Yunzhao Ren, the clinical pharmacology acting team leader in the Division of Inflammation and Immune Pharmacology.

DR. STEVENSON: Dr. Wu?

DR. WU: Hi. This is Qianni Wu. I'm the clinical pharmacology reviewer from Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology.

DR. STEVENSON: Thank you, everyone.

I will hand it back to the chairperson.

DR. AU: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for the discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We

look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to refrain from discussing the meeting topics during breaks or lunch. Thank you.

Dr. Stevenson will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration, FDA, is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory

Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweighs their potential financial conflict of interest, or

when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of a new drug application, NDA, 214697, for epinephrine nasal spray, submitted by ARS Pharmaceuticals Inc, for the proposed indication of emergency treatment of Type I, allergic reactions, including anaphylaxis in adults and children weighing 30

kilograms or more. This is a particular matters meeting during which specific matters related to ARS Pharmaceuticals will be discussed.

Based on the agenda for today's meeting and all financial interests supported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Dawn Carlson is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Carlson's role at this meeting is to represent industry in general and not any particular company. Dr. Carlson is employed by Abbvie, Incorporated.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on

the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted, for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you, and I will hand it back to the chairperson.

DR. AU: Thank you.

We will now proceed with the FDA introductory remarks from Dr. Miya Paterniti.

FDA Introductory Remarks - Miya Paterniti

DR. PATERNITI: Good morning to you, esteemed committee members, the ARS team, my FDA colleagues, and members of the audience. My name is Miya Paterniti, and I'm a practicing allergist and a clinical team leader in the Division of Pulmonology, Allergy, and Critical Care here at FDA. On behalf of the agency, I would like to welcome you to this Pulmonary Allergy Drugs Advisory Committee meeting, where we will discuss the new drug application for epinephrine nasal

spray, ARS-1, proposed for the emergency treatment of Type I allergic reactions, including anaphylaxis in adults and children weighing 30 kilograms or more.

We would like to note that this differs from the indication included in the applicant's briefing document, and for the purposes of today's advisory committee meeting, we will discuss the indication included on this slide, as it aligns with the indication included in the NDA submission. I will now provide some brief opening remarks to begin our meeting.

ARS-1 is an epinephrine nasal spray, as shown in the figure. Epinephrine is approved and available as an injection product. ARS-1 is a novel route of administration for epinephrine, proposed for emergency treatment of Type I allergic reactions, including anaphylaxis in adults and children weighing 30 kilograms or more. Type I allergic reactions are also known as immediate reactions that involve IgE antibodies, resulting in release of histamine and other inflammatory

mediators. It is important to emphasize that this novel route of administration for epinephrine has no established regulatory pathway, and therefore, your advice to us today regarding this application will be impactful.

ARS-1 is a single-use device, which delivers 2 milligrams and 100 microliters via one nasal spray. The device used for ARS-1 is the same as the device in other approved nasal sprays, including naloxone nasal spray. The proposed directions for use instructs that if symptoms progress after 10 minutes, or an error is made in administering ARS-1, patients should administer a second dose with a new device.

Although many on the committee are familiar with anaphylaxis, I would like to review the pertinent characteristics of anaphylaxis to provide context for understanding the approach to support efficacy for ARS-1. Anaphylaxis is a severe, potentially fatal, reaction that occurs suddenly, usually after contact with an allergy to which a patient is sensitized to. Symptoms include, but

are not limited to, hives, swelling, difficulty breathing, GI symptoms such as vomiting, diarrhea, and abdominal pain, as well as hypotension.

Epinephrine is considered first line, standard-of-care therapy for anaphylaxis and is the only life-saving treatment. Although there is limited information as to how many patients need a second dose of epinephrine, those requiring a second dose is not uncommon and ranges as high as 20 percent. Generally, fatal anaphylaxis occurs secondary to respiratory and/or cardiac arrest, and generally occurs within 5 to 30 minutes after exposure.

The estimated prevalence of anaphylaxis is 0.69 per million, equating to approximately 230 deaths per year. Although fatal anaphylaxis is rare, there is a large population at risk for anaphylaxis, and therefore affected daily by the potential risk. Food and drug allergy affects about 10 percent each for the U.S. population, and hymenoptera venom allergy affects about 3 percent. The lifetime prevalence of anaphylaxis ranges from

1.6 to 5.1 percent.

As mentioned previously, epinephrine is approved and available as an injection product. Here in the United States, epinephrine is available as an autoinjector, a prefilled syringe, and single and multi use vials. Auto-injector and prefilled syringes can be used in the community, whereas vials are used in the medical setting. Autoinjectors are available as 0.15 and 0.3 milligram injections, and one autoinjector, Auvi-Q, is available as a 0.1 milligram injection.

In the community, epinephrine is administered as a fixed dose based on weight, starting at 7.5 kilograms, with doses ranging from 0.1 to 0.3 milligrams. In the medical setting, for children weighing less than 30 kilograms, epinephrine is dosed as 0.01 milligram per kilogram, up to a maximum dose of 0.3 milligrams, and for children weighing 30 milligrams or more, epinephrine is dosed as 0.3 to 0.5 milligrams. Due to lack of randomized controlled trials of epinephrine for the treatment of anaphylaxis,

whether there is a safe and effective dose above or below these doses is unknown.

Although we have several approved epinephrine injection products, the approval process for epinephrine is unique, primarily based on its long regulatory history. Epinephrine has been marketed in the U.S. since 1901, predating the original Federal Food and Drugs Act of 1906, which laid a foundation for the FDA. In 1938, the Federal Food, Drug, and Cosmetic Act, or FD&C, required that new drugs demonstrate that they are safe for approval.

In 1962, Congress passed the Kefauver Harris Amendment to the FD&C Act, adding the new requirement that new drugs must be shown to be effective, as well as safe, to obtain approval. This amendment also required FDA conduct a retrospective evaluation of the effectiveness of drug products that had been approved by the agency as safe between 1938 and 1962.

The agency's administrative implementation of the effectiveness evaluation was called the

Drug, Efficacy, Safety, and Implementation, or Desi, process.

Since epinephrine had been marketing since 1901, preceding the passage of the 1938 FD&C Act, it was not subject to DESI review; however, epinephrine was still required to comply with good manufacturing procedures and adequate labeling to ensure safe use. In 1987, EpiPen and EpiPen Jr. were the first epinephrine injections approved that remain on the market today.

EpiPen was approved by FDA based on literature support for efficacy and safety. Clinical trial and PK and PD data were not required. More recent approvals of epinephrine injection products utilize the 505(b)(2) regulatory pathway, which permits FDA to rely on previous findings of safety and effectiveness of an approved epinephrine injection product.

In addition, chemistry, manufacturing, and device data, along with human factors assessments, were required. Human factors assessments assess interactions between people and user interfaces, as

outlined in the briefing document. Subsequent epinephrine injection products were not required to assess PK or PD to establish a scientific bridge to approved epinephrine injection products because of similarity of the formulations and route of administration between the new epinephrine injection product and the approved reference epinephrine product.

There were several new development considerations that were introduced for a new route of administration for epinephrine. ARS proposed to develop an epinephrine nasal spray under the 505(b)2) regulatory pathway, relying on previous findings of safety and effectiveness of an approved epinephrine injection product. As epinephrine nasal spray is a new route of administration, additional information would be required to establish a scientific bridge to approved epinephrine injection products.

Whether a scientific bridge could be accomplished relying on PK/PD in healthy subjects alone was uncertain due to potential differences in

PK and PD in patients with anaphylaxis. Based on these uncertainties, the need for clinical efficacy trials was considered, and clinical trial scenarios were discussed, but feasibility concerns were acknowledged. As you listen to the presentations today, we ask you to consider whether PK and PD is sufficient or if clinical trials are needed.

Establishing a scientific bridge based on PK and PD introduced challenges due to the limited PK and PD data for approved epinephrine injection products, as PK and PD were not required for approval of epinephrine injection products. This resulted in several knowledge gaps, including which PK endpoints are critical to establish advocacy and how to interpret PK and PD similarities, as approved doses of epinephrine have not been validated by dedicated clinical efficacy trials.

In addition to the limited PK/PD data, there's also variability in PK profiles across epinephrine injection products. Due to this variability, the applicant and FDA agreed to a bracketed approach in which the PK profile for

ARS-1 would be bracketed between two different approved epinephrine injection products. There were also questions regarding the impact of intranasal epinephrine on absorption, as topical administration of epinephrine causes constriction of local blood vessels, which has the potential to change the absorption of epinephrine in the nasal mucosa and impact systemic plasma concentrations. This is of particular concern for a second dose of epinephrine. The applicant agreed to evaluate the epinephrine PK/PD profiles following a second dose in a repeat-dose study.

There were also questions raised regarding the impact of anaphylaxis on absorption. Rhinitis and nasal congestion can be features of anaphylaxis, and alterations of the nasal mucosa such as vasodilation may affect the local absorption of epinephrine. FDA and the applicant agreed that nasal allergen challenge of subjects with allergic rhinitis may reasonably mimic the nasal findings that could occur in anaphylaxis; therefore, the applicant agreed to evaluate

epinephrine PK and PD profiles of ARS-1 under nasal allergen challenge conditions.

Lastly, developing an epinephrine nasal spray for pediatric subjects was discussed due to the importance of epinephrine treatment in pediatrics. Due to nasal anatomic differences, the FDA requested that the applicant conduct pediatric PK and PD studies to determine appropriate doses for children of different ages and body weights. The clinical pharmacology program to support ARS was designed to address some of the development considerations for epinephrine nasal spray. The FDA presentations later this morning will discuss these trials in more detail.

The program initiated with dose ranging studies, EPI 11b, to determine an appropriate dose based on PK similarities to EpiPen and Symjepi. Once the dose was determined, a PK study, EPI 15, was conducted to bracket a single dose of ARS-1 to EpiPen and Adrenalin with comparable safety and PD profiles. A repeat-dose study also within Epi 15 was conducted to assess the PK/PD and safety

of 2 doses of ARS-1 compared to 2 doses of EpiPen.

To assess the impact of nasal congestion, a PK and PD and safety study, EPI 16, was conducted in patients with seasonal allergic rhinitis pre- and post-nasal allergen challenge compared to Adrenalin 0.3 milligrams and 0.5 milligrams. EPI 17 assessed if self-administration of ARS-1 changes the PK and PD and safety compared to Adrenalin. And lastly, EPI 10 assessed the PK and PD and safety of various single doses of ARS-1 in pediatric subjects. The indication includes pediatric subjects who weigh 30 kilograms or more, therefore, today's presentation will focus on pediatric subjects enrolled in EPI 10 that weighed 30 kilograms or more.

I will now review the PK/PD result in brief. These will be discussed in detail in Dr. Wu's presentation later this morning. Overall, the epinephrine PK profile, following a single dose of ARS-1 in healthy adults, demonstrated different trends across studies in the first 10 minutes compared to Adrenalin 0.3 milligrams; but after

10 minutes, ARS-1 was reasonably bracketed by both Adrenalin 0.3 milligrams and EpiPen milligrams. Two doses of ARS-1 administered in the same or opposite naris demonstrated lower PK in the first 20 minutes and similar PK 20 minutes post-dose compared to 2 doses of EpiPen.

In the nasal allergen challenge study, a faster absorption rate and faster decline rate at about 10 to 20 minutes was observed following ARS-1 under nasal congestion conditions compared to without nasal congestion and compared to Adrenalin 0.3 and 0.5 milligrams. Two doses administered under nasal congestion conditions was not studied. Pediatric subjects weighing 30 kilograms or more, who were administered a single dose of 2 milligrams of ARS-1, demonstrated similar PK in the first 10 minutes and higher PK thereafter compared to ARS-1 in adults.

PD markers that were assessed were systolic blood pressure, diastolic blood pressure, and pulse rate. For single and repeat doses of ARS-1 in healthy adults, generally higher and more sustained

PD was observed compared to Adrenalin and EpiPen. The PD and nasal congestion conditions followed a similar pattern as PK, faster onset but lack of sustainability, compared to Adrenalin. PD was slightly lower in pediatric subjects weighing 30 kilograms or more compared to adult subjects.

I will revisit these conclusions in my charge to the committee later today, with a focus on what we would like the committee to discuss based on these conclusions.

As you consider the PK/PD results for ARS-1, I would also like to remind the committee that although we have several approved epinephrine injection products, barriers to epinephrine use still exist. We know that epinephrine is life-saving, and rapid administration can decrease the risk of death. Despite this, many patients, caregivers, and healthcare providers underuse or delay administration of epinephrine. The reason for this is multifactorial and are listed here.

Some patients, caregivers, and healthcare providers may not recognize the signs of

anaphylaxis. In addition, some patients may not have access to epinephrine due to supply chain issues or high costs. Another reason for underuse or delayed use of epinephrine is that patients and caregivers may fail to carry epinephrine with them at all times because they did not fill the prescription, its burdensome to carry, or they don't anticipate that they will encounter the allergen.

Lastly, patients and caregivers may hesitate to use an injection device even when it's available to them at the time of anaphylaxis. This can occur because patients or caregivers may not believe that the reaction is serious, they don't understand how to use the device, or they're afraid of the injection.

The FDA recognizes that development of new routes of administration for epinephrine is important to address some of these barriers, but as noted here, the underuse of epinephrine is complex and multifactorial. We want to thank those that submitted public comments to the public docket and

those who are planning to participate in the open public hearing later today. Many of the written public comments emphasize the importance of a noninjection route of administration for epinephrine.

For a drug to be approved for marketing in the United States, the FDA must determine that the drug has substantial evidence of effectiveness and that the benefits outweigh the risks to patients. Due to feasibility concerns with conducting clinical efficacy trials, efficacy relies on PK/PD comparability to approved injection products.

Challenges with a PK/PD approach without clinical efficacy studies are multiple, therefore, it is necessary to decrease uncertainty based on the available PK/PD data. A benefit-risk assessment for ARS-1 requires careful consideration of the evidence, and importantly, the remaining uncertainties about the benefits of ARS-1.

The agency recognizes the need for epinephrine products with a noninjection route of administration, as it addresses some aspects of

underuse or delayed use of epinephrine; however, the evidentiary standard must still be met. As ARS-1 is for emergency treatment for a potentially fatal condition, minimizing uncertainties is critical and may require additional data. We ask you to consider the benefit-risk assessment and how PK/PD uncertainties affect this assessment in your deliberation today.

Before I conclude my opening remarks, I would like to share the questions which we will be asking you to discuss this afternoon. I will go over them now and present them again during my charge to the committee.

Question 1 is a discussion question. We ask the committee to discuss the PK/PD approach for establishing efficacy for ARS-1 epinephrine nasal spray for the emergency treatment of Type I allergic reactions, including anaphylaxis, specifically: the PK/PD bracketing approach using approved epinephrine injection products; 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.

We also ask the committee to discuss 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.

The next two questions are voting, questions. We ask you to vote whether the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of Type I allergic reactions and anaphylaxis? If you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus the risks of ARS-1.

Finally, in question 3, we ask you to vote on whether the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children less than 18 years of age and weighing 30 kilograms or more for the emergency treatment of Type I allergic reactions and anaphylaxis? If you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus the risks of ARS-1.

Thank you for your attention, and I will now turn the meeting back to Dr. Au to proceed with today's meeting.

DR. AU: Thank you, Dr. Paterniti.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including ARS Pharmaceuticals' non-employee presenters, to advise the committee of

any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with ARS Pharmaceuticals Inc.'s presentation.

Applicant Presentation - Richard Lowenthal

MR. LOWENTHAL: Thank you.

On behalf of ARS Pharmaceuticals, I would like to express our appreciation to the advisory committee members, the FDA review team, and the public representatives for their support at today's advisory committee for neffy, our epinephrine nasal spray product.

My name is Richard Lowenthal. I'm one of the co-founders of ARS Pharmaceuticals and will be your moderator in today's discussions. I have been in drug development for over 30 years. I started my career working at FDA as a new drug reviewer, and since that time, I've been in industry for the last 25 years. Some products that I have helped developed, then get approved, include Narcan nasal spray for the emergency treatment of opioid overdose and Valtoco nasal spray for the emergency treatment of acute repetitive seizures. With neffy, we're using the same nasal spray device and a similar development strategy as these other FDA-approved products.

As you know, epinephrine is highly effective for the treatment of anaphylaxis if administered in a timely fashion. The problem is that major barriers limit the rapid use of epinephrine in the community setting. Many patients fear a needle and are not comfortable with self-injection. There is also the impracticality of carrying the current available devices and using them in public. Our

goal in developing neffy was to address the community-use issues with current epinephrine devices that limit the proper use of this life-saving medication.

neffy is a needle-free, easy-to-carry, and easy-to-use approach to administer epinephrine rapidly for the emergency treatment of severe Type I allergic reactions, including anaphylaxis. neffy's intuitive and proven device has the potential to address these significant unmet medical needs.

neffy is a saline-based epinephrine nasal spray that combines three well-established FDA-approved components. neffy includes the proven efficacy and safety of epinephrine, which has been used effectively for more than 100 years. The unit dose sprayer device has been approved for more than six drug products in the United States and is easy to use without training. This is the same proven device used in the community under stressful emergency situations with products such as Narcan nasal spray, Valtoco, and Nayzilam.

Epinephrine, if administered intranasally in a simple water-based formulation, is not absorbed into the systemic circulation. What makes the injection-like pharmacokinetics of neffy possible is an absorption enhancing agent called dodecyl-maltoside, which is also known by trade name Intravail. Intravail is a generally recognized and safe GRAS food additive that is non-irritating and functions by loosening tight junctions in the nasal mucosa to allow rapid absorption of epinephrine. Intravail is already used in two other FDA-approved nasal spray products, Tosymra and Valtoco.

ARS has been working on packaging to allow patients and caregivers to carry their neffy devices at all times to ensure epinephrine is available when needed. One of our concepts we hope to make available at launch is this slim neffy carrying case that will hold two devices and directions for use and have a QR code that directs users to a video on proper administration. This easy-to-open zipper package, like this, will make

neffy quickly accessible, even to children, when needed. The case will also have an alligator clip and can hold your keys, or latch on to a backpack, or inside of a purse, so it's readily available, and can even include a tag if you lose it that can be quickly found.

The proposed indication for neffy is identical to the other epinephrine injection devices used in the community. neffy 2-milligram is proposed for the treatment of Type I allergic reactions, including anaphylaxis, in adults and children who weigh more than 30 kilograms. ARS is also committed to the future development of neffy and have now completed enrollment of over 20 children weighing 15 to 30 kilograms, with a 1-milligram dose of neffy in our EPI 10 pediatric Type I allergy patients. We plan to file a supplemental NDA application for neffy 1 milligram in these lower weight children shortly after approval of this current NDA.

We are also conducting phase 2, placebo-controlled trials with neffy in refractory

urticaria, where we observed rapid and near complete responses, as well as in patients with persistent asthma. Given the efficacy studies in this indication are neither ethical nor feasible, and knowing that binding of androgenic receptors and pharmacodynamic responses would not differ in patients experiencing severe anaphylactic reactions, ARS and FDA agreed that clinical pharmacology studies could support the assessment of neffy's benefit-risk.

We agreed that neffy needed to demonstrate a pharmacokinetic profile bracketed within the range observed with approved epinephrine injection devices and that pharmacodynamic responses observed with neffy should be as good or better than other approved epinephrine injection products. The PK bracket and PD response therefore became co-primary endpoints in all ARS studies. ARS has generated more data on epinephrine than any other single organization to date, with over 1100 administrations dosed once or twice in more than 600 subjects.

Here we list the primary studies we'll review today. EPI 15 was conducted in healthy volunteers with neffy, and injection products were administered by healthcare providers at the site. EPI 16 was conducted in Type I allergy patients under normal and nasal allergy conditions to induce rhinitis and rhinorrhea as a worst-case nasal challenge, and EPI 17 as a real-world study conducted in patients with Type I allergy. The patients in EPI 17 self-administered neffy without instruction under simulated allergy emergency. EPI 10 is the largest pediatric allergy patient clinical pharmacology study ever conducted with epinephrine in over 80 subjects enrolled with 3 doses of neffy in children 4 to 17 years old.

The FDA has pointed out several areas for the advisory committee to consider when reviewing the data today. There is agreement about the clear unmet medical need for a needle-free route of administration in this indication that neffy, if approved, could address. The context is important because many patients are not being adequately

treated because they or their caregivers refuse to carry or administer in a timely fashion injectable products. These patients have no accepted current therapy to protect them from their disease.

We will show you that the PK data are highly variable with the approved injection products, which led to our agreement with FDA to use a bracketing approach for pharmacokinetic data in conjunction with the assessment of pharmacodynamic response. While FDA acknowledges that neffy is reasonably bracketed by IM injection and EpiPen, starting 10 minutes post-dose, they know to lower epinephrine concentration with neffy at some time points within the first 10 minutes in one study, our EPI 15 study.

We agree that absorption at these early time points is an important consideration; however, these early time points, the pharmacokinetics are highly variable, and as FDA notes in there addendum, it is mainly due to IM injection. More importantly, in our EPI 17 real-world, self-administration study in Type I allergy

patients, epinephrine concentrations from neffy were greater than IM at all time points.

It is also critical to consider that PD data as raising systolic blood pressure is more important and not just the biomarker. It is the clinical goal of treatment with epinephrine. We will explain the physiological factors that result in neffy having a greater effect on systolic blood pressure than IM epinephrine injection or EpiPen.

We will also show there is a statistically significant correlation between epinephrine plasma concentrations and systolic blood pressure, or heart rate, and we'll demonstrate why the physiologic advantage of avoiding direct injection into muscle accounts for the difference in the magnitude of effect between neffy and IM injection. Finally, we will share the data supporting that neffy is comparable to IM injection for patients even under nasal challenge conditions.

As you review the evidence today, we ask you to consider the totality of data supporting neffy across the three primary studies, as well as

supportive studies, all of which met their prespecified criteria, including a PK profile appropriately bracketed between IM injection and EpiPen across various parameters, and typically better pharmacodynamic response.

Specifically, the induced rhinitis study, EPI 16, FDA also asked you to consider the PK/PD sustainability after 20 minutes under worst-case rhinitis conditions. While the PK declines below IM after 20 minutes, adequate levels are still sustained. We can see this in the pharmacodynamic response, as systolic blood pressure remains above IM injection through 40 minutes and is the same through 60 minutes and beyond.

Additionally, FDA is asking if another study is necessary to determine if a second dose of neffy under rhinitis conditions will give PK similar to the first dose, or more like under normal conditions, given epinephrine reverses symptoms of congestion and rhinorrhea. Another study would significantly delay access of neffy to patients and caregivers without informing us further on neffy's

benefit-risk, given the first dose should be clearly effective.

Approval of neffy has the potential to help address many significant unmet medical needs in the community for patients seeking an alternative to current approved injection products. This need has been emphasized by treating allergists' recent literature and the outpouring of support in more than 600 public comments to this docket for today's meeting.

In addition to our presenters today, Dr. Thomas Casale, Dr. Sarina Tanimoto, and Dr. John Oppenheimer, we have a number of distinguished experts with us today to answer your questions. All outside experts have been compensated for their time to attend today's meeting but did not receive any other equity-based compensation.

Thank you for attention. I'd like to now turn the presentation over to Dr. Casale, who will present the unmet medical needs in the allergy community, including the history of epinephrine use

and comparison of current approved injection products.

Applicant Presentation - Thomas Casale

DR. CASALE: Thank you, Rich.

My name is Dr. Thomas Casale. I'm a professor at the University of South Florida and chief of Clinical and Translational Research in the Division of Allergy and Immunology. I'm formerly the chief medical adviser to FARE, Food Allergy Research and Education, and I've been president and executive vice president of the American Academy of Allergy, Asthma, and Immunology, chair of the American Board of Allergy and Immunology, as well as a member of the boards of directors of both the World Allergy Organization and the American Thoracic Society. My primary research focuses on the treatment and determination of the pathophysiologic mechanisms involved in allergic and respiratory diseases, and I've published over 500 papers on these areas.

As you know, Type I allergic reactions are generally caused by exposure to a specific allergen

such as food, venom, or a drug. There are an estimated 35 to 45 million people in the U.S. who have a severe systemic Type I allergic reaction, where more than one organ system is involved. Patients with these allergies experience a significant impact on their quality of life, as avoidance of the allergen is the primary treatment. This comes with anxiety, depression, and social isolation. Additionally, if a reaction is not treated with epinephrine in a timely manner, patients can experience higher morbidity, hospitalization, biphasic reactions, and in rare cases, death. treatment for these severe type one allergic reactions

Epinephrine is the first-line for these severe Type I allergic reactions and is the only effective therapy to stop the progression of an allergic reaction to a more severe anaphylactic event. Current FDA-approved epinephrine products are shown here, and include devices that can inject both by intramuscular and subcutaneous routes of administration. All of these products were

approved with no clinical data, and most without any PK data.

The first approved autoinjector was EpiPen in 1987. EpiPen was approved without efficacy, safety, or PK data, solely based on reference to the FDA-approved IM or subQ injection with needle and syringe. In practice, while all approved injection devices, including standard IM or subQ with needle and syringe, have very different pharmacokinetic profiles, and as you will see, blood levels can be highly variable. Nevertheless, they all work well and have been used interchangeably in clinical situations.

Epinephrine has been used for more than 100 years, and it's a well-known pharmacology and mechanism of action. The alpha-1 adrenergic receptor increases blood pressure that relieves hypotension and decreases mucosal edema. The beta-1 receptor increases heart rate. The beta-2 receptor relaxes bronchial smooth muscle to improve airflow and also inhibits mediator release from mast cells and basophils to stop the pathological

effects of mast cell degranulation. Heart rate and systolic blood pressure increase with epinephrine, and this has been well established through pharmacodynamic markers that can predict efficacy in severe Type I allergic reactions.

While people generally think of epinephrine as a vasoconstrictor, in fact it's both a vasoconstrictor and a vasodilator, depending on how alpha-1 and beta-2 adrenergic receptors are activated. This figure helps explain how alpha-1 receptors in the peripheral system are activated by epinephrine, causing blood vessels to contract. This results in an increase in systolic blood pressure. However, the vessels in the skeletal muscle are rich in beta-2 receptors, and when activated by epinephrine cause vasodilation.

When you inject epinephrine into the thigh, the high local concentration causes more significant vasodilation and diastolic blood pressure drop, which can suppress the systolic blood pressure increase. With IV infusion or other routes of administration that avoid direct

injection into the skeletal muscle in the thigh, we see less impact on diastolic blood pressure and a better overall increase in systolic blood pressure.

A PK/PD correlation of epinephrine exposure with heart rate and systolic blood pressure was reported based on several studies referenced in the 2012 FDA clinical pharmacology review of epinephrine injection for treatment of hypertension related to septic shock. As shown in these figures from the FDA review, there's a positive correlation between the change in blood pressure and heart rate versus epinephrine concentration. For diastolic blood pressure, there's a negative correlation.

While there are no controlled studies demonstrating the efficacy of epinephrine, there's no doubt that epinephrine is highly effective at treating severe Type I allergic reactions. Available formulations include intramuscular or subcutaneous injection products, with needle and syringe used primarily in the clinical setting and emergency departments.

Autoinjectors are mainly used in the

community setting and can be either intramuscular or subcutaneous, depending on dosing technique and body mass of the patient. Epinephrine is a systemically acting drug, so no matter how it gets into the blood, it will have an effect. Resolution of symptoms is typically observed in 5 to 10 minutes regardless of the route of administration and device used.

Based on an analysis of 12 published studies that specify the injection device used, a single dose of epinephrine is effective in resolving the symptoms of a systemic Type I allergic reaction in approximately 90 percent of the cases. If symptoms are not resolved after the initial injection, guidelines recommend administering the second dose. In about 10 percent of allergic events, a second dose is needed regardless of the device used. The need for a second dose is typically when the event is more severe, often occurring when treatment is delayed. Thus, despite differences in pharmacokinetics, there's no apparent difference in efficacy or time to effect between injection

devices.

Prompt administration of epinephrine is the most critical factor to achieve good clinical outcomes. Typically, patients know they're experiencing a reaction within minutes of exposure to an antigen. Common symptoms include flushing, hives, bronchospasm, gastrointestinal effects, angioedema, and hypotension.

Epinephrine treatment early after symptoms are detected almost always results in good clinical outcomes regardless of the device used; however, even when patients and caregivers are carrying their epinephrine product, they typically wait to dose from 5 to 18 minutes until the event is severe enough to justify injection.

The hesitation to dose is often due to fear of the needle and the pain of injection, and can significantly increase the risk of abnormal vital signs, need for repeat doses of epinephrine, hospitalization, biphasic anaphylactic events, or progression to a life-threatening reaction. This reinforces the timely administration of epinephrine

is the most important consideration in treatment of a severe allergic reaction.

Despite our efforts to educate patients and caregivers about the importance of carrying an epinephrine product and using it when symptoms are first detected, 43 percent of the 6 million epinephrine prescriptions given to patients are not filled. Based on literature of approved autoinjectors, we know that about 3.3 million people have filled their epinephrine prescriptions in the past three years. Of those who fill their prescriptions, more than half do not carry their autoinjectors, and less than 20 percent carry two devices, which is recommended by guidelines.

Finally, even when carrying the device, between 25 and 50 percent of patients will not use it immediately in an allergy emergency, and another 40 to 60 percent delay use, allowing for disease progression. Thus, of the approximately 6 million people who receive prescriptions for epinephrine devices, only 5 to 10 percent carry and use them appropriately. There's a real unmet medical need

for a large portion of the population with allergic reactions who are not adequately being treated with currently available device options.

Additionally, injection devices carry some risk related to the needle itself. In particular, lacerations and bone injections are not uncommon. The most serious reactions may be due to IV bolus-like injections. Based on the literature, IV bolus injection of epinephrine is well known to have a much higher rate of more serious adverse reactions, and current FDA labeling for autoinjectors contains a warning for such events.

It's also relatively common that people accidentally inject themselves in their hand or fingers, with approximately 3500 events reported each year. These are relatively serious events, especially when a caregiver or patient self-injects a finger. The patient ends up not receiving the epinephrine, and both the patient and caregiver end up in the emergency room for treatment. Other issues with autoinjectors include pulling the device out too quickly after initial penetration of

the needle, as well as errors using the device or device malfunctions. Injection site pain also leads to use hesitancy. To conclude, needle-free epinephrine options can fill a great unmet medical need for our patients and their caregivers.

Epinephrine is a systemically active drug, and the route of administration should not impact efficacy; in fact, efficacy is the same across all approved epinephrine injection products despite PK differences and variability in exposure. The efficacy and safety profile of epinephrine is well established, but delayed administration is a major factor in reduced epinephrine efficacy.

Delays in dosing lead to significant worsening in clinical outcomes. One of the most significant issues is the reluctance to dose or hesitation to dose, as patients do not like to self-inject, and caregivers hesitate to inject the loved one, especially in public locations. As a result, there's a significant unmet medical need for a needle-free, easy-to-use, easy-to-carry, safe and effective epinephrine treatment option.

Thank you. I'll turn the presentation to Dr. Tanimoto to review the data supporting neffy.

Applicant Presentation - Sarina Tanimoto

DR. TANIMOTO: Thank you, Dr. Casale.

Good morning. My name is Sarina Tanimoto, chief medical officer and one of the co-founders of ARS Pharmaceuticals. As previously mentioned, our focus at ARS has been to provide a needle-free option for the treatment of severe Type I allergy. Let me begin with an overview of our clinical development program.

In an extensive development program of neffy, we have treated more than 600 Type I allergy patients and healthy volunteers, with over 1,000 doses, ranging from 0.5 to 4 milligrams. With both 1 and 2 milligrams of neffy, we have conducted single- and twice-dose administration, self-administration, which replicates real-world use, and various challenging studies. Additionally, we have studied neffy in more than 80 pediatric patients with Type I allergy, ages 4 to 17 years old, weighing 15 kilograms or

greater. We also have an ongoing study for neffy 1 milligram in children weighing 15 to 30 kilograms, which we look forward to providing to FDA.

ARS also has other completed and ongoing studies. Our EPI 14 study in patients with upper respiratory tract infection, such as flu and cold, has been completed and summary data filed to FDA. EPI U01 is a placebo-controlled trial with neffy 1 and 2 milligrams in patients with refractory urticaria. Rapid onset of effect within a few minutes and a near complete resolution of symptoms in approximately 10 minutes have been observed. EPI A01 is also an ongoing study, comparing neffy with albuterol and placebo in patients with persistent asthma.

Before sharing the results, let me further explain the bracketing approach used in our development program. The objective of this approach was to demonstrate PK comparability across the prespecified parameters of Cmax, TMax, and early partial AUCs, which we defined as 0 to 20 and

0 to 45 minutes.

This is a summary of PK data with approved injection products. Cmax is the maximum concentration; Tmax is the time to reach Cmax. There are several studies for EpiPen and IM, and there is striking variability with respect to Cmax by more than 2-fold. There is also marked variation in Tmax across studies. Auvi-Q and Symjepi tend to fall within the same range with respect to Cmax and Tmax. All of these injection products are efficacious and can be used interchangeably despite these significant PK differences.

The variability of PK led us to define a bracketing strategy. This is a mean concentration versus time figure based on the ARS clinical studies. The Y-axis shows mean epinephrine concentration; the X-axis is the time in minutes after dosing. There are significant differences between these injection products with EpiPen, in blue, generally being the highest Cmax, and IM in orange and SC in black being the lowest.

Conducting a controlled-randomized study in patients with anaphylaxis is considered unethical; therefore, our development program focused on establishing that neffy can deliver epinephrine effectively and safely by demonstrating a PK profile within the range of approved injection products that include intramuscular and subcutaneous injections by needle and syringe or by all injectors.

IM subQ injection is the benchmark for efficacy at the lower range of the PK profile and was also the basis for approval of EpiPen. EpiPen is the higher end of the range of injection products but is the benchmark for safety. Having all PK within the range of approved products was supported by both the FDA and European Medicine Agency. Epinephrine increases both blood pressure and heart rate when it activates adrenergic receptors; therefore, measuring and comparing the blood pressure response of neffy to the approved products would seem to provide a meaningful appraisal of efficacy.

Now, let's look at the results, beginning with the single administration of neffy. The solid green line shows the integrated PK results for Studies EPI 15 and 16 dosed by HCP, representing caregiver administration. The dashed green line is EPI 17 patient self-administration. The results are similar for HCP and self-administration. Both neffy gives PK profile between IM, subQ, and EpiPen.

For our NDA submission and consistent with FDA guidelines, we submitted both arithmetic and geometric means. For FDA's presentation, we show the geometric mean data here, as not to obscure any differences based on variability. We also show the CV percentage, which is the coefficient of variation, the extent of variability in relationship to the mean. All of epinephrine products have high variability in the PK parameters. With either HCP or self-administration, neffy is within the bracket of approved injection products, based on the Cmax, Tmax, and mean early partial AUCs.

Here, I share the results from the EPI 10 study in pediatric patients, 30 kilograms or greater, who received either neffy 1 or 2 milligrams. While we are seeking approval of neffy 2 milligrams, 1 and 2 milligrams shows good dose proportionality. The neffy 2-milligram result in children is comparable to the adults.

These data are also supported by the pharmacologically based absorption model and PopPK model. This table summarizes the Cmax and Tmax from ARS studies, as well as publicly reported studies with EpiPen. neffy results are also included. The table orders the studies on the basis of a Cmax from highest to lowest. You see the neffy PK data highlighted in blue are bracketed by just EpiPen studies. This is true for Cmax and Tmax. Moreover, the variability of neffy studies is much less than that of EpiPen being in the middle altogether.

While the PK profile following neffy is reasonably bracketed by IM and EpiPen, FDA is asking the committee to consider the clinical

implication of differences in concentration at the early time points before 10 minutes. This slide and the next slide shows two figures from the FDA briefing document. Here, we have the PK results of Adrenalin 0.3 milligram from EPI 17 in green, for neffy EPI 15 in red, and EPI 17 self-administration in blue. In both studies, neffy exceeds the mean concentration over epinephrine 0.3 milligrams at all time points.

This is figure 1 from the FDA briefing document, and shows the result for EPI 15 only. In this figure, neffy, in red, appears to have low exposures at early time points compared to IM in blue. Let's look at the actual geometric mean results with the statistical analysis between neffy and IM.

Here, you can see the concentration for EPI 15. FDA points out that the absolute concentrations are higher for IM through the first 10 minutes. In EPI 17, our real-world study, where patients self-administered neffy without any instructions, neffy is higher at every time point.

In EPI 16, we can see that neffy was similar to IM through 10 minutes.

Now, let's highlight the numbers with statistical significance. What we can see is that in EPI 15, IM was higher at 4 and 6 minutes, then neffy is higher at 12.5 minutes and later. In EPI 17, neffy was higher from 2 to 6 minutes, then at 15 minutes and later. There are no statistical differences in EPI 16 and through 15 minutes when neffy becomes higher. FDA clarified in their addendum that the difference seen in the first 10 minutes in EPI 15 is mostly due to the IM-PK variability. This figure is also a PK plot of the first 20 minutes, showing neffy is always higher than subQ, which as we know is an effective approved therapy.

Now, let's look at the clinical implications of this data. These are pooled PK data from Studies EPI 15 and 16. neffy exerts immediate effect on systolic blood pressure and heart rate as early as 1 minute. Systolic blood pressure and heart rate increases results from activation of

adrenergic receptors that reverse the anaphylaxis symptoms, surrogate endpoints for efficacy.

Now, let's discuss the FDA's consideration of 100 picograms per milliliter. In the FDA's addendum, they use 100 picograms per milliliter as an arbitrary threshold, but its relevance to acute administration of epinephrine is unknown. The concept of 100 is based on a single study by Clutter in 1980. In this study, six healthy subjects received increasing epinephrine concentrations as a continuous IV infusion. After each step-wise concentration increased, epinephrine levels were measured in 15 minutes. As a result, there was no change in systolic blood pressure and heart rate until around 100 picograms per milliliter, which may be very short for continuous IV infusion in this study design.

What about these responses in acute epinephrine administration? Here again, I show the systolic blood pressure and heart rate responses with neffy in the first 20 minutes. Based on these data, with more than 70 subjects, systolic blood

pressure and heart rate showed immediate increase as soon as one minute when the epinephrine level is still below 50; that's all symptom effects occur far below 100 with neffy. If we evaluate the proportion of subjects who reached 100 threshold in the first 60 minutes after single administration, neffy ranged from 83 and 100 percent, a similar range with IM, which was between 84 and 97 percent.

We can also look at the proportion of people achieving this threshold over time. On the left is EPI 15. FDA noted that at 5 minutes, neffy had a lower proportion of subjects who reached 100. On the right is EPI 17. Here we see that neffy performed better than IM at all time points on both 100 and 200 picograms per millimeter. Again, as FDA mentioned, the difference at 5 minutes in EPI 15 is likely due to high variability, and there is no meaningful difference between neffy and IM.

Now moving to the neffy PK data for repeat dosing or 4-milligram total dose, guidelines suggest that if a response is not observed in the first 5 to 10 minutes, a second dose should be

considered. A second dose is needed for more severe allergic reactions or due to delayed administration of the first dose. This occurs approximately 10 percent of the time. Given the severity of the reaction and the potential for hypertension, it is even more important to achieve higher exposures of epinephrine to ensure efficacy.

Here you see that based on Cmax, neffy is dose proportional between once and twice dosing. The Cmax for 2 doses is approximately 2 times that of the single dose, whether the second dose is administered to the opposite nostril or the same nostril. In contrast, IM and EpiPen are not dose proportional for first and second doses. With EpiPen, in multiple studies, we only observe a slight increase in exposure from a second dose, which was only 1.4 times of the first dose. For IM, the second dose resulted in 1.65 times that of the first dose. Again, for more severe reactions, we believe achieving higher exposure is an important consideration.

Based on extensive PK data, neffy exposures

are well within the range of injection products. Importantly, PD effects occur almost immediately with neffy, which is highly reassuring from a clinical perspective. Single-dose administration demonstrated more rapid and greater exposures compared to IM, which ensures efficacy. neffy shows a more consistent and lower Cmax than EpiPen, which ensures neffy's safety.

neffy achieved a doubling in exposure with the second dose, providing confidence that a treatment effect will be achieved if a second dose is needed for more severe allergic reactions or when treatment is delayed. Finally, data on pediatric patients were consistent with adults, with those proportional exposures between 1 and 2 milligrams. Additionally, PK modeling in pediatric patients supports that exposures are bracketed by injections.

Moving now to PK/PD correlation, FDA noted in their briefing document addendum that the PK/PD relationship is different among epinephrine products. The left Y-axis in blue shows mean

epinephrine concentration. The right Y-axis in red shows systolic blood pressure change from baseline on the top figures and heart rate change on the bottom. The X-axis represents each time point. You see that the red and blue curves move together, meaning PK and PD are well correlated for each product; however, the degree of PK and PD correlation varies. neffy generally has a lower epinephrine PK profile than EpiPen but has generally higher more sustainability response.

The key to answer this question about the difference in systolic blood pressure change is the difference in diastolic blood pressure. There is a poor PK/PD correlation for diastolic blood pressure because beta-2 receptors in the thigh widen vessels that increase the blood flow into the thigh. More blood flow in the thigh decreases the blood in the systolic systemic circulation. This causes a decrease in diastolic blood pressure, in red, which is more pronounced when injecting into the thigh.

Since the blood in the systemic circulation is reduced, systemic blood pressure increased is

also suppressed following injections. By avoiding injection in the thigh, neffy has a higher and more sustaining PD response, despite lower epinephrine PK profile, than EpiPen.

Now let's review PD response, including systolic and diastolic blood pressure and heart rate as predictors of efficacy. This figure shows the mean systolic blood pressure change from baseline on the Y-axis, with time on the X-axis. neffy shows a greater mean increase than IM and EpiPen. The figure on the right compares the mean Emax. Emax is the peak change from baseline and a benchmark for the overall magnitude of the treatment effect. neffy was not significantly different from EpiPen, but significantly greater than IM.

Here we see diastolic blood pressure did not change meaningfully after neffy but declined with both IM and EpiPen. In terms of Emax, neffy showed the greatest increase. The effects on heart rate demonstrate that neffy and EpiPen have similar increases. This is also observed on Emax. These

box and whisker plots show changes from baseline for systolic blood pressure on the left, diastolic blood pressure in the center, and heart rate on the right with once and twice dosing. The outlines are shown to highlight the maximum change observed.

In systolic blood pressure, the maximum individual changes are observed with EpiPen that is presumed to be from accidental ingestion in the blood vessel, resulting in rapid increase of blood pressure. For heart rate, neffy showed the greatest change. The changes in systolic blood pressure and heart rate observed across all studies with neffy are within normal physiologic changes observed with exercise.

ARS also tested neffy under various adverse nasal dosing scenarios. The studies include a dog anaphylaxis model designed to induce severe hypotension; a nasal allergen challenge study, or NAC, to study the effect of rhinitis on absorption; and an upper respiratory tract infection study.

Starting with the dog anaphylaxis model, given that we cannot ethically induce anaphylaxis

in humans, we conducted a GLP dog study to evaluate the impact of hypertension on neffy absorption using the same device we plan to market for humans. These results show the change from baseline in epinephrine concentration in the normal state, in green, and during severe anaphylaxis with significant hypertension in blue. The results support the concept that during actual anaphylaxis, absorption of neffy is unimpaired. In the figure, it appears that the absorption is slightly better with anaphylaxis than the normal state, which may be related to increased permeability during an allergic reaction.

Second, we assessed the impact of epinephrine absorption after the nasal allergen challenge or NAC-induced rhinitis. This is figure 2 from the FDA briefing document showing the EPI 16 results. In this study, we directly expose the nasal mucosa to an allergen and dosed where nasal symptoms such as congestion and rhinorrhea occurred.

FDA is asking you to consider the

sustainability of neffy. Considering that 90 percent of events respond in 5 to 10 minutes after the first dose and do not reoccur, having adequate epinephrine exposures in the first 20 minutes should ensure effect. To further address this question, let's look again at the actual PK parameters and concentrations.

These are the overall PK parameters that shows neffy rhinitis has a faster Tmax and higher Cmax compared to IM. The more rapid absorption with NAC-induced rhinitis is likely due to increased permeability of the nasal mucosa membranes. The more rapid clearance may be caused by rhinorrhea, or runny nose, which occurred in 30 of 34 patients. With NAC-induced rhinitis, epinephrine exposures, represented by partial AUCs, were significantly greater for neffy as compared to IM from 2 to 30 minutes. At 45 minutes, the overall epinephrine exposures were similar and not significantly different.

Based on epinephrine concentrations, neffy was also greater than IM for the first 15 minutes

and similar at 20 minutes. Again, we see the effect of epinephrine within the first 10 minutes, and in 90 percent of people who respond with first dose of epinephrine, symptoms do not reoccur. Thus, during the time when clinical effect is observed, even with rhinitis, exposures of epinephrine from neffy are greater than that of IM.

Turning to the PD results, the overall PD results with NAC-induced rhinitis are shown here. Maximum change in systolic blood pressure is shown on the left, diastolic blood pressure in the center, and heart rate on the right. The PD response, based on Emax, is lower with neffy rhinitis than neffy under normal conditions. This difference is likely due to the rhinitis condition. You may consider rhinitis as a local reaction, but actually it is reported to trigger systemic inflammatory effect.

FDA figure 12 shows systolic blood pressure was higher with neffy rhinitis compared to IM under normal conditions, through 40 minutes and comparable after that. Considering that systolic

blood pressure is the most important clinical outcome, the FDA's analysis of systolic blood pressure supports that neffy is as durable as IM under normal conditions. Heart rate results are also similar between neffy rhinitis IM under normal conditions.

Finally, in an upper respiratory tract infection study with patients that had similar congestion and rhinorrhea symptoms compared to EPI 16, there is no meaningful impact on the absorption of epinephrine, as represented by mean plasma concentration curve on the left. There is also no significant impact on PD responses, as represented by systolic blood pressure increase on the right.

The overall conclusion from our primary nasal challenge studies with neffy helps establish that even under worst nasal conditions, the PK and PD response is as good as IM under normal conditions.

I will now turn to neffy safety. Overall, ARS treated over 600 subjects with more than

1100 administrations across all studies and doses. Approximately 96 percent of all events with neffy were mild and quickly resolved. The most triggering events with neffy given once were mild nasal discomfort and mild headache. There are no SAEs observed in neffy or IM during any ARS studies.

There is no meaningful adverse events from neffy once or twice, or nasal pain, irritation, or smell. Minimal to no pain was reported using a validated visual analog scale, or VAS, and mean pain scores of 5 to 8 out of 100. No clinically meaningful nasal irritation was observed after neffy administration. Nasal discomfort did not appear to correlate with pain or irritation. Finally, there is no measurable impact on the sense of smell.

TEAEs for neffy were consistent with known adverse reactions for IM. Three moderate adverse events were reported in one subject on neffy. These included vomiting, dizziness, and heart rate decrease, which was similar to those observed with

IM. Severe events were reported with neffy in one subject, including syncope and hypotension. With IM injection, events of syncope, asthenia, and hypotension were observed in two subjects.

With twice dosing of neffy, meaning 4 milligram total, safety results were similar. One hundred percent of neffy TEAEs were mild in severity, and they resolved quickly. Time to resolution of events ranged from minutes to a couple of hours. No moderate or severe events were observed. With IM, one subject reported a moderate adverse event of vomiting, and no subjects reported a severe event.

Safety in the pediatric population was similar to adults. With neffy, there are 32 adverse events in 12 patients and 2 moderate events in one patient, including nasal discomfort and sneezing. Overall, safety of neffy was shown to have a low frequency of adverse events in adults and pediatric subjects treated with neffy dose once or twice. Most of the adverse events were mild and they resolved in minutes to a few hours with no

sequelae.

I'll now turn the presentation to Dr. John Oppenheimer, who will present his clinical perspective of the neffy data. Thank you.

Applicant Presentation - John Oppenheimer

DR. OPPENHEIMER: Thank you, Dr. Tanimoto.

My name is Dr. John Oppenheimer, and I'm a clinical professor of medicine at Rutgers University, UMDNJ. My research focuses on the needs of patients with severe food and venom allergies and how we can make treatments easier to use and administer. I'm happy to provide my clinical perspective on the neffy data.

The safety and efficacy of epinephrine is long-standing and irrefutable. While we have many IM and autoinjector options approved for our patients, the challenge we face as providers is a large majority of our patients and their caregivers struggle to use these bulky, needle-bearing injection devices. They fail to fill the prescriptions, carry their devices, and are hesitant to use their devices during an allergy

emergency due to needle phobia or fear of adverse reaction. This leads to significant delays in needed treatment and more severe patient outcomes.

The unfortunate reality for many patients is they have no real option that they're willing to use. neffy provides an alternative as a needle-fee discrete formulation of a proven product within a proven device. Thus, the key considerations for today's deliberations is if neffy can provide adequate epinephrine exposure to effectively and safely stop a severe allergic reaction.

While PK for IM injection and EpiPen are highly variable, we know that both are equally effective in practice. Looking at the PK results and the clinical experience with injection products, the data predicts for comparable efficacy to that of IM injection and EpiPen. neffy's pharmacokinetics are bracketed between that of IM injection and EpiPen, based on Cmax, median Tmax, or mean early partial AUC.

FDA raised some concerns about the early time points in the first 10 minutes. Specifically,

we saw these results are highly variable, and across all studies, neffy's pharmacokinetic results are not meaningfully different from IM injection in the first 10 minutes. As you review the data today, I suggest you consider the totality of data supporting neffy across three primary studies, all of which met the prespecified criteria of the PK profile, appropriately bracketed between IM injection and EpiPen across various parameters and at least comparable PD results.

While FDA noted in one study, EPI 15, the AUC 0-to-10-minute time point, the absolute value for IM was higher than neffy, this was not significantly different. Also, all other time points for partial AUC in all studies were numerically better for neffy compared to IM, with some statistically greater. While PK is reasonably bracketed, what's important for clinicians is the early and robust PD response observed with neffy, which is greater than IM injection. This should translate to good clinical outcomes for neffy.

Data on the pharmacodynamic response with

neffy is also encouraging, with single-dose systolic blood pressure, heart rate, and diastolic blood pressure all falling within a similar range with EpiPen, and greater than IM injection. Additionally important is that neffy is dose proportional with the second dose and gives increase in systolic blood pressure that's statistically better than EpiPen. This is important given that when a patient needs a second dose, the reaction is typically severe, and patients may be hypotensive. This greater increase in systolic blood pressure is very important. Overall, as a clinician, this brings me a sense of comfort that this should translate to excellent efficacy, even during anaphylaxis.

The safety results for neffy show an expected and acceptable safety profile, with mild adverse events. The lack of needle is a safety advantage, as there's no potential for IV bolus injection, accidental injections into extremities, or other needle-related injuries.

To conclude, patients and caregivers need

options with alternative administration methods to facilitate carriage and actual use in an emergency event. neffy has a great potential to overcome the challenges of existing injectable epinephrine, allowing patients to be treated in a timelier manner while providing exposures of epinephrine within the range of approved products.

The considerations raised by FDA are understandable, but the totality of data in both adults and children support that neffy should be both safe and effective in real-world use. Early exposures in the first 10 minutes show that neffy does not have statistically significant differences in PK across all studies. Additionally, the data in subjects with induced rhinitis demonstrate that there's a better epinephrine exposure in the first 20 minutes, clinical effects are observed in 5 to 10 minutes, and there shouldn't be concerns about sustainability of effect after 20 minutes once symptoms have resolved. If they don't resolve, as per guidelines, we give a repeat epinephrine dose.

At the same time, the pharmacodynamic response is as good, or better, than injectable epinephrine. The SVP in heart rate response is well correlated with exposure, and the differences across products is likely due to the physiologic difference between injection in the muscle and administration by intranasal or intravenous routes.

For me as a clinician, neffy's consistent increase in SVP and and heart rate, and less pronounced diastolic blood pressure drop, compared to IM injections is reassuring and will be a benefit for my patients. The PK/PD results in both healthy volunteers and subjects under nasal challenge adequately inform us on the expected benefit-risk for patients experiencing allergic reaction.

neffy represents the first needle-free alternative to current injection products, and I would very much like to have an armamentarium of epinephrine options for my patients. Thank you. I'll now return the podium to our sponsor to take your questions.

MR. LOWENTHAL: Thank you.

Clarifying Questions to the Applicant

DR. AU: We will now take clarifying questions for ARS Pharmaceuticals. Please use the raise-hand icon that indicates that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name, for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so that we may move on to the next panel number.

Dr. Troendle?

DR. TROENDLE: Hello. I'm James Troendle, statistician. I think my question is for Dr. Tanimoto, I believe. I have three questions,

really, but some of them have multiple parts.

The first general question is, before the studies were run, was there any discussion about an actual time range for bracketing that would be needed for the PK studies, before the studies were actually done within your discussions with the FDA?

Then the second thing is, why did you claim that -- you brought up FDA figure 1, so I'm going to have to ask about it. I wasn't going to ask you guys about it. But you claim that there was a difference in the first 10 minutes; FDA figure 1. You seemed to claim -- I'm not sure if I got it right -- that the first 10-minute difference is due to variability in the Adrenalin 0.3 milligram. And I wanted to get that straight. How could there be a difference that's based on variability? There could be a non-difference based on variability, so I wanted to understand that.

Then the third thing is FDA figure 2, since you brought that up, I had some questions about how that supports bracketing and what was meant by nasal challenge. All the arms in that figure, are

all of the Adrenalin arms in the same study, are they under a nasal challenge?

DR. TANIMOTO: For the first question, in the pre-NDA meeting, actually, FDA suggested 0 to 30 and 0 to 60 minutes. ARS kept 0 to 20 and 0 to 45 minutes. Then the discussion about 0 to 1 was the first time when we received the FDA briefing document.

The second question about the variability, yes, we acknowledge that there is high variability in any injection product, as I mentioned, but the variability in this -- based on our understanding, the variability between studies, EPI 15 is the only one that looks like neffy's smaller, the exposure is smaller, but when you compare it to EPI 17 and 16, it looks better or comparable. So what we meant is just the variability of studies.

DR. TROENDLE: My question is figure 1, though. You brought you figure 1, and you seemed to explain a way of difference in the first 10 minutes due to variability. So you weren't referring to this figure.

MR. LOWENTHAL: Sorry. We would just like to explain. On the previous slide, as you saw, we acknowledged that there were two time points that are different -- I'll put that back up.

DR. TROENDLE: Okay.

MR. LOWENTHAL: It's better to see the data because figures are deceiving. We like to look at actual data, and numbers, and statistics. If you just throw up a figure, figures don't necessarily represent the reality of what's happening.

If you look at EPI 15 -- and this is where we're showing you the statistical differences, and everything else is really the same -- you can see the coefficients of variation are enormous here. They're very large, so these are very highly variable numbers. FDA is correct, at 4 and 6 minutes, there is a statistically higher value in EPI 15 for those two time points; so at 4 and 6 minutes, it's statistically different. At 8 minutes, it's not different. At 10 minutes, actually, neffy is higher numerically but not statistically different.

But again, you're a statistician. If you look at the variability there, it's a very high variability. And when you start looking at individual time points from study to study, you can just always find one time point that might be different than the other because of high variability.

EPI 17, where people are self-administering, you could see the first three time points are statistically higher for neffy. There are then three time points that are the same statistically, not different, and then neffy becomes higher thereafter; 16, again, no difference through 12-and-a-half minutes, and then neffy was higher from 15 minutes on.

So that's what we mean by across studies, and if you look at the numbers across the studies for IM -- so if you look at EPI 17, EPI 16, and then go to EPI 15, the numbers for IM in EPI 15 were very much higher than the other studies. So that's what FDA even wrote in their addendum; that it appears like the difference is more due to that

discrepant number from IM in EPI 15 at these two time points, where it was much, much higher than in other studies.

Does that help explain it?

DR. TROENDLE: Yes. I would still say the first 10 minutes on healthy volunteers, if you required bracketing the first 10 minutes -- I don't know how important it is, but I'm just pointing out that it hasn't been demonstrated, except after maybe 8 to 10 minutes. But anyway, okay; that's fine.

MR. LOWENTHAL: Just to clarify that point, as Dr. Tanimoto mentioned, in FDA's pre-NDA meeting minutes, they actually asked that we bracket between 30 and 60 minutes. We actually felt that 0 to 20 and 0 to 45 were better. So in the protocols, the prespecified bracketing time points were through 20 minutes and through 45 minutes, and they do bracket at 0 to 20 and 0 to 45.

DR. TROENDLE: Well, wait a minute. When you say 0 to 20, I'm thinking it's got a bracket from 0 all the way up to 20, and it doesn't bracket

all the way from 0 to 20.

MR. LOWENTHAL: No. It's a partial AUC that accounts for the partial -- there is never bracketing discussed with FDA based on absolute values. This is absolute values.

Can we get the partial AUCs up? Sorry. Just to be clear for everybody, the criteria that were prespecified in the protocols was a partial overall exposure through 20 minutes and a partial overall exposure through 45 minutes. So that's what the prespecified bracketing criteria are; they're partial exposures, not individual time points. That was never discussed with FDA prior to FDA's briefing document.

In addition, it was never discussed, prior to FDA's briefing document, that 0 to 10 was a criteria for bracketing. So what we're doing now is post hoc analysis, and we understand FDA is concerned about the first 10 minutes, but the first 10 minutes was never defined prospectively as a criteria, either by concentration or by partial AUCs.

DR. TROENDLE: Okay. Thank you.

MR. LOWENTHAL: Can we get the slide with the blow-up, the lag in EPI 15?

I just want to point out one more point on this that might be helpful for you and the committee. If we blow up the difference in EPI 15 -- that's what you're seeing here. On the left is the EPI 15 profile that FDA showed, you can see where the IM is higher than neffy in the early period. If we think about what that Tlag is there, the Tlag is around 2-and-a-half minutes.

I'd like to actually get Dr. Camargo up to talk about this a little bit and what the meaning of this is. If you look on the right, the pharmacodynamic response in neffy is showing that it's having a response immediately, and much greater than IM even from 1 minute. So that Tlag is not translating to clinical effect.

Dr. Camargo?

DR. CAMARGO: Hi. This is Carlos Camargo. I'm a physician-epidemiologist from Boston, professor of emergency medicine, medicine, and

epidemiology at Harvard. I guess for me, looking at this slide, the pharmacodynamics show a very clear story that product is having an effect. And as Rich just said, in the first 10 minutes, there are these minor differences, 2 minutes, 2.5 minutes.

But I would just remind everyone that this is a t0 set by a protocol. In the real world, the t0 is whenever the patient initiates the treatment, and in the real world, we've heard already from many people, including some data that was presented, that this product would be given earlier; in fact, many minutes earlier. So all of this becomes somewhat moot. The products delivered earlier will have its effect, pharmacodynamic effect, very well in those first 10 minutes, and I'll just leave it at that. Thank you.

MR. LOWENTHAL: And finally, on your last question, there was no criteria set for the rhinitis study. That was purely an experimental study to see what happens with rhinitis. And also, there is no criteria set for twice dosing with FDA,

so there's no prespecified criteria for that. That was just to see what happens with twice dosing. And there, the remarkable finding in our studies, from very early studies, with even 1 milligram and twice dosing with injection and 2-milligram twice dosing injection is, really, IM is not dose proportional. Nasal is dose proportional; IM is not. So that was really the remarkable finding in that study.

DR. TROENDLE: And the figure that compared the different groups in the nasal challenge, what does that mean by nasal challenge? And with the groups that got Adrenalin, were they under a nasal challenge?

MR. LOWENTHAL: Yes. So that's a good point. The neffy group, what happened is they were pre-tested for their allergen. We knew what kind of allergy they were allergic to, and they were also pre-tested where we sprayed pure antigen up their nose. So we literally spray antigen up their nose. We increase the dose until they have an allergic reaction and screening as a test. When we

get to the study, they're challenged with the antigen by spraying it directly into their nose. So it's a very rigorous study, and I can put that up.

They spray it into their nose. They're tested by TNSS, which is a scale that tests for congestion, runny nose, itching, and sneezing. They have to have a score of 5 out of 12. In our study, the way we ran this study, they all had very significant congestion and runny nose. We dose immediately after we test, so immediately after we get the scoring, they have congestion, runny nose, and we dose.

What I'd like to also clarify is that FDA focuses on congestion -- and if I can get the data slide up for that -- but really it's a complex situation. It's a really tough challenge on nasal absorption. It's never been done before with any other product approved for nasal administration. What you really see here is that congestion that FDA's focused on is not really correlated 100 percent to the Cmax, the concentration effect

that is absorbed. The congestion, from our experience and everything we know across many studies, accelerates the absorption. So what you're seeing as a faster absorption is due to the congestion, the edema, the permeability increase in the membrane. However, what's causing the more rapid clearance -- and it makes sense if you think about it -- is the rhinorrhea, the runny nose. So when you have more rhinorrhea, more severe rhinorrhea, you get more rapid clearance, and the drug drains down more quickly.

So that's the difference here. And as we said, clinically, the question is what does this mean? Most clinicians are not too concerned about this. FDA's briefing document is the first time we've seen very serious concern about this. But really, there's a question of sustainability, and you go back to the pharmacodynamic response, and that shows very clear sustainability that's as good or better than IM, based on systolic blood pressure, which is really the primary measure of clinical effect.

Here we see the FDA figure on this. This is a median systolic blood pressure change. We could also look at mean, but the median that FDA presents, obviously, through 40 minutes, systolic blood pressure is higher than the reference, which is 0.3 milligrams IM, and then the same is referenced through 60 minutes, and actually goes beyond 60 minutes. So that's basically what is done in that study.

DR. TROENDLE: Okay. Thank you.

DR. AU: Thank you.

I'm going to call on people on the order of my screen, so I apologize if someone raised their hand prior, and I'm getting this out of order.

Dr. Kelso?

DR. KELSO: Yes. I still don't have a great explanation for why there's this apparent disconnect between PK and PD. There clearly looks like there were some time points, particularly early on, where there is by PK, meaning there's literally less epinephrine in your bloodstream, and PD, where despite that, your heart rate or your

blood pressure is higher. It's a good thing that you're having the PD response; I just haven't gotten a grip on the explanation for why there's that apparent disconnect.

MR. LOWENTHAL: Dr. Tanimoto?

DR. TANIMOTO: This has been the question -- we received this question from FDA in an early meeting because with every study, we observe higher PD response following neffy, even 1 milligram.

The preclinical study, the full figures?

This preclinical study was helpful to understand the physiology. This study induced anaphylaxis in dog, and on the top left is blood pressure. First, they induced anaphylaxis, and then after that, that blood pressure drops. After the blood pressure drops, they administer epinephrine by IV bolus, IV infusion, IM, subQ, and control, and you can see there's a drop following IM here. When you look at the pulmonary wedge pressure on the right, and then cardiac output on the left, you see, again, there's a drop following

IM. Pulmonary wedge pressure and cardio output can be an indicator for the amount of blood in the body and in venous return.

Based on this, this was helpful to understand because it looks like following IM, there's a reduced venous return. Here, it's easier explained. When the epinephrine goes into the thigh in the skeletal muscle, the beta-2 receptor is activated, and there's vasodilation. That decreases peripheral vascular resistance, followed by increased blood flow into the skeletal muscle in the thigh. As you know the thigh is a big organ that can hold lots of blood vessels, because when you run, you need blood vessels. That's how Adrenalin works. And then, reduced venous return causes DBP drop and then also suppressed SVP increase.

This is how it looks, and that's what's going on when you inject epinephrine in the body, but the difference is when you inject the epinephrine into the thigh, 100 percent of epinephrine will go through the thigh. Therefore,

this flow effect will be much more than intranasal, where there's only 15 to 20 percent of epinephrine from the systemic circulation that goes into the thigh.

MR. LOWENTHAL: We see this drop in diastolic blood pressure from injection into the thigh with every study we've done. So every time you inject in the thigh, you're going to get a drop in diastolic, and that's suppressing the systolic blood pressure. neffy doesn't do that, intranasal or IV; so IV we should say also doesn't do this, and that's why you're getting a greater increase in systolic blood pressure.

DR. KELSO: Okay. And then along those same lines, comparing the PK and the PD, can you put up CO-39? Is there an analogous PD slide?

MR. LOWENTHAL: We do have PD from each study, yes.

DR. KELSO: With these early time points, which are the ones we are most interested in, where we can see --

MR. LOWENTHAL: Well, let's look at 15.

This is EPI 15, as FDA pointed out, they're concerned about those early time points, and we blow it up to the first 20 minutes to match the numbers we just showed. You can see there that blood pressure and heart rate far exceed IM, so the higher concentration of IM is not translating the clinical outcomes.

DR. KELSO: Okay.

Just a couple, not necessarily -- well, maybe questions. It would seem like we've used IM as the comparator for the bulk of these comparisons, when in fact it would seem like EpiPen is the better comparator because what patients are using in the field is not drawing it up, IM, out of a syringe; they're using some sort of autoinjector. But the bulk of the comparison seems like they have been with IM.

There does seem to be some pretty striking differences, which is sort of the question part of this, which is why would injecting the same amount of epinephrine in your thigh muscle with an autoinjector versus a syringe and needle lead to

such different pharmacokinetics with the EpiPen having a much higher and quicker peak?

DR. CASALE: John, those are good questions. This is Tom Casale. I think as you're aware, the needle and syringe is what's typically used in the emergency departments. I think there's better control of how that's delivered, whereas with an EpiPen, depending upon whether the patient's obese or whether they have problems with the device, they may not deliver it to the same depth as what you do with a needle and syringe.

Nonetheless, it was clear that the PD effects for both did not correlate very well with the PK, probably due to that activation of beta-2 receptors in the thigh, whereas with the intranasal, there clearly was a good correlation with PD. I think ARS did a good job comparing all the different devices to the intranasal preparation. True, there's more comparison with the needle and syringe, but I think there's a sufficient amount of EpiPen data to show that the drug works as good, or better, in regards to the PD

response.

DR. KELSO: Okay. Then finally, there's been some kind of alluding to some concern in one of these studies, where it appeared that the intranasal administration, the level sort of fell off too soon or something, and I guess we don't really know. When we give somebody a dose of epinephrine for anaphylaxis obviously we need an early response right away, but I don't know if the patient is still better half an hour later because they've recovered or because they still have a certain amount of epinephrine in their bloodstream, and it might be the latter.

So whatever that pharmacokinetic concern is about a level falling off too soon, what happens pharmacodynamically during that time as the level comes down?

MR. LOWENTHAL: Well, let's put up, again. FDA's figure on the systolic blood pressure. If you recall the figure from the PK, the PK was much more rapid and higher for neffy epinephrine and then crossed IM around 20 minutes, and was a little

lower, but still kept a relatively flat profile after that.

What you see in the pharmacodynamics is here, and then I'm going to refer to Jay Lieberman, who's on the phone -- he's on on the line -- for the discussion about the sustainability of effect.

At least from a systolic blood pressure perspective, if you look at FDA's figure, the red line and the light blue line, the red line is neffy with rhinitis; the orange line is neffy without rhinitis on blood pressure, so it is lower after 10 minutes or 15 minutes compared to without rhinitis. But even compared to IM, the blood pressure remains up, so it shows activation of receptors in effect, and it's higher than IM through about 40 minutes, and then about the same through 60 minutes and beyond. So this would imply that there is not really a concern about sustainability.

Jay, I don't know if you're on.

DR. LIEBERMAN: Yes.

MR. LOWENTHAL: Why don't you speak to this

a little bit?

DR. LIEBERMAN: Yes, happy to. It's a great point, Dr. Kelso. There are a couple things I would say about this. Number one is, somewhat, in my opinion, the proof's in the pudding on this slide for instance; that if you do get a little drop in the PK tail or the sustainability, it doesn't appear, based on all the data that ARS has produced, that there is a pharmacodynamic correlation with that drop in PK.

Does it matter? The answer is no one knows. The question's a little bit academic in my opinion. That's also because in the real world, what's going to happen is if I'm, during a food challenge, given an allergy injection, or telling my patient what to do, I'm dosing. If I don't see a response, I'm redosing, and I am having that patient go to the emergency room. So if that PK durability is truly clinically relevant, will it be relevant in the real world in a true anaphylaxis case? I don't think so because what we'll continue to tell our patients is if you're not getting clinical response

after the first dose, redose within 2 to 5 minutes; no problem. If that sustained response isn't there, you need to go to the emergency room, which is what I would do with my patients and what I would tell them anyway.

So that's kind of the way I view the PK durability.

DR. KELSO: Okay. Then this slide where it's labeled Adrenalin 0.3, other slides, it says Epi IM 0.3. I assume when the slides are labeled Adrenalin 0.3 milligrams, that means IM administration.

MR. LOWENTHAL: Yes. It's the same. Just on our slides, we tended to label it one way, and this is FDA's slide, which they label it a different way, but it's the same, of course.

DR. KELSO: Okay. Great. That's all for me for now. Thank you.

DR. AU: Thank you. For the record, that was Dr. Kelso.

Can I ask committee members to please state their name, for the record?

Dr. Le?

DR. LE: I think you're calling me. Jennifer Le.

DR. AU: Yes. Sorry about that.

DR. LE: Sure. Hi. Jennifer Le. I am clinical pharmacy and pediatric infectious diseases at UC San Diego. I wanted to first commend ARS for already initiating clinical trials for young children at 1-milligram dose. Definitely, this demonstrate your support to address an unmet medical need in that population, which is very important as well.

I have two questions, the first one being related to the mild adverse effects in adults versus children. I think these are slides 69 and 73. Can you provide some insights why you see more adverse effects in children -- only focusing on the mild ones -- versus adults?

MR. LOWENTHAL: Yes. I don't think we would say that it's more. We treated 21 children. This is from the safety update to FDA, so it's more than the PK number that FDA shows or we show, but

there's 21.

I'd like to actually ask Dr. Fleischer to come up. Dr. Fleischer was one of the major investigators in this study, and I think he could speak to how the kids tolerated it. And the side effects are, as we said, relatively minor and infrequent, or most of them are single event type of events.

DR. FLEISCHER: Hi. Dr. Fleischer from Children's Hospital Colorado, University of Colorado School of Medicine. Yes. We were one of the sites for the studies, and the patients tolerated it very well. As you see, there are very mild symptoms that were infrequent. They're more frequent when compared to the adults because they're lower numbers compared to the over 100 adults that were done.

But they're well tolerated, and it's all very quickly in all the patients without any side effects and anything that happened days later or anything like that; so very well tolerated. I hope that answers your question. Thank you.

DR. LE: Can I have a follow-up on that? On this slide here, there's a report of vein rupture, the very last one. Can you provide a little bit more information on that?

MR. LOWENTHAL: Yes. That was a result of the venous puncture of taking the blood out of the arm, so that was also reported. Everything's reported. We don't differentiate. Some of these events, too, could be caused by the procedures that were done to the children. It's a relatively tough study. In our smaller kids, we're actually finished because we did enroll 21 kids 15 to 30 kilograms with the 1-milligram dose. So once neffy's approved, we'll be able to file that immediately to expand the use to the smaller kids. They tolerate it really well. They get even higher blood levels as you go down in age. I think we had four 4 year olds, so we have really brave kids and brave parents in this study.

We also have a commitment -- by the way, the European Pediatric Committee, PDCO, has a postmarketing requirement in Europe that we have to

go down to age 1, so we will be developing a product, a lower dose, for down to age 1, where we will have to modify the device, get a modified device, to be able to be sure that we can dose in that age population; 4 and up seems to be fine with the current device.

DR. LE: One other question related to pretty much I guess that recommendation. Given that there is a delay, at least to the maximal absorption -- for this formulation here, I think up to 10 to 20 minutes or so -- what would be your recommendation in terms of what time to administer the second dose?

MR. LOWENTHAL: Could we put up the PK slide one more time?

I just want to clarify one thing. FDA talks about differences in the first 10 minutes, but it's not a 10-minute delay. As we said, there's one study which showed -- and these are highly variable results -- two time points at 4 and 6, and what it is, is it's a 2-and-a-half-minute delay; so the delay between that absorption, getting to the same

level as 2-and-a-half minutes.

By the way, in the repeat-dose study, you get those proportional results with neffy, not with IM or EpiPen, and it doesn't show this type of problem in the repeat-dose study.

DR. CASALE: Hi. Tom Casale. I think the recommendations that we typically follow are those that Dr. Lieberman stated. If a patient does not significantly get better in five minutes, we tend to redose, and if they don't get better in another 5 or 10 minutes, then we think about whether we have to activate EMS or do something of a higher degree.

DR. LE: Okay. Thank you.

DR. OPPENHEIMER: This is John Oppenheimer. I'd like to make one other comment. First of all, if you look at 15 and 17, they're essentially replicate studies. One is healthcare providers and the other one is real world, but you can see totally different results. So I don't know that we want to focus on just one study; again, look at it in total.

The second thing, what Dr. Camargo said I think is really important. What we're really asking is, is the unmet need delay? Because if there's a 2-minute lag, if I wait an extra 10 or 15 minutes to give my first dose, is that a bigger concern? And I think you need to think about this in total as you make your decision.

DR. LE: Thank you very much. That's all I have on my end.

DR. AU: Thank you.

I just want to acknowledge that we're going well past the agenda timeline, and I think that's fine for the context of the follow-up questions for the sponsor, and then we'll try to find time later in the agenda to make up.

Let me go to Dr. Jones, please.

DR. JONES: Yes. This is Dr. Bridgette Jones. I had some additional questions about the pediatric study. I know your sample size of children, I think you said it was 21 children that were in the studies total, I believe.

MR. LOWENTHAL: There's a little over

80 children in total, but the group that is 2 milligrams and 30 kilograms above is a little over 20; it was 21, yes.

DR. JONES: Okay. And your age range is 4 to 17. Can you talk a little bit or provide some data on the proportion of ranges of ages in the study, of the kids in the study? And also, did you see any age-related differences in PK or PD? Are we able to look at that at all?

MR. LOWENTHAL: Okay. I can show you the distribution of demographics for the 2-milligram group, and then we could talk a little bit about the age and PK-related differences.

At least with the 2-milligram group, these are the older children that are under review right now. FDA is considering approval of neffy for 30 kilograms and above in children of that body weight. We'll file a supplemental NDA after approval for the smaller kids, so I think we should focus on the ones that FDA is considering for approval.

In the population, the age range in this

population was from 8 years old to 17 years old, and the median age was 14 years old. So median, 14 year olds these days, they're relatively large, so they're getting close to adults, and then male/female was pretty evenly split between the groups, and then you can see the other race and ethnic backgrounds, and weights. The mean weight was 54 kilograms weight, and there was a distribution around that from 31 to 86 kilograms.

If you put up the interim results again from our core deck, you can see we also had 25 1-milligram kids as supportive. We had started with the 1-milligram dose, and then increased to 2 in the children. So we've actually enrolled -- and this is PK so, again, 25 in one group and 16 with PK in the other group. The other five are available but we didn't have time to get them in the NDA, and FDA asked us to submit whatever we had at that time in the NDA.

So again, that's the number of kids we have in the NDA that have PK, and you can see the PK between 1 and 2 milligrams very nicely dose

proportional. The kids do get slightly higher blood levels than adults. Based on the PopPK modeling, there is not a big weight effect or age effect with neffy, with intranasal. There is with injection a weight effect, but there is not with intranasal. So the difference in PK here may be the weight a little bit or it could be that the children just had better permeability; we don't know.

DR. JONES: Then in the briefing materials, in figure 18, it appears to show a difference in the PD effect between children and adults. Can you comment on that?

MR. LOWENTHAL: Yes. This is not unexpected; actually, this is very expected.

Dr. Fleischer, do you want to come back up and talk about this a little bit? Children obviously are children, and have much more elastic arteries and better reflex.

Do Dr. Fleischer can speak a bit, and if you want that slide up, you can put it up.

DR. FLEISCHER: Sure. As you know, children

are not adults. They're not just small adults. They have differences in their vascularity and in responses.

PK 113, you can put up. This is just differences in exercise, and Dr. Casale can comment on some of the receptors and things, too. But in seeing little dips in the systolic blood pressure, you'd be compensated with the heart rate that went up as well. So I think that shows the effect that it's going to have significant effects on these kids, and we've seen it work well. I have confidence in that.

MR. LOWENTHAL: Based on the exercise, literally, the difference we see between adults and children on systolic blood pressure is actually quite predicted from the literature on exercise.

DR. JONES: Okay. Can you go back to figure 18? The explanation is it looks like the blood pressure response is actually lower for both doses in kids compared to the adults overall.

MR. LOWENTHAL: Yes, correct.

DR. JONES: And the heart rate response as

well.

(Crosstalk.)

MR. LOWENTHAL: Right, and that's expected. That's expected, as we said. If you go to exercise literature -- let's put that slide back up again just to remind them -- this is a summary from some of the literature, where adults are on the right and kids are on the left. And you can see as you go down in age, the blood pressure and heart rate differences are going to be -- this is systolic blood pressure but we can do the same for heart rate. You just don't get the same increase, and kids don't have the same increase in systolic blood pressure from exercise as adults. So this is actually very well predicted by the literature.

DR. JONES: Do you think that could be related at all to the ontogeny of receptor function, what may be behind that? Could that be relevant to the pharmacodynamics, to the actual effectiveness of the drug in young kids?

DR. CASALE: This is Tom Casale. I could say that in my own research, looking at alpha,

beta, and cholinergic receptors at various age groups in lung samples, there's really no difference in the affinity or binding of those receptors based on age, and I don't think that there's any reason that there would be.

DR. JONES: Yes.

I have one other question about the pediatric age group. As far as some of the human factors studies, did you see any differences in the pediatric use of the device compared to adults? I assume the nozzle size is the same. It's not a smaller nozzle --

MR. LOWENTHAL: Yes.

DR. JONES: -- so particularly in the younger kids, was there any difficulty in administering the drug?

MR. LOWENTHAL: Yes. We actually did two large studies. We did a full validation study of 90 subjects, and 30 of them were children; 15 had prior EpiPen experience and 15 did not. And in that study, nobody had any dose errors, and they were not trained. They just were able to look at

the instructions on how to do it, and they were all able to do it well, without training, and the age there was from 10 to 17, just so you know what we defined as children in that study, and it was down to age 10.

In the post-validation bridging study, we did see some use errors. That was attributed to actually to where we actually had to use an empty device because the site did not want to use saline as in our first study. They requested IRB approval if we used saline, so we used an empty device, which means the device, as I'm showing here, has a vial in it. It's filled with liquid, and when you fire it, it fires. And it has some resistance. When you don't have that vial in there, there's no resistance, and it fires.

So I think five of the untrained children, when it's fired, the snap was so hard that they did lose control of the device, so we say it popped out of their nose. Whether or not they would have got the full dose is not clear. Then when we trained the adolescents -- that was untrained -- there was

only one that did that.

But we really attributed it to the empty device and the fact that there was no resistance because we know from other human factors studies, across the other six products that have been approved, two of them, as I said -- or three of them. Actually, I have been intimately involved in all the work, and the NDA filings, and representing them to FDA, and this kind of thing has never been seen before. So we think it was just due to the fact that we had to use the empty device for the site.

As you know, Narcan with this device is now approved OTC, so it's going to be used without any direction at all, and I think the FDA has pretty high confidence in this device being able to be used without training.

DR. JONES: Thank you.

DR. AU: This is David Au, and I'm going to take the privilege of interrupting here; I'm sorry. We have seven questions, and we're already 15 minutes over the allotted time.

What I would suggest is that we're going to continue on, but in follow-up from now, I would like both the committee, as well as the sponsor, limit the number of questions and responses, so that we can actually try to get ourselves back, otherwise, we're going to go well over.

MR. LOWENTHAL: And we'd be happy to answer other questions during the discussion session, as well, if needed.

DR. AU: Right. I understand. Hopefully this will address some of that, and we can make it up during that time.

I'm going to call out the order for the next two people. It will be Dr. Greenberger and Dr. Nelson.

Dr. Greenberger, can you please ask your question?

DR. GREENBERGER: Thank you. Dr. Greenberger. I'm just going to ask one question instead of two, and that is for Dr. Tanimoto or Lowenthal.

What was the position of the study subject

in terms of body? Are they supine in the study or not? Also, EPI 15, the nasal challenge, I assume the challenge is when the person's seated. How is this used or administered in terms of body position? Thank you.

MR. LOWENTHAL: Yes. Good question. FDA required us to have everybody in an upright sitting position, which is worst case for intranasal. So they were not reclined. They were all sitting straight up, and they were kept straight up the entire time.

DR. GREENBERGER: And that's all the data we're seeing is the seated study.

MR. LOWENTHAL: Yes. We know from other studies that if they are in a semi-supine, or a supine position, they would actually get probably better exposure with intranasal, so this is a worst-case scenario. We actually have a lot of situations here with worst case, including for IM, where we know body mass impacts IM very much, and especially EpiPen if it's not intramuscular, if its subQ in a heavy person. We limited our body mass

in these studies, so it actually favors IM in that regard.

DR. GREENBERGER: Thank you.

DR. AU: Thank you very much.

DR. L. NELSON: Thank you. Lewis Nelson from Rutgers New Jersey Medical School in Newark, New Jersey. One comment, which you can choose not to respond to, but that would be fine either way, and then one quick question.

The comment is that autoinjectors differ from needle and syringe, and I just wanted it to be clear that everybody understands this. An autoinjector has a pressure head, so when it injects the drug, it sort of diffuses a little bit through the tissue, whereas --

MR. LOWENTHAL: Correct.

DR. L. NELSON: -- needle and syringe winds up in a reservoir, in fact, at the tip of the syringe, so the kinetics of the two are quite different.

MR. LOWENTHAL: Right

DR. L. NELSON: And that's why when we

compare the EpiPen to needle and syringe, they look quite different --

MR. LOWENTHAL: Absolutely.

DR. L. NELSON: -- because even at the high end, their mechanism of actually injecting into the tissue is quite different.

MR. LOWENTHAL: Correct. And EpiPen also has a much deeper injection. It goes much deeper than an IM needle would.

DR. L. NELSON: Good. Yes. That's all I wanted to say, and thanks for the comment.

So my question is -- and I appreciate that we needed to try to mimic clinical reality by inducing a rhinitis and using an allergen, and that does help to explain the absorption kinetics. I guess what's missing is the hypotension and the other effects that are going on in a human being when they are suffering from anaphylaxis.

Now, I understand the dog model was attempting to try to account for that, but what I don't know is whether or not a dog's nose and what we can expect to see from that absorption is

characteristic that's similar to a human, because I assume it's not. I don't know enough about dog noses, and there are all different kinds of dogs with different kinds of noses. Humans tend to be a little bit more similar. But how well can we adopt this dog anaphylaxis biology, which does mimic hypotension but doesn't mimic nasal absorption, to a human, which does the opposite?

MR. LOWENTHAL: Dr. Casale can answer as well.

DR. CASALE: Hi. Tom Casale. Thanks for the question. We would assume that hypotension would not have any effect on the nasal administration and the effects of the nasal administration; however, we do have to consider that if a patient has anaphylaxis, they often have nasal symptoms that would be similar to those that the patients have with the nasal allergen challenge. So locally, that gives me more confidence that under those conditions of a nasal allergen challenge, that the PK and PD effects were therapeutic in regards to bracketing between the

other devices that were measured.

DR. M. NELSON: Just a quick comment. So you're saying that hypotension won't affect absorption characteristics of the drug in the nose? I mean, blood flow would be reduced, I assume.

DR. CASALE: I'm not aware of any studies to show that, unless --

MR. LOWENTHAL: There's a study up there; that study.

DR. CASALE: Well, I mean in humans. He's asking in humans because dog's noses are bigger than -- except for me --

(Laughter.)

DR. CASALE: -- they tend to be bigger.

MR. LOWENTHAL: One thing to also point out, we did this study, actually, because Europe asked to understand the same question. The Europeans wanted us to do this animal model in order to help answer that question.

The increased absorption during anaphylaxis seen here is most likely due to increased permeability due to the anaphylaxis itself -- blood

vessels become more permeable -- and also edema because edema makes the mucosal membrane more permeable. So what's more likely to happen -- certainly hypotension doesn't affect it, and we know that from Narcan, too. Narcan's administered in people that are in respiratory arrest, and it works very, very well, Narcan nasal. So what's more likely to happen, even in a human, is that the anaphylaxis event itself may actually improve absorption intranasally.

DR. AU: Great.

(Pause.)

DR. AU: Dr. Nelson, you're on mute, if you're speaking..

DR. L. NELSON: Oh. I'm sorry. I thought my question was answered. Thank you for your answer. I appreciate it.

DR. AU: Okay. Great.

Dr. Peden?

DR. PEDEN: Thank you. This is Dave Peden from the University of North Carolina. My question is simply, is there any knowledge that nasal

administration brings epinephrine to the central nervous system, and is their central mediation of the effect of epinephrine that might explain the difference in nasal administration versus systemic administration more distally?

MR. LOWENTHAL: Yes. It's very unlikely. There's a very small olfactory center that, in theory, people have theorized, some drugs can penetrate in the brain, but it's never really been proven well in humans, and it's very unlikely. We've never looked at it, but we don't think that's at all involved in here.

I don't believe they're -- I mean, it's a cardiovascular effect, so I don't know if there's receptors in the brain that would affect the cardiovascular function, systolic blood pressure, heart rate, or beta-2 response to mast cells. So I don't think that that would be a factor, but we've never actually tried to look at it, and it's been only looked at in animals, to be honest with you, and one or two drugs that I'm aware of.

DR. PEDEN: Thank you.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: Thank you. James Tracy, University of Nebraska, and really a very simple question. We seem to be going back to slide 39 quite a bit, and one of the things that Dr. Oppenheimer's sort of alluded to was the similarities in populations between EPI 15 and EPI 17, and they're really very similar, one being healthy and the other being relatively asymptomatic.

I know we have the dog model for anaphylaxis, and I was just wondering -- and maybe you can and maybe you can't comment on this -- but do we have any anecdotal reports, really anywhere, including Europe, with somebody that has utilized this product actually during anaphylaxis?

MR. LOWENTHAL: Yes, actually there is, and they'll be speaking at the public session, I believe, because there is a patient using it that has very severe allergies, and they see immediate effect within a few minutes.

DR. TRACY: Thank you.

MR. LOWENTHAL: Sorry. Dr. Casale?

DR. CASALE: Jim, I was also going to say that we do have patients with acute urticaria, and we see rapid resolution of the urticaria in those patients. And we are conducting a study in asthma to look at the reversibility of airway obstruction just to assure everyone that the drug has the appropriate physiologic effects, which it does.

DR. TRACY: I mean, ultimately, the real question here is efficacy, and that's an important element.

MR. LOWENTHAL: Yes. We can show some of those things, if you need, but it's helpful.

DR. TRACY: Thank you.

DR. AU: Ms. Schell?

MS. SCHELL: Thank you. I just have a question, more than anything, on slide CO-39. It has healthcare provider administration versus self-administrating, and it seems to appear there was a difference in self-administration compared to the healthcare provider administration.

Can you explain that?

MR. LOWENTHAL: Actually, there wasn't much difference between healthcare provider and self-administration with neffy. I think FDA showed that as well in their briefing book, that the curves are very, very similar between the two, so there wasn't a significant difference with neffy. And when we say healthcare provider, it was a site person at the clinical site that dosed everybody.

Actually, where we tend to pool -- and here this is FDA's figure, just to put that up. So you can see that there's really not a meaningful difference between the two curves. They crisscross a little bit, but it's really kind of normal PK variability. But with either self-administration or site administration, meaning a person at the site, which we call healthcare provider, there's not really a difference.

Just for one more point of clarification, really, we consider FDA 15 and 16 to be almost identical in that they're both conducted at the same site. The same person was actually dosing

both of those studies. Seventeen is a different study because that's people self-administering, so that's not healthcare provider or site administration, but 15 and 16 -- and that's why we often put those together, to get better power, to get bigger numbers because, literally, it's the same site, same people. They're both dosing IM. They're both dosing neffy, and those are really provable studies. We don't tend to pool self-administration for that reason.

MS. SCHELL: Thank you.

DR. AU: Thank you.

I have one question, and I thought I would just save it to the end to give the committee an opportunity.

Part of the rationale is that there will be better access and delivery. What direct evidence -- and I am asking about direct evidence -- do you have that this will actually be delivered in a greater proportion than, let's say, EpiPen?

MR. LOWENTHAL: Yes. We've done a lot of

research on this, a lot of patient research, surveys, and other information. There's also a lot of literature. The allergists will know the literature on this, the delayed administration, carrying, and all these problems in the community. What we know from our research and surveys is that people will carry this device much more often.

(Showing device.)

MR. LOWENTHAL: It's much smaller, easier to carry, and as we mentioned earlier, we're doing everything we can to facilitate carrying it. I can have this in my pocket all the time with my keys, or I can hook it in a bag and really help facilitate. Because if it's not with the patient, all these things we're discussing about PK/PD, it doesn't matter. If they don't have it with them, it's a moot point. They don't deliver, they don't have drug, they go to the hospital. And they delay administration because they have to get to the hospital to get a dose of epinephrine. So that's one.

From our patient surveys, basically, we

believe that the rate of carriage will increase significantly by about 35 percent, and right now, 55 percent with current dose or current products, and that matches the literature well from our studies, and also we believe we will increase to roughly about 85 percent with neffy. And you'll hear at the public session, and you saw the public comments on this, so I don't think there's -- I mean, it's a pretty huge number of public comments, over 600, which is almost unheard of in advisory committees.

Then we also did a recent study. We've done multiple studies. This is actually a study we did recently in 200 people that have actually dosed in EpiPen within the last 12 months, so they had very recent experience, and 100 where caregivers and 100 were patients. The survey explored different things, but one of the things it explored was the time to dosing, and it appears that people were much more willing to dose the intranasal more quickly, and would dose, really, almost five minutes sooner with the intranasal. We have other

studies that actually imply they would dose even 18 minutes sooner in people that didn't have recent experience.

These are people that actually use EpiPen, and they're willing to use it very quickly, and people that are less willing to use it or that haven't used it in a long time, the difference seems to be much greater and up to 18 minutes delay. But in this study with people that actually use it, that have used it just recently, they still see close to a 4-to-5-minute advantage with the nasal spray. So we think there will be significant impact on the unmet medical need with this.

DR. AU: Thank you so much. And I'm not following my own rule. This was David Au speaking, for the record. Thank you very much. I appreciate that.

I think this is a time for a break. I know that we're well over, and we were originally going to give a 10-minute break. Can we go ahead and just make this a five-minute break or a six-minute break, and have us come back at 45 after the hour?

I just want to thank everyone for their willingness to engage. I thought this was a very robust conversation. So let's take a break, and we'll see each other in six minutes. Thanks so much.

(Whereupon, at 11:39 a.m., a recess was taken, and meeting resumed at 11:45 a.m.)

DR. AU: Welcome back, everyone.

We will now proceed with FDA's presentation, starting with Dr. Jennifer Lan. Thank you so much.

FDA Presentation - Jennifer Lan

DR. LAN: Good morning. My name is Jennifer Lan, and I'm a practicing allergist, as well as a medical officer in the Division of Pulmonology, Allergy, and Critical Care here at the FDA. I am the primary clinical reviewer for this program, and it is my pleasure to share this presentation with you today.

The FDA presentation will be divided into three parts. First, I will provide an overview of the clinical PK/PD program. Next, my colleague, Dr. Qianni Wu, will provide an overview of the

clinical pharmacology results. I will close the FDA presentation by providing some clinical considerations of the clinical pharmacology results, and then risk-benefit considerations for ARS-1. I will now begin with the overview of the clinical PK/PD program, starting with the background on development of the ARS-1 program.

Given the agency's recognition of the unmet need, as discussed earlier by Dr. Paterniti, the agency worked with ARS on a regulatory pathway for this new route of administration. The agency and ARS agreed that the 505(b)(2) pathway may be a reasonable pathway by establishing a scientific bridge to an approved drug.

With the 505(b)(2) pathway, clinical studies may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the approved drug. During development, whether clinical efficacy trials are necessary for development of noninjectable epinephrine products for the treatment of

anaphylaxis was considered; however, after careful consideration of potential trials and trial design challenges, such as the scenarios listed here, it was unclear if a clinical trial would be feasible or provide meaningful data to support the indication. Therefore, the agency and ARS agreed on moving forward with a clinical pharmacology program; however, the agency noted that whether clinical efficacy studies would be needed would be a question that would be discussed with an advisory committee.

There are two other emergency treatment nasal programs I would like to highlight, which sheds light on the uniqueness of epinephrine and anaphylaxis and how development is not straightforward. The first is naloxone nasal spray, which is for the emergency treatment of known or suspected opioid overdose for all ages.

Naloxone was approved based on one PK trial in healthy adults. Unlike epinephrine, naloxone has a wide safety margin, so surpassing the therapeutic threshold of naloxone injection was not

a major concern. Given the wide safety margin and high exposure level, surpassing the therapeutic threshold with the nasal route, there were no major concerns translating healthy volunteer PK data to patients of opioid overdose.

Diazepam nasal spray is approved for acute treatment of intermittent stereotypic episodes of frequent seizure activity. Unlike with epinephrine, efficacy was already established for the original rectal route with adequate, well-controlled trials. The nasal route was approved based on comparable bioavailability via PK studies in healthy subjects and in patients with epilepsy to address potential PK differences.

As one can see, although there have been other emergency products approved via the nasal route, the unique characteristics of epinephrine and anaphylaxis introduces certain challenges that need to be addressed. These challenges will be discussed in the next few slides.

First, the critical PK parameters that are needed to determine efficacy are unknown. Since

there is limited PK/PD data for epinephrine injection products, and clinical efficacy trials have not been conducted to determine these PK/PD parameters, it is unclear which parameter should be relied upon as endpoints for intranasal epinephrine development.

Second, there is high inter-product and intra-product PK variability of epinephrine injection products. Dr. Qianni Wu will highlight this in more detail in her presentation, but how to determine bioavailability of a new route of administration in the background of variable PK adds another level of complexity to the development of intranasal epinephrine.

Third, epinephrine is a known vasoconstrictor. We did not know whether epinephrine would impede absorption of a second dose of epinephrine in the nasal mucosa, which may be needed in some patients with anaphylaxis.

Fourth, it is unknown whether we can extrapolate the PK measured in healthy adults to those with anaphylaxis. Anaphylaxis can lead to

changes in hemodynamics and affect PK/PD; therefore, it is unclear if the PK/PD data assessed in healthy subjects could translate to patients with anaphylaxis. One specific concern was whether nasal edema, which can occur in anaphylaxis, would alter the absorption of epinephrine.

Fifth, initial trials of intranasal epinephrine were designed with investigator administration of ARS-1. Given that ARS-1 could be self-administered, there were concerns that there may be differences in PK and safety if ARS-1 was self-administered versus investigator administered.

Lastly, developing an epinephrine nasal spray for pediatric patients was discussed due to the importance of epinephrine treatment in pediatrics; however, it was unclear how the pediatric nasal anatomy and size difference would affect intranasal epinephrine absorption. Due to nasal anatomical differences, the FDA requested that ARS conduct a pediatric PK/PD study to determine appropriate doses for children of different ages and body weights.

To try to address the first two challenges, the clinical pharmacology program was designed to assess ARS-1 by bracketing between two approved epinephrine injection products. To account for the known local vasoconstrictive effect of epinephrine on a repeat dose, the pivotal trial, EPI 15, was designed to assess PK/PD in a single and repeat dose. To assess whether nasal congestion could affect epinephrine absorption, a nasal allergen challenge trial, EPI 16, was conducted to address this question.

A self-administration trial, EPI 17, was conducted to assess if there were any differences in PK/PD in those who self-administered ARS-1 compared to those who had ARS-1 administered by study staff. In all the other trials, ARS-1 was administered by study staff. Lastly, EPI 10, a single-arm, dose-ranging, pediatric PK/PD study was developed to determine appropriate doses for children of different ages and body weights.

The summary table displayed here is the clinical pharmacology program conducted to support

2-milligram doses of ARS-1. Besides the four trials we described in the previous slides, the programs also included a dose-ranging trial, EPI 11b. The four remaining trials displayed in this table -- 15, 16, 17 and 10 -- were used to help answer the challenges we laid forth in the previous slides.

EPI 15 is the pivotal PK trial assessing a single dose of ARS-1 and repeat dose of ARS-1 in comparison to Adrenalin and EpiPen. EPI 16 is a nasal allergen challenge trial assessing the effect of nasal congestion on the PK/PD of a single dose of ARS-1 compared to Adrenalin. EPI 17 is the self-administration trial assessing a single dose of self-administered ARS-1 compared to staff administered. And finally, EPI 10 is the pediatric PK trial assessing the PK/PD of various single doses of ARS-1 in pediatric subjects.

I will now hand the presentation over to Dr. Qianni Wu, who will now present the results of the clinical pharmacology program in her presentation.

FDA Presentation - Qianni Wu

DR. WU: Thank you, Dr. Lan.

Good morning. My name is Qianni Wu, and I am the primary clinical pharmacology reviewer of this application. It is my pleasure to present the clinical pharmacology findings for the ARS-1 program. My presentation will be composed of two parts. I'll first cover the background information of the general PK and PD characteristics of epinephrine and FDA's scientific and regulatory thoughts for the ARS-1 clinical pharmacology program. In the second part, I'll present the major clinical pharmacology results from the PK/PD studies shown in the table that Dr. Lan just described. First, I will start with the background of epinephrine general PK/PD characteristics and FDA's thoughts.

Epinephrine is a non-selective, endogenous alpha and beta adrenergic agonist. Literature reported that the baseline mean plasma concentration of endogenous epinephrine in healthy subjects is approximately 35 picograms per mL. In

the ARS-1 program, the median baseline endogenous epinephrine plasma concentration was approximately 20 picograms per mL in healthy subjects. During the treatment of anaphylaxis administered, exogenous epinephrine is expected to result in a much higher plasma and tissue concentration to correct the pathological conditions of anaphylaxis in a timely manner.

The plasma half-life of epinephrine is fairly short, approximately 2 to 3 minutes. Epinephrine metabolizing enzymes are widely expressed in human body. Epinephrine plasma concentrations following the approved intramuscular administration route demonstrated high inter-subject and inter-subject variability. Based on the clinical pharmacology review by the agency for Auvi-Q, an approved epinephrine autoinjector, the coefficient of variation of mean Cmax and AUC for the autoinjectors ranged from 51 percent to 80 percent, and the Tmax ranged from 5 to 60 minutes.

The slide displays cross-study comparison

results of epinephrine injection products used in the ARS program. These figures include results from previous studies conducted to support 1 milligram of ARS-1. The highly variable nature of epinephrine PK was also observed in the ARS program. In total, three approved epinephrine injection products were used as comparators in the program, including an autoinjector, EpiPen, and a prefilled syringe, Symjepi, both of which were approved for use in a community setting, and a needle syringe product, Adrenalin, which is approved for the medical setting.

The two figures on the left side shows a cross-study geometric mean PK profile comparison for EpiPen at the top and Symjepi at the bottom. An up to 4-fold cross-study difference of epinephrine systemic exposure was noted for EpiPen, and an up to 1.5-fold cross-study difference was noted for Symjepi. A substantial inter-batch difference was also observed for EpiPen even within study comparison.

This figure on the right shows a cross-study

comparison for intramuscular administration of Adrenalin with up to 1.8-fold cross-study difference noted. The cross-product PK comparison for all injection products generally demonstrated an earlier Tmax, a higher Cmax, and generally early partial AUCs with 60 minutes post-dose for EpiPen compared to Adrenalin and Symjepi.

During the IND stages, we discussed a reasonable scientific and regulatory path forward for the ARS-1 program, considering the high PK variabilities for the epinephrine injection comparators observed across study products and batches. We considered there is a high risk and uncertainty if ARS only used one approved epinephrine injection product throughout their intranasal epinephrine program for PK matching purposes. We worked with ARS, exploring multiple options with different doses, different routes of administration, and different injection products at the early stage of the ARS-1 program.

The agency and ARS eventually settled on a program, which used PK profiles from two approved

epinephrine injection products, with one being an autoinjector to bracket exposure of the intranasal epinephrine product. This approach may provide a feasible and a reasonable foundation for the ARS-1 clinical program. This bracketing approach using two injection products not only helped reduce uncertainty and risk due to the PK variability of the approved injection products, but also provides some flexibility during the drug development, as the strict match of PK profiles and bioequivalence establishment of certain PK parameters are highly challenging, given the different administration routes.

Last but not the least, the agency believes that the different administration routes may introduce different absorption patterns of epinephrine and unlikely affect the central distribution and elimination pattern of epinephrine; therefore, comparison of epinephrine absorption profile is most critical in the ARS-1 clinical pharmacology program.

At the IND stage, in addition to the PK

data, the agency also considered how to weigh PD or vital sign data in support of the ARS-1 program. The agency initially considered that if similar PK responses with similar PK profiles, following different administration routes, could be observed, the similar PD responses could be considered a strong piece of evidence to support the ARS-1 drug product. However, as we will present the PD results later, the first challenge we encountered is that the trend of PD response relative to PK profile appears substantially different between different administration routes without a clear mechanism.

The second challenge is the high variability of PD responses. The high variability not only occurs at the inter-subject level, but also shows the real-time relationship with PK. Overall, there is a relatively weak PK/PD relationship observed in the ARS-1 program in contrast to some literature reports following continued epinephrine IV infusion with fixed rates. Based upon available data, we're also concerned that the PD responses following

ARS-1 can be influenced by nasal conditions, which will be further discussed later.

Lastly, there are more uncertainties in translating the PD responses from healthy subjects to patients with anaphylaxis. Other than the different hemodynamic conditions between the two populations, nasal edema can be associated with anaphylaxis and can impair the PD response, as we will go through the results later. Due to these challenges, the agency currently considers the PD only plays a supportive role.

Now I'm going to present results from the ARS-1 clinical pharmacology program, starting with the study EPI 11b. Study EPI 11b is a dose-ranging and formulation exploration study that supports the selection of a 2-milligram dose. Study EPI 11b is a randomized, single-dose, crossover study conducted in two groups of healthy adults. Group 1 received ARS-1 up to 1.8 milligrams in comparison to Symjepi, while group 2 received ARS-1 up to 2 milligrams in comparison to EpiPen.

The formulations used in Study EPI 11b are

slightly different from the to-be-marketed formulation. The figure in the slide shows the PK profile comparison for group 2 plus the Symjepi arm from group 1 for additional reference purposes. Overall, the PK profile of ARS-1 2 milligrams, as shown in the red color, was higher than Symjepi after approximately 10 minutes post-dose, and higher than EpiPen approximately 15 minutes post-dose. However, the mean epinephrine concentration for ARS-1 2 milligrams was lower in both EpiPen and Symjepi within 10 minutes post-dose.

Based on the PK results from this study, 2-milligram dose was selected for ARS-1 and carried over to the pivotal PK and PD study, EPI 15. Higher doses were not explored. At the IND stage, the agency did caution ARS about potential safety concerns with the higher doses, given that systemic exposure with the 2-milligram dose of ARS-1 appeared higher than EpiPen in Study EPI 11b. The agency noted the small sample size in the study. Due to the uncertainty in dose selection, the

agency recommended conducting the pivotal PK/PD study, EPI 15, before initiating other trials.

Before I discuss the results of the pivotal PK/PD studies, I'd like to introduce how the agency analyzed and presented the PK results. We placed more emphasis on the results from individual dedicated clinical pharmacology studies in this program, rather than PK comparisons, pooling PK data from multiple studies. We believe that data from a dedicated relative bioavailability study is a more appropriate approach to establish a scientific bridge between ARS-1 and epinephrine injection products.

We did not use baseline adjusted values, mainly to avoid the negative values during the PK analysis. In addition, the mean and median baseline concentrations were similar across all treatments, and generally no greater than 10 percent of mean Cmax values following all treatments. The agency considers that the early PK profile of epinephrine is critical during the treatment of anaphylaxis; therefore, 60 minutes

cutoff was arbitrarily chosen for our analysis. Subjects with less than 3 PK samples collected within 30 minutes were excluded from the analysis.

In our presentation for Study EPI 15, we aligned with applicant's approach for subject exclusion; thus, our AC presentation for EPI 15 will be slightly different from what is in the FDA briefing document. Sensitivity analyses did not identify any meaningful changes in our interpretation of the results. All the plasma concentration time profiles in this presentation were graphed with the geometric mean concentrations to reduce the influence by some outlier values.

Now I will present some major findings in the pivotal PK/PD study, EPI 15, which was designed with a concept of PK bracketing strategy in healthy adults. EPI 15 was a two-part, six-treatment, six-period, single- and repeat-dose partial crossover PK/PD study, which means not everyone participated in both part 1 and part 2.

Part 1 is a single-dose study. Part 2 is a repeat-dose study during which 2 doses of

intramuscular injection or intranasal products were administered, separated by 10 minutes. The design of part 1 of the study will be presented in the next slide. The sample size for both part 1 and part 2 are 42 healthy adults. Only 26 enrolled in both parts with PK data available. One adult with less than 3 PK samples collected within 30 minutes was excluded.

The nasal conditions of these healthy adults were assessed at baseline and predose of each dosing period. Only adults with a nasal congestion score of zero at baseline and prior to dosing, indicating no congestion, were enrolled. The nasal congestion score is abbreviated as NCS in this presentation.

Part 1 of Study EPI 15 was a single-dose crossover study in which healthy adults were randomized to receive one of the following treatments in each period: a single intranasal dose of ARS-1 2 milligrams in the left naris, a single intramuscular dose of EpiPen 0.3 milligrams in the left thigh, and single intramuscular dose of

Adrenalin 0.3 milligrams in the right thigh.

This slide displays the baseline unadjusted epinephrine geometric mean PK profiles from the single-dose part of the pivotal study, EPI 15. The injection comparators used in this part were Adrenalin 0.3 milligrams and EpiPen 0.3 milligrams administered intramuscularly. The 60-minute PK profile for both injection comparators showed 2 peaks following intramuscular administration.

In general, the PK profile for EpiPen, as shown in green, demonstrated a higher first peak occurred within 10 minutes post-dose, followed by a relatively flat second peak, around 30 minutes post-dose, while the PK profile for Adrenalin, as shown in blue, demonstrated a low first peak within 10 minutes post-dose, followed by a higher second peak, around 45 minutes post-dose. The 60-minute PK profile of ARS-1 demonstrated a single peak that occurred around 30 minutes post-dose.

A lower epinephrine mean plasma concentration for ARS-1 compared to both EpiPen and Adrenalin was noted within 10 minutes post-dose,

likely attributed to a slower absorption rate by comparing the slope of the PK curve minus the three products. After 10 minutes, the mean PK profile of ARS-1 was reasonably bracketed by Adrenalin and EpiPen. Additional bioequivalence analysis is not presented in the slide but is available in the backup slide. The result is consistent with the PK profile comparison. In addition, a higher PK interceptor variability was noted for ARS-1 compared to injection products in this study.

Due to the high PK variability of epinephrine, there is an uncertainty by just comparing the mean PK profiles between ARS-1 and injection products. To examine if potentially there is an unbalanced number of healthy adults who had very low PK profiles among different treatments, we explored the proportion of healthy adults who achieved certain arbitrarily selected plasma threshold concentrations, 100 and 200 picograms per mL. These concentrations were reported to be associated with noticeable vital sign responses in healthy adults following

continuous epinephrine IV infusion based on published literature.

The figures in this slide demonstrate the proportion of healthy adults who achieved these concentrations at different time points within 60 minutes post-dose. The three different colors represent three different treatments. As you may notice, a higher proportion of healthy adults achieved both 100 and 200 picograms per mL following EpiPen at all time points evaluated when compared to ARS-1 and Adrenalin. The proportion in both Adrenalin and ARS-1 are initially lower than EpiPen, and gradually catch up.

The proportion of healthy adults achieving 100 picograms per mL was similar between Adrenalin and ARS-1 at most time points; however, the proportion in ARS-1 is noticeably lower than EpiPen Adrenalin within 5 minutes post-dose, which is consistent with the PK profile comparison results. Moreover, although the proportions of healthy adults achieving 100 picograms per mL are similar between Adrenalin and ARS-1 at 30 minutes

post-dose, which is around 80 percent, the proportion in the Adrenalin group further increased to 95 percent at 60 minutes due to the emergence of the second peak concentration, whereas no increase is observed for ARS-1.

This slide displays both PK and PD profiles following single dose. The PK profile is on the left, which is the same graph shown in the previous slide. The PD profile for systolic blood pressure changed from baseline, as shown on the right. Reduced influence of some outlier values, and median values are displayed for PD profiles. The error bar represents the 25th and 75th percentile of the PD values. We cannot use geometric mean here because some PD changes from baseline values are negative.

Within the first 10 minutes post-dose, the median systolic blood pressure response is bracketed by EpiPen and Adrenalin. After 10 minutes post-dose, the systolic blood pressure response is higher and more sustainable for ARS-1 compared to EpiPen, which is different from the PK

comparison, as the mean epinephrine concentration for EpiPen is overall higher than ARS-1, as shown on the left. The methods of action that caused this PK/PD discrepancy is unclear. There is uncertainty if this PD response can be replicated in anaphylaxis patients with different hemodynamic conditions and nasal conditions, as we'll discuss later.

This slide displays other PD endpoints following the single dose, which are pulse rate on the left, and diastolic blood pressure is shown on the right. The comparison of pulse rate response following ARS-1 demonstrates a generally higher and more sustained response than EpiPen despite the low PK of ARS-1 compared to EpiPen.

The diastolic blood pressure profile for ARS-1 is more stable from baseline compared to the two injection products. Of note, the discrepancy between PK and PD comparisons was consistently observed between ARS-1 and EpiPen throughout the ARS-1 clinical program in healthy subjects with normal nasal conditions.

Now we return to the second part of Study EPI 15. The second part of EPI 15 is also a crossover study that compared 2 doses of ARS-1 with 2 doses of EpiPen. Healthy adults were partially randomized to receive 2 doses of ARS-1 2 milligrams ipsilaterally or contralaterally in treatment period 1 and 3, and 2 doses of EpiPen 0.3 milligrams intramuscular injection in treatment period 2. The two ARS-1 treatment periods were separated by one EpiPen treatment period to mitigate a risk of carryover effect with an adequate washout period.

This slide displays PK results following repeat dose of ARS-1 and EpiPen. Note that there isn't the Adrenalin comparator unlike the single-dose study. Epinephrine PK profiles are generally similar between ARS-1, administered in the same naris and opposite naris. The epinephrine concentration following 2 doses of ARS-1 are lower than the 2 doses of EpiPen within 20 minutes post-first dose, and become comparable thereafter.

This slide displays the PK comparison

between single dose and repeat dose for ARS-1 and EpiPen. We noticed that the epinephrine exposure is proximately doubled following 2 doses of ARS-1 compared to a single dose of ARS-1, while 2 doses of EpiPen only increased the Cmax by 20 percent and AUC within 60-minutes post-dose by 50 percent compared to the single-dose EpiPen. The difference in PK proportionality between ARS-1 and EpiPen explains why epinephrine exposure following 2 doses of ARS-1 can catch up to that of 2 doses of EpiPen, whereas the epinephrine exposure following single-dose ARS-1 is generally lower than that of single dose of EpiPen. The mechanism of a less-than-dose proportional PK for EpiPen is unclear.

The proportion of subjects who achieved epinephrine plasma concentrations of 100 picograms per mL and 200 picograms per mL was also explored for the repeat-dose study. Consistent with the repeat-dose PK profiles, the proportion of healthy adults who achieved these threshold concentrations are initially lower following repeat-dose ARS-1

compared to the repeat-dose EpiPen. The proportion of repeat-dose ARS-1 gradually catches up over time, reaching a similar proportion of repeat-dose EpiPen at around 60-minutes post-dose.

This slide compares the PK/PD profile following repeat dose. The PK profile is on the left, while the PD profile for systolic blood pressure change from baseline is shown on the right. Similar to PD results from single dose, the systolic blood pressure change is initially lower following 2 doses of ARS-1 compared to 2 doses of EpiPen within 10 minutes post-first dose, and become higher afterwards despite that epinephrine PK following ARS-1 is lower than EpiPen within 20 minutes post-first dose and is similar afterwards.

Other PD endpoints following the repeat dose are shown in this slide. The pulse rate results are shown on the left and diastolic blood pressure results are shown on the right. A similar trend was observed for pulse rate response. The pulse rate change from baseline is higher following

repeat-dose ARS-1 than EpiPen after about 12 minutes post-dose. We also noticed a more stable diastolic blood pressure profile following a repeat dose of ARS-1 compared to EpiPen. The diastolic blood pressure profile following repeat dose of ARS-1 is also more stable than following single dose of ARS-1.

After we have discussed the major findings for the pivotal PK/PD study in healthy adults, I will now discuss the PK findings in the self-administration study, EPI 17. Study EPI 17 is a single-dose, two-period, crossover study in adult patients with Type I allergies to evaluate the impact of self-administration of ARS-1 on the epinephrine PK profile. Patients were randomized to receive either self-administration 2 milligram of ARS-1 or staff-administered Adrenalin 0.3 milligram intramuscularly in each treatment period.

This slide displays the PK results from EPI 17 and cross-study comparisons of PK for both ARS-1 and Adrenalin. The figure on the left shows

the PK results from Study EPI 17. The self-administered ARS-1 PK from EPI 17 is shown in the blue, while the staff-administered Adrenalin from EPI 17 is shown in the green. The ARS-1 results from pivotal PK/PD study EPI 15, as shown in the red, is also displayed in a graph in a cross-study manner.

Both ARS-1 from Study EPI 17 and EPI 15 show higher mean epinephrine concentrations at all time points over 60 minutes post-dose compared to Adrenalin results from EPI 17. This comparison result was different from the single-dose part of Study EPI 15, in which the mean epinephrine concentrations following ARS-1 was lower than that of Adrenalin within 10 minutes post-dose. The PK profile of ARS-1 from EPI 17 and EPI 15 appear similar based on the cross-study comparisons.

The different PK comparison results between EPI 15 and EPI 17 is likely attributed to the high PK variability of Adrenalin. Please keep in mind that the primary objective for EPI 17 is not to evaluate the relative bioavailability of ARS-1,

bracketed by two injection products, but rather to evaluate the self-administration PK profiles and impact of potential human errors on epinephrine PK for ARS-1.

The figure on the right overlays the ARS-1 results from EPI 15 and EPI 17, as the red solid line and blue solid line, respectively, on top of all Adrenalin results from the ARS program, as shown in the dotted lines in a cross-study manner. As previously discussed, a substantial PK variability was noted for Adrenalin following intramuscular administration.

Based on the cross-study comparisons, the mean epinephrine concentrations following ARS-1 appear to be bracketed by all Adrenalin results within 10 minutes post-dose, although our assessment for the adequacy of the scientific bridge between ARS-1 and approved injection products focus on the within-study comparisons, based on the dedicated PK/PD study, EPI 15, with knowledge that the approved epinephrine injection products demonstrated high PK variability, and we

also acknowledge that a different PK comparison result between ARS-1 and Adrenalin was observed in EPI 17 in contrast to EPI 15.

Regarding the clinical meaning and the different methods for comparing epinephrine PK profiles between ARS-1 and Adrenalin, especially for the comparison within 10 minutes post-dose, we defer to the panel discussion.

The next study I will discuss is the PK study in allergic rhinitis patients with induced nasal congestion. This study was designed to mimic changes in nasal mucosa expected in anaphylaxis. Study EPI 16 is a single-dose, four-treatment, partially-randomized, crossover study in adults with allergic rhinitis. The sequence adopted a sandwich design to have ARS-1 administered in treatment periods 1 and 4, and two dosing levels of Adrenalin administered in treatment periods 2 and 3.

Patients' nasal conditions were assessed by the total nasal symptoms score, abbreviated as TNSS, which is a standard patient-reported

questionnaire that evaluates various symptoms, including congestion, runny nose, itching, and sneezing, each on a scale of 0 to 3; 0 corresponds to no symptoms, while 3 corresponds to severe symptoms. The nasal congestion score, NCS, is one of the components that measure congestion conditions. As patients were assessed out of their allergy season, they would not be expected to have rhinitis symptoms at time of enrollment and before undergoing the nasal allergen challenge.

In the first treatment period, patients received ARS-1 in the left naris under normal nasal conditions with no apparent nasal edema, and the congestion defined by NCS score less or equal to 1 out of 3 prior to dosing, while in treatment period 4, patients received ARS-1 following nasal allergen with induced nasal congestion in the right naris, defined by the NCS score greater or equal to 2 out of 3 prior to dosing. Different nares were used for the two ARS-1 treatment periods to mitigate risks of carryover effect.

This slide shows the PK profiles of ARS-1

with or without nasal allergen challenge in comparison to two dosing levels of Adrenalin administered intramuscularly. The PK profile for ARS-1 with a nasal allergen challenge is shown in the red color, while ARS-1 without a nasal allergen challenge is shown in the orange color. The dark blue is Adrenalin 0.3 milligrams, and the light blue is Adrenalin 0.5 milligrams.

The PK profiles for Adrenalin 0.3 milligrams intramuscular injection were similar to those observed in Study EPI 15. The results demonstrated roughly dose proportional PK profiles between 0.3 milligrams and 0.5 milligrams, Adrenalin. The PK profile of ARS-1 under normal nasal conditions, which is without a nasal allergen challenge, was in the range of single-dose Adrenalin following two different approved doses, which are 0.3 milligrams and 0.5 milligrams.

The PK profile of ARS-1 following the nasal allergen challenge demonstrated a different pattern compared to that following normal nasal conditions. With the nasal allergen challenge, the PK profile

of ARS-1 shows initially a faster absorption rate followed by a faster decline rate after about 10 minutes post-dose. The overall AUC within 60 minutes post-dose of ARS-1 following the nasal allergen challenge is lower than all other treatments.

Lack of PK sustainability for ARS-1 following the nasal allergen challenge may result in reduced effectiveness in patients with sustained anaphylaxis who also experienced a nasal congestion condition. Of note, a numerically lower mean concentration of epinephrine following ARS-1 under normal nasal conditions compared to Adrenalin 0.3 milligram in the first 10 minutes is also observed in Study EPI 16.

The applicant currently proposes to mitigate reduction of PK sustainability under nasal edema conditions by labeling with administration of a second dose; however, there is uncertainty regarding what the epinephrine PK profile looks like following a repeat dose under nasal edema conditions, especially if the second dose is

administered in the same naris as with the first dose. Of note, a repeat-dose study was not conducted under nasal allergen challenge conditions in the ARS-1 clinical pharmacology program.

This slide shows the systolic blood pressure response following ARS-1 with or without the nasal allergen challenge in comparison to the 2-dose levels of Adrenalin. Similar to the trend observed in the PK profile comparison following ARS-1 with nasal allergen challenge, as shown in the red color, the median systolic blood pressure response is initially higher followed by a decline after about 15 minutes post-dose when compared to ARS-1 without the nasal allergen challenge, as shown in the orange color. This suggests that the nasal congestion may have impact on the PD response as well.

This slide displays other PD responses with or without nasal allergen challenge, with pulse rate response on the left and diastolic pressure response on the right. The median pulse rate profile for ARS-1 following the nasal allergen

challenge is similar to the systolic blood pressure profile results with an initially higher response followed by a fast decline below the baseline level after 5 minutes post-dose. This negative median pulse rate response raises efficacy concerns, as it is apparently lower than that following Adrenalin 0.3 milligrams intramuscular injection. The decline was not seen in either dose levels of Adrenalin within 60 minutes post-dose. In addition, the diastolic blood pressure profile for ARS-1 following the nasal allergen challenge, as shown in the graph on the right, is less stable than ARS-1 under normal nasal conditions.

To further explore how nasal congestion impacts PK and PD following intranasal administration, we explored subgroup analyses with various severity levels and duration of nasal congestion following the nasal allergen challenge. The first figure shows the effect of nasal congestion severity on the PK. Patients were grouped by NCS obtained after nasal allergen challenge but prior to ARS administration. The NCS

of zero indicates no congestion, while a score above zero indicates congestion, with a higher score corresponding to a greater severity.

In subjects with the highest NCS, shown in the red color, the epinephrine concentration appeared to have a faster initial increase followed by a faster decline when compared to subjects with low NCS, as shown in the blue color. For reference, ARS-1 without the nasal allergen challenge arm is shown in green in the figure which does not show a fast decline. A similar effect of nasal congestion on epinephrine PK was also observed in the pediatric study. The result is available in the backup slide.

The second figure shows the effect of post-dose nasal congestion duration on the systolic blood pressure response within 60-minutes post-dose. We identified 10 patients who continued experiencing the nasal congestion on NCS above zero more than 30 minutes post-ARS-1 treatment. These subjects tend to have reduced systolic blood pressure response, as shown in the orange color,

when compared to subjects whose post-dose nasal congestion duration was less than 30 minutes, as shown in the blue color. For reference, the PD response for ARS-1 without the nasal allergen challenge is shown in the green color, which does not demonstrate a fast decline.

We acknowledge that these subgroup analyses our exploratory by nature with a small sample size; however, these analyses may add more evidence to different PK/PD behaviors of ARS-1 following the nasal allergen challenge or under nasal congestion conditions. The diminished PK and PD results associated with nasal congestion increases uncertainty of translating higher PD responses observed in healthy adults to anaphylaxis patients who experience nasal congestion conditions.

The last study I will discuss is the pediatric PK/PD study. The applicant conducted a single-dose, single-period, PK/PD study in children having Type I allergy with body weight between 15 and less than 30 kilos and 30 kilos or more. The study was ongoing at the time of NDA

submission, and only an interim report was available. As the applicant proposed an indication for children weighing 30 kilograms or more, in this presentation, we will only discuss the results for children in this weight group.

A total of 42 pediatric patients weighing 30 kilos or more were enrolled as of the cutoff day of interim reports. Sixteen received 2 milligrams, while 26 subjects received 1 milligram. One subject from the 1-milligram group was excluded for PK analysis due to insufficient sample above limit of quantification. The median baseline body weight for these 42 pediatric patients was 54 kilograms, ranging from 31 to 95 kilograms, and the median baseline age was 14 years, ranging from 8 years to 17 years.

This figure displays the dose-ranging epinephrine PK profiles in children 30 kilograms or greater who received either a single dose 1 mg ARS-1, as shown in the orange color, or a single dose 2 milligrams of ARS-1 as shown in the blue color. For reference purpose, the epinephrine PK

profile for healthy adults with ARS-1 2 milligram in Study EPI 10 is also displayed here in a cross-study fashion as shown in the green color.

The comparison results demonstrated that the pediatric epinephrine PK profile following ARS-1 2 milligrams is similar to that of adults following the same dose within 15 minutes post-dose and higher than that of adults after 15 minutes. Meanwhile, the epinephrine PK profile following ARS-1 1 milligram in children 30 kilos that were greater is similar to that of adults within 10 minutes or lower than that of adults after 10 minutes, with knowledge that 1 milligram is not being proposed as a dose for children weighing 30 kilograms or more.

Despite that, the 2-milligram pediatric PK profile is similar to that of adults within 15 minutes, and higher afterwards. The systolic blood pressure and pulse rate responses are generally lower in children compared to adults. The underlying reason is unclear; however, we noticed the body posture for drug administration

and vital sign measurements is different between the pediatric study and adult studies. The pediatric study adopted a semi-supine position, while all adult studies adopted a sitting position. Different body postures may have impact on PD.

Now I will end my presentation with a summary of PK/PD results, based on the observations from the clinical pharmacology program of ARS-1 as follows. For PK/PD study results for healthy adults, based on EPI 15, epinephrine PK profile following a single dose of ARS-1 is reasonably bracketed by Adrenalin and EpiPen after around 10 minutes post-dose. However, epinephrine concentrations for ARS-1 were generally lower than Adrenalin and EpiPen within the first 10 minutes post-dose.

A similar trend was observed in Study EPI 16 with normal nasal conditions, but not in self-administration study, EPI 17. We acknowledge that there is also cross-study comparison evidence to support the bracketing, but we will defer the totality of PK comparison results within 10 minutes

to the panel discussion.

Epinephrine PK profiles following a repeat dose of ARS-1 in the same or opposite naris are similar to repeat dose of EpiPen 0.3 milligram after 20 minutes post-dose; however, epinephrine concentrations following repeat-dose ARS-1 were generally lower than EpiPen within the first 20 minutes post-dose.

A lower proportion of healthy adults achieved 100 picograms per mL in ARS-1 and Adrenalin within first 10 minutes post-dose than EpiPen, following both single dose and repeat dose. Generally, higher systolic blood pressure and pulse rate responses were noted following single-dose and repeat-dose ARS-1 than EpiPen after about 10 minutes post-dose, despite ARS-1 profile being generally lower than EpiPen.

For PK/PD results from nasal allergen challenge study, the epinephrine PK profile following single dose ARS-1 in allergic rhinitis patients without nasal allergen challenge is within the range of single-dose Adrenalin following two

different approved doses, which are 0.3 milligram and 0.5 milligram. Under nasal allergen challenge conditions, the epinephrine PK profile following ARS-1 increased more rapidly than Adrenalin injection, followed by a rapid decline, resulting in an epinephrine concentration lower than all comparator arms 10 to 20 minutes post-dose. A similar pattern of systolic blood pressure and pulse rate responses was also observed. Baseline nasal congestion severity and post-dose congestion duration may impact epinephrine PK/PD profile for ARS-1.

For PK/PD results from the pediatric study, pediatric patients weighing 30 kilograms or more, following 2 milligrams of ARS-1, had a similar to slightly higher epinephrine PK profile compared to that of adults. The pediatric systolic blood pressure and pulse rate responses were slightly lower compared to adults.

This concludes my presentation, and I will now hand it back over to Dr. Jennifer Lan to further discuss the safety and benefit-risk of this

program.

FDA Presentation - Jennifer Lan

DR. LAN: Thank you, Dr. Wu.

I will be conducting the FDA presentation for providing a clinical interpretation of the PK/PD results that Dr. Qianni Wu just presented, followed by an overview of the safety profile ARS-1. I will then conclude by summarizing the findings we presented today under the benefit-risk framework for ARS-1.

In the previous segment, Dr. Qianni Wu presented the clinical pharmacology results of the pivotal trials. There are a few areas of uncertainties I would like to highlight in the following slides, as these findings may be clinically relevant and important for discussion today.

ARS conducted three pivotal trials, EPI 15, the dedicated PK/PD trial; EPI 16, the nasal allergen challenge model; and EPI 17, the self-administration trial. In the pivotal trial EPI 15, ARS-1, shown in red, showed a lower

epinephrine concentration during the first 10 minutes in comparison to Adrenalin shown in dark blue. In EPI 16, the trend for epinephrine PK in the first 10 minutes following ARS-1 in subjects without nasal allergen challenge, shown in red, is not distinctly different compared to Adrenalin 0.3 milligrams, shown in dark blue. In EPI 17, ARS-1 PK, shown in red, is seen higher than Adrenalin, shown in green, in the first 10 minutes.

The agency believes these differences are due to the variability seen with Adrenalin. PD responses for ARS-1 were similar to or higher compared to Adrenalin and EpiPen. Given that EPI 15 was the pivotal PK/PD study that included both EpiPen and Adrenalin for the purposes of bracketing the PK of ARS-1, FDA believes it is important for the AC panel to note the lower exposure of ARS-1 in the first 10 minutes in Epi 15, and consider the available data across the studies to discuss whether there are potential clinical implications.

Also, in EPI 15, the PK for 2 doses of ARS-

1, dosed 10 minutes apart in the same naris, shown in red, or opposite nares, shown in orange, demonstrated similar PK 20 minutes post-dose compared to 2 doses of EpiPen shown in green. Similar to the single dose, the PK was lower than EpiPen in the first 20 minutes; however, conclusions regarding the lower epinephrine exposure with repeat-dose ARS-1 compared to EpiPen in the first 20 minutes is limited, as the repeat-dose study was not bracketed by both Adrenalin and EpiPen.

Despite the PK being lower for ARS-1 compared to EpiPen, higher PD responses, specifically median systolic blood pressure and pulse rate, were observed with both single and repeat doses of ARS-1 compared to Adrenalin and EpiPen. This difference in PK/PD relationship between epinephrine products adds uncertainty to establishing a scientific bridge.

The last finding I would like to highlight in healthy adults is the figure displayed here. Less than 80 percent of subjects who received

single or repeat doses of ARS-1, shown in blue, reached the threshold of 100 picograms per mL during the first 10 minutes. This was similar to Adrenalin, shown in orange, but lower than EpiPen shown in gray. The single dose shows in the graph, but it's similar to what was seen for repeat doses. The clinical significance for this lower proportion of subjects, that reached a threshold of 100 picograms per mL, is uncertain and is also a topic for AC discussion.

I would next like to highlight the findings found in the nasal congested state. A clinical pharmacology study was conducted in subjects with allergic rhinitis pre- and post-nasal allergen challenge to assess the PK and PD in subjects with altered nasal mucosa and to mimic nasal mucosal changes during anaphylaxis. In subjects with allergic rhinitis without nasal allergen challenge, shown with the orange curve, the PK of ARS-1 was similar to Adrenalin 0.3 milligrams, shown in dark blue, and Adrenalin 0.5 milligrams shown in light blue.

The PK results show that ARS-1 post-nasal allergen challenge, shown in red, increased more rapidly than Adrenalin 0.3 and 0.5 milligrams; however, the PK followed a rapid decline, which results in the epinephrine concentration of ARS-1 being lower than the comparator arms, approximately 10 to 20 minutes posts-dose. PD for ARS-1 is not shown here but showed the same trend as PK.

Nasal congestion in subjects continue to be reported in about 30 percent of subjects who received ARS-1 post-nasal allergen challenge, suggesting that nasal congestion may persist if a second doses is administered. The PK/PD with repeat doses of ARS-1 under the nasal congested state has not been studied.

Since patients with anaphylaxis may require a second treatment with epinephrine, and since the PK and PD declined rapidly 10 minutes after ARS-1 administration in the nasal allergen challenge study, repeat doses of ARS-1 may be needed. Since repeat-dose studies have not been performed in the nasal allergen challenge model, and proposed

labeling includes repeating a dose if symptoms persist, there's residual uncertainty in the PK/PD response following a repeat dose, and thus uncertainty about ARS-1 efficacy in the treatment of anaphylaxis. Whether additional dose ranging and/or repeat-dose nasal allergen challenge study would be necessary is a topic for AC discussion.

Finally, in considering the pediatric program, pediatric extrapolation from the adult PK/PD program is necessary, given the limitations of the single-arm pediatric study. Given that there is a high degree of similarity in anaphylaxis between adult and pediatric patients and an established response to treatment with epinephrine in pediatric patients, extrapolation here is reasonable.

In EPI 10 for subjects weighing 30 kilograms or more who received a 2-milligram dose, the pediatric PK was similar to the adult counterparts in the first 15 minutes; however, the pediatric PD trend is lower compared to adults in the first 15 minutes. It is unclear as to why the PD trended

lower despite similar PK during the first 15 minutes and whether this is clinically relevant. This discrepancy adds to the level of uncertainty in the use of PK/PD bridging.

I will now give an overview of the safety profile of ARS-1. The safety review of ARS-1 primarily relies on the determination of safety of epinephrine injection-listed products, provided that the epinephrine exposure with ARS-1 is not higher than approved products. Due to lack of randomized-controlled clinical trials of epinephrine for the treatment of anaphylaxis, the true incidence of adverse reactions associated with systemic use of epinephrine is unknown. The adverse reactions reported in observational trials and case reports are listed here. These adverse events reported are consistent with the known pharmacological effect of epinephrine.

The safety database of ARS-1 include a total of 134 subjects who received ARS-1 2-milligram dose across the three pivotal trials, EPI 15, 16, and 17. Although a larger number have been exposed to

ARS-1 at various doses, our primary safety analysis focused on these three trials, as these were the trials that assessed the 2-milligram dose. There were some subjects who received more than one exposure to ARS-1 per study, which equaled a total of 260 exposures of ARS-1 across the three trials. There were no deaths or serious adverse events. The safety profile is however limited given the small population in that almost half only received one dose, and therefore the frequent use safety profile for local toxicity is unknown.

The most common systemic adverse events that occurred at or greater than 3 percent frequency in ARS-1 and greater than epinephrine injection were headache, dizziness, and nausea. There were no safety concerns related to higher PK and no notable PD-related adverse events such as elevated blood pressure or heart rate. The majority of adverse events were reported as mild.

Given ARS-1 is a new route of administration, the local safety profile cannot rely on the determination of previous injectable

epinephrine. The nonclinical studies in rats showed minimal ulceration at a dose 2.3-fold higher than the 2-milligram dose. Further details on the nonclinical studies are provided in the briefing document.

Nasal exams were performed during the trials. The most common local adverse events that occurred at or greater than 3 percent frequency in ARS-1 and greater than epinephrine injection include nasal discomfort and rhinorrhea. Ten percent of those who received ARS-1 reported nasal discomfort and 3 percent reported rhinorrhea. Local adverse events reported as minimal.

For pediatric safety, there are 21 subjects weighing 30 kilograms or more who received the 2-milligram dose at the completion of EPI 10. The age ranged from 8 to 17 years, with the majority of subjects being enrolled in the cohort of subjects 13 years of age and older. Common adverse events are listed and are in line with the known safety effects seen as systemic epinephrine injectable products in those found in the adult program. In

general, the adverse events reported were numerically higher in the pediatric population of EPI 10 compared to the adult population; however, safety conclusions from EPI 10 are limited due to the small size and single-arm design with no comparator.

I will conclude FDA's presentation by framing the high-level points under the benefit-risk framework. For a drug to be approved for marketing in the United States, the FDA must determine that the drug has substantial evidence of effectiveness and that the benefits outweigh the risks to patients. A benefit-risk assessment for ARS-1 requires careful consideration of the evidence and, importantly, the remaining uncertainties about the benefits and risks.

We ask that you consider the benefit assessment and how PK/PD uncertainties affect this assessment in your deliberations today. We acknowledge that a needleless route of epinephrine may lead to earlier and more frequent epinephrine use. There are multiple uncertainties relying on

PK/PD data to support the efficacy of ARS-1 that we need to consider.

First, there is no clinical efficacy trial to determine the efficacy of ARS-1. The benefit of ARS-1 relies on establishing a scientific bridge via bracketed PK with supportive PD to approve epinephrine injection products. Second, PK/PD from epinephrine injection products are highly variable, making the scientific bridge challenging. Third, whether PK/PD in healthy subjects will be similar in anaphylaxis patients is unclear.

Finally, although much of the PK/PD profile of ARS-1 is bracketed by PK/PD profiles of approved epinephrine injection products, there are some differences that warrant consideration. For example, there is a lower PK of ARS-1 within the first 10 minutes of EPI 15 compared to epinephrine injection in normal nasal congestion conditions; however, this trend is not seen in EPI 16 and EPI 17.

In the nasal allergen challenge study, epinephrine PK and PD dropped to below the

epinephrine injection comparator at around 15 minutes, and we do not have PK/PD data for a repeat dose, raising questions regarding durability of effect. For risk, the single repeat-dose studies did not raise safety concerns; however, it is uncertain that there would be adverse events, particularly local adverse events, from more frequent use.

I will now give a few concluding remarks. Anaphylaxis is a severe and potentially fatal reaction that affects millions of people in the United States. The agency acknowledges that this new route of administration may address some of the barriers to epinephrine use we see with injectable products; however, the evidentiary standards for ARS-1 must rely on establishing a scientific bridge.

In light of no clinical efficacy trial and taking into consideration the severity of the indication and the availability of approved safe and effective products, we need to have confidence that efficacy and safety of epinephrine

administered by this novel route of administration have been established. Minimizing uncertainty in a PK/PD bridge is key.

A high level of confidence in both PK and PD results and confidence in bridging the PK/PD findings to clinical efficacy in the setting of anaphylaxis are necessary to support a favorable benefit-risk assessment of ARS-1. We have raised some issues for the AC panel discussion, which include the PK/PD bridging and bracketing approach; the lack of sustained PK response seen in the nasal allergen challenge; and the different PK trends seen in the first 10 minutes for ARS-1 compared to Adrenalin across the three pivotal trials.

In considering the benefit-risk assessment for ARS-1, we ask the AC panel to consider if any additional data would be needed, whether further PK/PD data are needed, or if clinical efficacy data would be needed. We ask the AC panel to consider the results and questions we have presented to you today in the setting of the benefit-risk framework in your deliberation today.

This ends the FDA presentation, and I thank the AC panel for their time and advice on this important topic.

DR. AU: Thank you very much.

I think I'm going to change the agenda a bit. Given the fact that it's almost 1:00 p.m. Eastern, I think what we're going to do is adjourn for lunch until 1:30, at which time we'll go ahead and start the open public hearing, then we'll address FDA questions, or questions to the FDA, after that point in time, as well as any other questions to the sponsor.

I would ask two things of the committee. One is to go ahead and write down your questions so that after the open public hearing, we can readdress questions to the FDA, and please do not discuss any parts of this discussion with each other during lunch. So I look forward to seeing you back at 1:30 Eastern. Thank you so much.

(Whereupon, at 12:54 p.m., a lunch recess was taken, and meeting resumed at 1:30 p.m.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. AU: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson.

For today's open public hearing, each presenter has been allocated three minutes for

their presentation. I will provide you a 15-second warning when you get to 2 minutes and 45 seconds, at which point in time I will ask you to wrap up, and then we will move on to the next person starting promptly at the end of your three minutes. So I just wanted to to say that explicitly. We appreciate your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin to introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes. Thank you very much.

DR. LEPORE: Hello there. My name is Dr. Mark Lepore. I offered to speak during this session because I might bring a unique and independent perspective for our ADCOM colleagues. First, I'm a physician, board certified in pediatrics and allergy clinical immunology, with a decade of experience treating adults and children with anaphylaxis. Second, I'm the father of three children, all of whom have suffered from food allergy-related anaphylaxis. And lastly, I'm a

drug developer with many years of experience working through issues of bioequivalence of drug device combination and inhalation products, and co-founder of Transpire Bio, an inhalation pharmaceutical company.

Recently, I was a panelist in an FDA workshop on the challenges associated with bioequivalence for inhalation products. I have worked in the past to develop alternatives to epinephrine by autoinjector, although I have no financial relationship with ARS. I'm here today to strongly encourage the ADCOM to recommend approval for ARS' nasal epinephrine.

I'd like to speak today to the challenges associated with the clinical regulatory pathway for this therapy. Safety aside, the real scientific challenge for us is determining the efficacy of the product. The simple answer, of course, is we don't know, because there isn't a clinical trial model of anaphylaxis. Because of this, we're left with an approach that relies on PK and PD in healthy subjects. Unfortunately, there are no proven or

validated thresholds for the PD biomarkers or the PK parameters, which establish when anaphylaxis treatment may or may not be efficacious, and the translation from healthy subjects to patients is poorly understood.

While we know that injected epinephrine works, relying on injected epinephrine as a benchmark is not so straightforward. First, the therapeutic epinephrine easily cannot be distinguished in plasma from the endogenous form, and the baseline adjustment approach isn't perfect. Second, currently approved injected products demonstrate variable PK properties, both across subjects and across devices. Characteristics such as gender, skin-to-muscle depth, and injection location had significant impacts on the consistency of dose delivery.

Lastly, PK profiles from IM and subQ manual injections are very different, and therefore provide different benchmark targets; yet despite these challenges with variability, injectable epinephrine has been the mainstay of treatment for

decades.

The main question for you today is, does the data provide convincing evidence of comparability with an approved reference standard? For this, I leave you with two thoughts. First, to me, the data clearly demonstrates comparable bioavailability and PD changes when looked at in totality, providing some comfort that efficacy would be comparable. Differences appear to be small and clinically insignificant.

Finally, with this approach, there will always be some residual uncertainty, but the benefits definitely outweigh the risks. And while there are unknowns, the data supports the likelihood of efficacy through the pathway of bridging via PK and PD comparability. For these reasons, I strongly urge the committee to recommend this for approval so that the agency can approve this product for patients as soon as possible. Thank you.

DR. AU: Thank you very much.

Speaker number 2, please unmute and turn on

your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes.

MS. CRETER: Hi. I'm Christine Creter. This is my 12-year-old son, Colin, who has 15 anaphylactic food allergies, and I have developed five food allergies as an adult. My disclaimer, I am a professional trainer in the healthcare industry. I do volunteer with FARE, and I have also actively sought out the opportunity and do currently have a financial relationship with ARS to support future training on this new delivery system.

But why did I stalk a pharmaceutical company to try to work with them? It's because my son is terrified of needles. Since 5 months old, when he was diagnosed, he has yearly allergy skin tests requiring 30 to 40 individual needle pricks at a time. He does blood work, vaccines, but each experience is a nightmare. He's been combative. He's had to be restrained. He has extreme anxiety.

We can't even get him out of the car. And the only way to save his life when he has a reaction is to give him epinephrine by needle. How have we gone so long with no alternatives? We have noninjection therapies for seizures, pain overdoses, but nothing if you eat a food.

Colin has gone into anaphylaxis several times. Each time we waited longer than we should have to administer the epinephrine, largely because of the needle. The last time was just last year. We got Sushi from a place we know. We had it at home, and within a minute, he started complaining of feeling funny. His stomach hurt, his itchy throat, he said he was going to throw up. I thought, "Is this really a reaction? Is it really worth the injection trauma?"

So I waited. I got his pulse oximeter because that's one of his symptoms, is that his pulse ox drops. And I watched it start to go very quickly all of a sudden, to the 90s, to the 80s, and he looked at me with wide eyes, and he said, "I need it, Mom," meaning the epinephrine. I got it,

I fumbled. I was scared. I could tell this was getting bad very quickly, and I forgot to take the the cap off the Auvi-Q. His last words before going unconscious were, "Mom, the red cap."

I teach people how to do this. How could I be fumbling so much? I administered the Auvi-Q, and I began smacking his face and screaming for him to wake up. He was unconscious for what felt like forever, but it was probably only seconds, and the epinephrine worked. The whole experience was so traumatizing, though, and if we had just administered sooner, maybe it wouldn't have been that bad. But what if he hadn't woken up? How many other people wait? How many people die simply because they waited or didn't carry it at all?

Please review this different delivery mechanism, and assuming the efficacy is comparable to needle injections, please consider the benefit to kids like mine, who will go off to college in a few years and have to carry their own epinephrine, and maybe even have to make that decision to administer themselves. Just the option of a

needle-free delivery might mean he administers more readily, and just the option of a needle-free delivery may prevent the delay in administration by a caregiver like me, and we all can increase our likelihood of keeping allergic patients alive. Thank you for your time and consideration of this life-saving product.

DR. AU: Thank you very much.

Speaker number 3, please unmute and turn on your webcam. Will speaker number 3 please begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes.

MR. O'ROURKE: Hi. My name is Tom, and I am not affiliated with any pharmaceutical. I'm a dad of three children with life-threatening food allergies, multiple life-threatening allergies, and we've tried various treatments such as OIT and TIP, and traveled from the the East Coast to the West Coast. Despite tests indicating we are highly allergic, we've, to our knowledge, never had anaphylaxis.

My oldest has a severe needle phobia, so what does that mean? Well, like the prior speaker, yes, when they're little, they become very combative when they're going to get one of these skin tests or any sort of vaccine. I've seen my son just at the mirror, and he knew he was going to go to get a medicine that required a needle and literally fainted before we even left the house, and actually injured his knee.

My son goes to a university. Our first choice, where he was planning to go, oversold the dorm. They put three students in a room. We didn't think that was going to be a safe choice for him, so we opted to the second choice university, which offered singles. Now he's living in a single.

His RA at the dormitory is a bit of an absent RA. He went there the last minute, and didn't have the opportunity to go to orientation and didn't know that many people; ate at the cafeteria, had a weird feeling in his mouth, and went back to his dorm room and calls me, "I think

I'm having an allergic reaction. I don't know if I'm having an allergic reaction. My mouth feels weird." I'm saying, "Use the EpiPen." He's terrified of using the EpiPen.

So here I am, I'm about to have a heart attack. I'm calling the school security, campus security, things like that, and follow up with the allergist and he says, "He might have had a reaction, but I don't even think it was a reaction." They're not even sure.

So being able to have something that doesn't require a needle injection would be extremely helpful for the quality of life. So instead of being at a university right now, he has super strong academics, super strong extracurriculars, he's now working at a supermarket, unfortunately, and we're trying to figure out how we're going to get back on track. A needleless EpiPen could help with that and access to accurate testing. My son's 19. We're still doing these antiquated tests. We're not even sure what we are or not allergic to anymore.

Also, I just want to say, coming up through the public schools, 504 inequality, if you have a parent who's hired an advocate to get accommodations, they're going to get a lot more accommodations than a parent who can't hire that advocate. I think there needs to be a baseline 504 so these kids aren't given different levels of safety without going throughout the school experience, because this is a severe impact on their life.

Finally, I also hear from dermatologists Dupixent might help with --

DR. AU: I'm sorry. Mr. O'Rourke, we're going to need to move on. I apologize.

MR. O'ROURKE: Thank you.

DR. AU: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 please begin and introduce yourself? Please state your name and any organizations you are representing, for the record? You have three minutes. Thank you.

MS. BEE: Good afternoon, everyone. My name

is Amanda Bee, and I'm the mother of a child with food allergies, served as president of the nonprofit Utah Food Allergy Network, attended FARE at Congress twice, and participated in many local and national allergy awareness events. I'm an experienced advocate for the food allergy community and have a good grasp on why a needle-free epinephrine device is important.

My daughter Vivian was diagnosed with life-threatening food allergies at 6 months old. She has an exceptional 504 plan, great doctors, and a community of friends and family that are all aware of the severity of her allergies. She's now 11, and despite all of our precautions, I've had to stop her with an Epi nine different times to save her life.

My situation is not unique. This week alone, I received phone calls from two different parents in our community whose children had an allergic reaction that required Epi. In both cases, Epi was delayed while these parents weighed the risks of a potentially deadly anaphylactic

reaction against the trauma of holding their child down and stabbing them with a needle again.

They were both experienced food allergy parents, but they held back because the treatment is feared as much as anaphylaxis. We're told again and again, Epi first, Epi fast, but in the food allergy community, they can tell you that it's often delayed because of the fear surrounding needles. I asked both parents if they would have delayed treatment if nasal epinephrine had been available to them, and received an emphatic no.

Personally, I want to share with you my daughter's last anaphylactic reaction in July of 2022. Vivian was in our neighborhood playing night games with friends, when she started to have symptoms of anaphylaxis: full-body hives, scratchy throat, itchy years, cough, nausea. She knew she needed Epi, but even after years of therapy, her first instinct is always to hide her reaction so she won't have to be stabbed again. This fear response could kill her.

It took the strength of my husband and I

both to physically hold her down and inject her with Epi. Soon the medicine helped, and I held her while she sobbed and told me how scared she was. Vivian knows her allergies can kill her. She was diagnosed with anxiety following two back-to-back reactions requiring Epi when she was five. She is a smart, brave kid, but in those desperate moments, her terror of the needle outweighs everything.

When she was young, she was always with me, but my baby is growing up, and I have to rely on people around her to help keep her safe. We know it isn't if, but when she will go into anaphylaxis again. I know they would try, but I have little confidence that her 11-year-old friends, or even other adults, would be able to overcome both her fear and their own in time to hold her down against her will and stab her with Epi to save her life.

I cannot stress to you enough how much safer my child and millions more will be if they're able to simply spray a dose of epinephrine into their nose. Nasal epinephrine could save her life, and I hope you'll consider that when making your

recommendation. Thank you.

DR. AU: Thank you so much.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 please introduce yourself? State your name and any organization you are representing, for the record. You have three minutes. Thank you.

MS. MANDELBAUM: Hello. My name is Lianne Mandelbaum. I am the president of the food allergy advocacy nonprofit, No Nut Traveler. I'm also the mother of a 17-year-old boy who has a peanut allergy. I have no financial relationship with ARS.

For many people using a needle injector to treat an allergic reaction is an anxiety riddled process. Some people are reluctant to use, and may even delay immediate treatment. I have spoken to countless caretakers in my son's life who have admitted being reluctant to using his autoinjector. I want to share a quick anecdotal story.

We always train with are expired autoinjectors, and we use a grapefruit, and one of

the people participating with my older son, who has no allergies, his hand was shaking. He could not approach the grapefruit, and each time he approached it, he prematurely had the needle come out. So I tried to guide his hand, which was shaking, and he ended up shaking so much when we approached the grapefruit, he actually stabbed me in the thumb. After that, he told me I could never leave him alone with his younger brother because he would not be able to save him if he was exposed to his allergen, and that he would potentially die. This is a real fear, not just for the person, but for the people taking care of them.

As far as in the air, people have reported to my website that allergic reactions are taking place in the air. There are only vials available in emergency medical kits in the air, and even those may not be there. It's even more critical that we have a device that can be used and used quickly. People have also reported to my website that they have either injected with the cap on, injected backwards, and then didn't have a back up.

There are so many mistakes that can be made that wouldn't happen with a nasal device. A nasal device simply goes in the nose. It's that simple.

I want to leave you with the fact that no one is perfect, yet for those of us with food allergies, or have children with food allergies, falling short of the mark of perfection even once can be deadly. If you forget your autoinjector, if you take a bite of the wrong food, it's terrifying how little can go wrong for a death to occur.

As a teenage mom, everybody knows -- and research backs this up -- that a compact size will make it less conspicuous. Kids don't want to be different, and something that can fit in a purse or a back pocket is a game changer for us. Studies show that teenagers often don't carry, and this device may overcome the reluctance.

I think about a recent death in California of a young girl at her prom, where her autoinjector was left on the party bus, and other students were giving her CPR. She died in the parking lot because her autoinjector wasn't there. I think

about the fact that this nasal device could have fit in her purse. Would it have made a difference? These are the nightmares that keep me up at night.

There is so much that can go wrong, and we need to be able to adjust the odds. This device can adjust the odds. My son is also going off to college. I don't want him to leave his autoinjector in a room.

(Crosstalk.)

DR. AU: I'm sorry. We're going to need to move [indiscernible].

MS. MANDELBAUM: I strongly recommend that you --

DR. AU: Thank you.

Speaker number 6, would you please unmute and turn on your webcam? Will speaker number 6 please begin and introduce yourself? Please state your name and organization you are representing, for the record. You have three minutes. Thank you.

DR. ELLIS: Good afternoon. I'm Dr. Anne Ellis. I'm chair of the Division of Allergy and

Immunology at Queens University in Kingston Ontario, Canada. In terms of disclosures, I've served on advisory boards for Pfizer, who is the Canadian distributor of EpiPen in Canada; for Sanofi back when we had Allerject, distributed by Sanofi, and also I am on the advisory board to ARS, but obviously I didn't attend this morning session. I listened to it virtually, and a lot of the great comments that I had planned to say were already mentioned by some of my in-person advisors and colleagues.

A couple of things that I will just add that hasn't already been said is I've done research in anaphylaxis, specifically in biphasic reactions, and early administration of epinephrine was the only thing that universally prevented a biphasic reaction in my 2007 study. I know with my clinical practice, again, the reluctance to use epinephrine through an injector is high, and it does lead to a more increased rate of biphasic reactions if you delay the administration of Epi.

I think because it is always coming from a

needle, I also have collaborators who have looked at the injuries that occurred from children, who, again, have to be held down, as you've already heard from previous speakers. But they thrash more, and then they wind up with massive leg lacerations as a result.

So I think, again, having this as an option is going to be huge. It's going to make potentially a massive difference in the number of people who will actually use epinephrine as opposed to taking Benadryl and hoping for the best, which is not what we teach our patients, and yet they do it anyway.

So I will give some people back some time because I didn't want to reiterate too many things that have already been said, and I thank you for your attention on the panel.

DR. AU: Thank you very much.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 please introduce yourself? Please state your name and any organization you are representing, for the record.

You have three minutes. Thank you.

DR. DeMORE: Hi. My name is Dr. Nancy DeMore. I have no financial conflicts of interest. I am representing my daughter, not any organization, although I am a surgical oncologist at Medical University of South Carolina and co-leader of Developmental Cancer Therapeutics at Hollings Cancer Center. But I'm here on behalf of my 21-year-old daughter who has frequent and severe anaphylaxis. Her allergy is to coconut and its 4-page list of derivatives. So despite avoidance, she has oral anaphylaxis, inhalation, topical, and also to PEG and glycerin, and many medications.

She has anaphylaxis usually about 2 times a month. When she has anaphylaxis, she usually needs to use 2 or 3 EpiPens, and the EpiPens are extremely painful, so she does often delay, which is why she sometimes needs to use more than one EpiPen. The pain that she has is very intense from the EpiPen injection site. She has muscle cramping in her leg. It's very difficult for her to walk or sleep. The pain lasts for about 2 to 3 days. Her

primary care physician sometimes needs to prescribe narcotics.

She can't go to college in person, so she's an online college student, and when she has this, she can't do her work. She has to get extensions, and then she has a lot of anxiety because she has to make up her work. She did have to have a medical withdrawal last semester because of all of this. She now has PTSD every time she has the injection because of all the pain. It causes huge psychological issues.

Her allergist was able to get emergency use authorization for neffy from the FDA, and she's been using it now. She's had 9 episodes of anaphylaxis where she has used it. Her symptoms are abdominal pain, vomiting, nasal congestion, chest pain, wheezing, and bronchospasm, and when she uses the neffy, it works very well, usually in 3 to 5 minutes; one time in 10 minutes.

This is life-changing for her because she is now able to have quality of life. She has anaphylaxis, she gives herself a sniff, and she's

better, and that's it. And there's no 2 to 3 days of this horrific pain. She can go on and have a life. So I strongly urge you to approve this. This is so important for people with anaphylaxis. The pain is very real, and this is really a great solution. It really changes people's quality of life. So thank you very much for the opportunity to speak to you about this.

DR. AU: Thank you very much.

Speaker number 8, please unmute yourself and turn on your webcam. Will speaker number 8 please introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes. Thank you very much.

MS. S. SAIONTZ: My name is Stacy Saiontz, and this is my son, Jared Saiontz, and we are just representing ourselves.

MR. J. SAIONTZ: Hi. My name is Jared Saiontz, and I'm 15 years old, a freshman in high school. I have 26 anaphylaxis food allergies. I always carry my epinephrine with me, and this weekend I actually had an allergic reaction, and it

wasn't that bad, but I was very hesitant to give myself the EpiPen. I was with my brother, and I kept trying to give it, and then I was like, "No, I don't need it." But I need to give it because it was life-saving. And I feel like if we can get nasal epinephrine, it will be a lot better and a lot easier, and I won't have to worry as much when giving myself the EpiPen because I know that it's not going to hurt, and my fear of needles will not bother me at all. And I know that my life's just going to be safe if easier.

MS. S. SAOINTZ: My name is Stacy, and I'm the parent of Jared. Like others with food allergies, he always carries his two epinephrine autoinjectors on his person at all times. Currently, epinephrine autoinjectors are bulky and cumbersome to carry, especially for adolescents and teenagers. A non-autoinjector such as a nasal spray would be much less bulky and easier to carry, which would encourage greater compliance and accessibility. Many food allergy deaths occur because epinephrine autoinjectors are not

accessible at the time of reaction. Anything that makes compliance and caring epinephrine easier could greatly diminish this risk.

Jared has experienced anaphylaxis and thankfully been saved by prompt administration, but as a toddler, he was frightened by the needle and would need to be held down to administer the epinephrine. On a camping trip, he got stung by a bee and required two fathers to hold him down while my husband administered the epinephrine because of Jared's fear of the shot.

As he got older, he worried he wouldn't be able to give it to himself due to his anxiety about the needle; therefore, we've always met with teachers, basketball and soccer coaches, and camp counselors to educate them about it, and every time they see the epinephrine autoinjector, they immediately comment about the needle, and they often express similar reticence.

We always fear that they'll hesitate helping to administer his medicine because of the needle. In fact, we've been trying to convince New York

legislators to pass a bill for 12 years that would provide a one-time 10-minute training for teachers on administering epinephrine. The main argument that has prevented this bill from being passed into law is concerns by the teachers and the unions that learning how to administer epinephrine autoinjectors, they're afraid of it because of the needle.

During this time that we've been advocating for the passage of this life-saving bill, Narcan has become a regular occurrence all over the country. We believe that if the nasal spray epinephrine is approved, the nasal spray is much less intimidating, and more people would view it as accessible just like Narcan, and they'd be willing to give it without hesitating.

Let's please prevent another individual from dying of anaphylaxis by making the emergency treatment of epinephrine less complicated and scary. The needle-free alternative is life-saving, it's easy to use and carry for children, and prompt administration of epinephrine is more likely if

it's accessible, and caregivers and chaperones are not intimidated by the delivery of it.

As you heard, Jared had an anaphylactic reaction on Saturday night, and he was nervous to give himself the shot, so his brother put his hand over Jared's, and they administered it together. This would not happen if we had the nasal spray alternative. Thank you for listening to us, and we don't have any financial ties to any of the parties involved.

DR. AU: Thank you so much.

Speaker number 9 is no longer speaking.

Will speaker number 10 please unmute yourself and turn on your webcam? Will speaker number 10 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes. Thank you.

DR. WIEST: Hello. My name is Dr. Elani Wiest from Jacksonville, Florida. I have no conflicts of interest to declare. I'm a physiologist by training, but today I'm here as a

mother to two children with multiple anaphylactic food allergies. Our food allergy journey began with a rough start. Before he was 2, my older son, Philip, had to endure over 15 EpiPens. One time that will stay with me forever is when his teacher put off administering an EpiPen when he was having symptoms of anaphylaxis. She was trained but never administered an EpiPen, and was hesitant and scared. His reaction quickly progressed, and I watched paramedics administer 3 doses of epinephrine. The ER staff had to administer another dose of epinephrine, then inhaled racemic epinephrine, followed by IV epinephrine, and talks of intubating my child. I watched him fight for his life because his teacher was too scared to administer an EpiPen.

Another incident I think of daily is when my son at age 2 ate unsafe spaghetti while we were on vacation. We recognized the signs of anaphylaxis, and my husband immediately administered epinephrine to his right thigh; however, my son jerked away, and the needle jammed and sliced open his thigh.

In addition to having to get a second EpiPen in the other leg, he ended up with 10 stitches. He still remembers this event, resulting in him not speaking up when experiencing symptoms of anaphylaxis because he fears the needle.

Last December, he licked an unsafe cookie and immediately started wheezing. Despite him trying to convince me that it was not an allergic reaction and that he does not need an EpiPen, I was experienced enough to know to administer epinephrine right away. However, will a teacher act as fast as I did? Will a family member? Will his friend's mom act promptly?

These are the fears we as a family face every single day. Having a way to administer epinephrine without fear of needles will be a massive improvement in the treatment of anaphylaxis. It will make teachers less afraid to treat reactions, and it will make children less afraid to speak up when they know they're having a reaction. There will be less conversations about intubating children and less tragedies on the news.

Nasal epinephrine will also make oral food challenges less stressful. When our allergist wanted to do a milk oral challenge with Philip, he refused to drink the milk because he feared needing an EpiPen. It took two years to finally get him to participate, and he passed. When you're managing 8 food allergies in one household, passing an oral food challenge makes life significantly easier and cuts down on the grocery bill. Nasal epinephrine will help make oral food challenges less stressful and encourage children to participate. Having an affordable and non-invasive epinephrine device will make an immense positive impact on our families and other families like ours. Thank you so much.

DR. AU: Thank you. Thank you very much.

Will speaker number 11 please unmute yourself and turn on your web camera? Will speaker number 11 please began and introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes. Thank you.

DR. RICHARDSON: My name is Rachel

Richardson, and I'm here to speak on a personal level, as a mother with a daughter with multiple food allergies. I'm not affiliated with any organizations, although my husband and I are working on a foundation to help fund food allergy freedom therapies for kids due to the success my daughter has had.

A day in the life of a parent with a child with severe food allergies is riddled with anxiety and emotional stress. I am constantly worried about food consumption at my home, at school, at birthday parties, at a restaurant, and I'm concerned if I or somebody nearby will have access to epinephrine. Anytime there is wheezing, hives, or any skin abnormalities, I'm concerned with anxiety of what is the cause and how far it's going go.

I have all these bulky epinephrine devices in my home, shoved in my purse, in my car, at the grandparents' house, and at school; not just because I know that I might need it at some point for my daughter, but because I know most people

don't carry them around, so I do it for my daughter and I do it for others as well.

I see a benefit, a multitude of benefits, for a nasal epinephrine. First, it removes the fear of a needle. Many allergy patients and caregivers are reluctant to administer epinephrine not because they're worried about the drug itself but because they're worried if the needle is really necessary. Having to poke someone with a needle raises a level of concern and apprehension that a medicine, drug, or spray simply does not.

Today, I can think of two incidences where my daughter had downplayed her symptoms simply because she's terrified of needles, and I can recall five emergency visits to her allergist because I wasn't sure if I wanted to stick her with a needle and if it was warranted at that time. Only one of those, it was not warranted.

For me, shoving her in the thigh with a needle gives me Pulp Fiction vibes, and I'm sure it does other people as well. Just the other day, she went into pure freakout mode over pouring peroxide

over her skinned knees. You can imagine what a needle jabbed into her thigh would do. She's 8 years old. Having a non-invasive option will limit the anxiety and apprehension when it's medically necessary.

Secondly is improved ease of use. Another issue is many people administer epinephrine incorrectly. The two biggest mistakes in a high-stressed situation is not using enough force in the thigh and not keeping it in the full 10 seconds. These are serious errors that can prevent someone from getting enough drug necessary. A delivery through the nose can be more rapidly absorbed into the bloodstream and result in faster relief. It can mean the difference in me telling you about my daughter surviving another anaphylactic reaction or her getting it quick enough and becoming another food allergy angel.

Lastly, I'm a fan of competition. Anytime there's competition out there, it keeps the single manufacturer from price gouging, and what we're truly lacking here is innovation. My hope is that

this creative delivery mechanism opens the gates for more people to see how great the delivery is and wants it to continue to find alternative ways to administer the drug so that eventually it becomes more affordable, easier to administer, and potentially save our lives. And really, isn't that all we can hope for? Thank you.

DR. AU: Thank you very much. I apologize for interrupting.

Speaker number 12, please unmute yourself and turn on your webcam. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes. Thank you.

DR. POBLETE: I'm Dr. Sung Poblete, CEO of Food Allergy Research and Education or FARE. I have no financial disclosures, and I'm honored to add my voice in support of the approval for a needle-free epinephrine option. Today, I'm speaking in several capacities. I'm representing FARE and more than 32 million Americans with life-threatening food allergies, and I'm also here

on a personal note as a registered nurse and a food allergy sufferer myself. I know firsthand the risks and challenges that food allergies sufferers face on a daily basis and how critical it is to someone suffering an anaphylactic reaction to receive epinephrine in a safe, timely, and appropriate manner.

Every second counts in an anaphylactic emergency, and that's why a new and easy-to-use epinephrine delivery system is so important for me and all of us who live with the fear of ingesting a potentially lethal food allergy substance. Fear, access, options, and innovation play pivotal roles in epinephrine delivery methods. In fact, you may not realize how important needle-free options are in real life to the people using epinephrine in an emergency.

Fear is real. Children especially have a fear of needles in general, while parents and loved ones experience fear over improper administration of epinephrine or potentially hurting the very person they're attempting to help. There's also a

fear that the dosage of epinephrine might not be correct or there could even be confusion over where to inject the person. We all know that fear can be immobilizing, but in the case of an anaphylactic reaction, time is of the essence.

We saw in one survey of epinephrine autoinjector users that half of the adults and 30 percent of the children reported not having used epinephrine during at least one severe allergic reaction, in part, because of fear of needles. And if you're afraid to use epinephrine first and fast, your risk of death increases. It's that simple.

One closing thought; the nasal epinephrine spray you're considering today is a life changer. It's the first of what I hope will be many new needle-free delivery systems for epinephrine that highlight innovation in the food, allergy, and anaphylaxis space. It's an alternative to needles that takes the fear out of using a life-saving medication. It's a delivery system that allows a patient to use epinephrine more readily and promotes more consistent use, and it's a

significant step forward in providing options and hope for those whose lives depend on epinephrine. On behalf of all of us who live with life-threatening food allergies, I strongly support your positive consideration of this nasal epinephrine spray. Thank you.

DR. AU: Thank you very much.

Speaker number 13, please unmute yourself and turn on your webcam. Will speaker number 13 begin and introduce yourself. Please state your name and any organization you are representing, for the record. You have three minutes. Thank you.

MS. ANDERSON: Good afternoon. My name is Charmayne Anderson, and I'm the director of Advocacy for Allergy and Asthma Network. I'm also a mom to two children with severe food allergies, and I have no financial conflict of interest.

Allergy and Asthma Network is a national nonprofit that has been dedicated to ending needless death and suffering due to asthma, allergies, and related conditions since 1985. We appreciate this opportunity to provide comments on

this new nasal spray currently under review.

Up to 50 million people in the U.S. have experienced life-threatening allergic reactions to food, insect venom, medication, and latex, resulting in upwards of 1,000 deaths each year. Epinephrine is the first line of treatment, and access and response time is critical during an anaphylactic emergency.

Prevalence and burden of severe allergies is growing for millions of Americans. Avoidance of an allergen alone is simply not enough. Individuals and families live in constant fear of accidental exposure, impacting their quality of life. These are not nameless faceless statistics; these are real people with families, hopes, dreams, and fears.

Data show that death from anaphylaxis occurs more often when there is either a delay in administering epinephrine or it is not given at all. The causes of the delay vary. We have heard about needle phobia, to hesitation using an autoinjector, to reluctance to carry due to the

size of the autoinjector device. Access to epinephrine is critical, yet innovation has been lacking, as the first epinephrine autoinjector came to the market in 1987.

The network is optimistic about the continued advancements in scientific research and development of treatment for anaphylaxis, which include needle-free nasal sprays, among others, that give people additional treatment options. The need and patient preference for new anaphylaxis treatment options are further underscored in the voice of the patient report that followed the 2021 externally-led, patient-focused drug development meeting, which was attended by FDA. The report highlights patients and caregivers who want less invasive options in epinephrine treatment.

In closing, people with severe allergies are relying on FDA to ensure innovative products that are safe and effective reach the community it can help the most. Innovation without access breeds frustration. Quality-of-life considerations and patient preferences should play a key role in

driving treatment decisions for people, especially those with food allergy. Thank you.

DR. AU: Thank you very much.

Speaker number 14, please unmute yourself and turn on your webcam. Will speaker number 14 please begin by introducing yourself? Please state your name and any organization you are representing, for the record. You have three minutes. Thank you.

DR. CLEARY: Thank you for this opportunity to speak today in support of nasal epinephrine. I have no financial conflicts. My name is Kelly Cleary, and I'm a pediatrician, fellowship trained in emergency medicine with a strong background in mental health for children and young adults. I'm currently the senior director of education and support programs at FARE, which stands for Food Allergy Research and Education, but today I am here largely as a mother of four children, one of whom has multiple life-threatening food allergies.

My time as an emergency room physician has provided me the skills to medically care for my

11-year-old son's anaphylactic episodes, but my training cannot take away the fear and worry that come with having a food allergic child because my mind always races to what will happen if I am not there. I have watched my son turn blue, I have watched him become limp, I have been raced to the the emergency resuscitation area multiple times, and I've spent nights with my son in the intensive care unit. And in all of those instances, I was there, and injected him with epinephrine immediately.

But when I drop him off on a play date, or at school, or a sporting event, and I see the look of worry and fear in another parent, or teacher, or coach's eyes as I teach them how to use the epinephrine autoinjector, I worry about what happens if someone hesitates giving my son his epinephrine because they're anxious about giving him a needle. I've seen my son delay telling me about his own symptoms because of his own fear of needing that needle, and as he gets older, I need to allow him the independence that my other three

children will get, but with that comes the responsibility of being able to inject himself if he needs it.

As a physician, I know the importance of timely administration of epinephrine and anaphylaxis and that every second counts. A case that will forever follow me is one in which a patient had a very delayed administration of epinephrine in anaphylaxis because his mom accidentally injected herself instead of her child. Having witnessed the catastrophic effect of delayed epinephrine administration, I never want to see that for another patient, and I want to mitigate that fear for my own son and family.

A nasal epinephrine delivery system would take some of the fear out of an already anxiety-provoking moment. A nasal epinephrine delivery system would allow for easier administration for caregivers, school personnel, coaches, and for patients, especially those who are learning to take care of themselves. A nasal epinephrine delivery system would be life-changing

for our families. Thank you for the opportunity to speak.

DR. AU: Thank you very much.

Speaker number 15, please unmute and turn on your webcam. Will speaker number 15 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes. Thank you very much.

MS. HERNANDEZ: Hello. My name is Priscilla Hernandez, and I am president of a nonprofit organization. I'm a wife and a mother of two amazing boys, one who suffers from life-threatening food allergies, Zacky. I speak here today in support of expanding available options of the methods of delivery of epinephrine, the only known life-saving intervention drug for food-induced anaphylaxis. Our household is too familiar with the need to administer an autoinjector during an emergency. Though we're grateful for this life-saving drug, we seek needle-free epinephrine devices for anaphylaxis.

Food allergies are a first-tier health issue

affecting 33 million Americans but, unfortunately, the amount of research, FDA-approved drugs, and other resources are simply not enough for our community's needs. Expanding the method of delivery of epinephrine for those with food allergies will save lives. The needle of an autoinjector can delay delivery to a patient experiencing anaphylaxis, as we know the importance of time is of the essence.

Needles often exacerbate a situation already filled with fear and anxiety. We know this firsthand with our own story. One afternoon, my son's nurse called because she thought that maybe Zacky might have eaten his allergy. Shortly after the first call, things escalated quickly. She called back asking if I was nearby, and I was not. At that point, all I could hear on the phone was my baby screaming and crying in the background, "No, I don't want it. I don't want a shot."

My heart sank. The nurse said she was going to give him epinephrine as both the statement as well as verification. I could not verbally

validate with certainty over the phone because though we carried this epinephrine everywhere we went, I subconsciously never imagined myself or anybody else having to administer it to what I believe to be a larger-than-life needle into my son's skin. That day, my son suffered his first anaphylactic reaction, requiring epinephrine and a visit to the emergency room at the young age of 6 years old.

MR. MUNOZ: Hi. I'm Zacky. This happened five years ago, but it's a day I will never forget. What I remember most about the day is how I felt. It was scary. I'm here to say please make more options available for kids like me who have food allergies. You see, it's hard enough having to deal with food allergies, but knowing that if you have a reaction, my only option is to get a shot, it brings me fear. I hear other options may be less big and easier to carry, too. This way I will always have access because I know how important it is to always have it nearby and available. It's my lifeline.

MS. HERNANDEZ: I often ask myself is there an easier way, and there is. Innovative options will add ease and improve quality of life for those affected with food allergies. Like most people, we just want to enjoy life and navigate it as smoothly as possible.

MR. MUNOZ: Therefore, we respectfully ask the FDA and the committee to approve more options for delivery of epinephrine like the one being discussed here today. Thank you.

DR. AU: Thank you so much.

I think we're on to speaker 16. Speaker number 16, pleas unmute yourself. Will speaker number 16 please introduce yourself? State your name and any organization you're representing, for the record. You have three minutes. Thank you very much.

MS. KORANTENG: Good afternoon, everyone. My name is Ashley Dinah Koranteng, and I'm a public health professional and food allergy advocate from Sterling, Virginia. I have no financial associations or conflicts of interest. I'm happy

to be here and to be speaking to you all during Food Allergy Awareness Month. Approximately 32 million Americans have food allergies, including those that are at risk of experiencing life-threatening anaphylaxis. I am one of those 32 million Americans, and I have seven severe food allergies.

I was first diagnosed with food allergies at the age of 2, so this is something that I have managed for almost my entire life. Navigating life with severe food allergies can be challenging. It requires a lot of diligence in order to stay safe at home and when attempting to dine out. It requires a lot of communication and knowledge of manufacturing processes. It is a full-time job.

Currently, the only option we have to treat a life-threatening reaction is autoinjector epinephrine. I have personally had to administer this to myself and have had a nurse administer this to me. It's a painful experience and can be scary to have to do it, especially to yourself.

A nasal epinephrine option would mean a lot

to me and others with severe food allergies. For me personally, I've always known that in a situation where I may have inadvertently come in contact with something I'm allergic to, I have to use my EpiPen. It can be a daunting scenario knowing that the necessary step is painful, but that you have to do it to save your life.

Many people experience a greater sense of fear surrounding using autoinjector epinephrine that can unfortunately lead to them not using it at all or not using it soon enough, so this new drug would mean a non-daunting, painless option to save lives, and I believe that it should be an option. Thank you so much for your time.

DR. AU: Thank you very much.

Will speaker number 17 please unmute yourself and turn on your webcam? Will speaker number 17 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes. Thank you.

MS. CARVER: Good afternoon. Thank you for

the opportunity to provide this testimony. My name is Melanie Carver, and I'm the chief mission officer of The Asthma and Allergy Foundation of America and its Kids with Food Allergies division. Our nonprofit represents the over 100 million people in the U.S. who have allergic disease. We have received funding from Kaleo and Viatris.

Our mission is to save lives and reduce the burden of asthma and allergic diseases, and I'd like to express our perspective using some data from research we conducted and published in a survey called My Life with Food Allergy. It explains why having other epinephrine options is so important to our community.

We know that a severe allergic reaction known as anaphylaxis can be potentially fatal, and that a quick injection of epinephrine is the standard of care for stopping anaphylaxis, but far too often epinephrine is not used when it's needed. Our hope is that by expanding administration methods like through a nasal spray, that patients, caregivers, and first responders will have fewer

barriers when they encounter anaphylaxis.

The most common triggers for anaphylaxis are medicines, insect stings, and food, and per the most recent data from the CDC, 20 million people, including 16 million adults and 4 million children, have food allergies in the U.S. Food allergy anaphylaxis is leading to 90,000 emergency room visits per year, and there are also disparities related to food allergies and anaphylaxis.

Food allergies have increased over the past three decades, with the greatest increase among non-Hispanic black children. 9.6 percent of non-Hispanic black children have food allergies compared to 5.3 percent of non-Hispanic white children, and black individuals and older adults in the U.S. have the highest rates of death due to allergic reactions.

To capture the patient and family experience with food allergies and anaphylaxis, we surveyed over 2200 people who are either patients with food allergies, parents of a child with food allergies, or both, and the responses to our survey revealed

that there is room for improvement in treating anaphylaxis. Ninety percent of the surveyed parents reported that their children had experienced at least one severe allergic reaction; however, 3 out of 4 of those parents said that their child did not receive epinephrine to treat the severe allergic reaction. Forty-two percent instead opted to use an antihistamine, which cannot reverse the life-threatening symptoms of anaphylaxis, and 12 percent stated that the fear of injection was a reason for not using the epinephrine.

Only about 40 percent of parents, 19 percent of adult patients, and 17 percent of teens or young adults with food allergies felt very confident in using their epinephrine autoinjector. Fifty-eight percent of parents of teens and young adults with food allergies reported that food allergies cause fear and anxiety for them.

Based on what we hear and have surveyed from our community, we believe a nasal spray formulation of epinephrine will be easier to deliver and will

remove any fear of a needle-based injection. We ask the committee to consider the overall potential impact of nasal epinephrine in the ease of delivery and the potential importance of providing this alternative to increase adherence and confidence among those with a life-threatening allergy. And as someone who lives with anaphylaxis, I appreciate all of the patient advocates here today. Thank you for your time.

DR. AU: Thank you very much.

Speaker number 18, please unmute and turn on your webcam. Will speaker number 18 begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have three minutes. Thank you very much.

MS. CADES: Good afternoon. My name is Michelle Cades. I'm a licensed clinical social worker, food allergy, and special education advocate from Herndon, Virginia. I have no financial ties to these products. I cannot encourage you strongly enough to approve and expedite the availability of nasal epinephrine

spray. I myself have lifelong allergies to tree nuts and shellfish. My 22-year-old son is allergic to peanuts and tree nuts, and my 20-year-old son is allergic to milk and also has eosinophilic esophagitis or EoE.

Originally, I had an Ana-Kit, which required refrigeration and contained a vial of Epi, a glass syringe, and a string tourniquet. While I was the only kid in my elementary school with food allergies, now that number is 1 in 13. EpiPens hit the market when I was 16. Between my sons and I, we've had at least ten anaphylactic reactions requiring epinephrine, including at least one terrifying biphasic reaction. We now fill prescriptions for at least six sets of autoinjectors every year. With our privileged, very expensive health insurance, it still easily costs us over $250 annually for generic autoinjectors. Name brands are not in our formulary, and without insurance, would cost us $300 to $600 per two pack, or over $3,000 annually, which would be $60,000 out of pocket over my

50 something and my son's 20 plus years.

Having a reaction is horrifying. Between the three of us, we've experienced coughing, wheezing, massive congestion, full-body hives and flushing, vomiting, diarrhea, itchy mouth and throat, swollen tongues and lips, and my consistent first symptom, an immediate sense that something is very wrong, which is now actually called an impending sense of doom.

It is no surprise that I and so many people with food allergies also have a significant anxiety disorder. Self-injecting is terrifying, as is the anticipatory angst of trying to decide whether or not to inject. Restraining your child to administer epi is traumatic for the child, for the parent, and for bystanders. After witnessing her brother's reactions as a young child, my now teenage non-allergic child has PTSD panic attacks when hearing emergency rescue sirens. My friend's child cannot self-carry because she faints just thinking about having a needle in her possession.

In my allotted three minutes, I don't have

anywhere near enough time to describe our allergic lifestyle, but to say that the number one rule is, no epi, no eating. Having a small nasal epinephrine spray would be a game changer, and little carrying cases to attach to keyrings, lanyards, and backpacks will massively improve self-carrying rates and self-injection use. We must have alternatives to bulky, expensive, fear-inducing, needle-administered epinephrine autoinjectors. Our lives, my life, and those of my children depend on it. Thank you to all today's speakers, panelists, and experts for your time and effort.

DR. AU: Thank you very much.

Speaker number 19, please unmute and turn on your webcam. Will speaker number 19 begin and introduce yourself? Please state your name and any organization you are presenting, for the record. You have three minutes. Thank you very much.

MS. T. DAY: Hi. My name is Talia Day, and I am here simply as a mother of three children with severe food allergies. I want to thank you for the

opportunity to appear before you today to explain why a safe epinephrine nasal spray could have an enormous and positive impact on the 32 million Americans living with food allergies, and their families.

MR. Z. DAY: My name is Zachary Day, and I am 13 years old. As an infant, I was diagnosed with several severe food allergies and continue to have life-threatening food allergies to dairy, eggs, mustard, fish, and tropical food. When I was just 3 years old, I accidentally ingested dairy and had my first anaphylactic reaction. Almost instantly, my stomach began to hurt, followed by my face and eyes swelling up. And finally, I struggled to breathe. Luckily, epinephrine was promptly administered, and I recovered.

I wish I could say this only happened that once, but I can't. I've had multiple anaphylactic reactions, each one landing me in the emergency room, not knowing whether I would live or die, and paralyzing me with overwhelming fear and anxiety. However, if you ask me, when I was younger, what

was the worst part of the anaphylactic reaction, I would have told you the injection. I was feeling horrible and sick already, and could not understand why a mother would inflict more pain on me by jabbing a needle into my leg.

Of course with age, I've come to understand the importance of this life-saving medicine and try to act brave when I have to. My younger brother, though, is only 7 years old, and when he had an anaphylactic reaction a few months ago, he screamed and had to be held down in order for my mother to administer the epinephrine injection. I tried to help, but the fear of the needle overpowered him. No matter what I said, he was scared and could not calm down. A simpler, less painful method of administering this life-saving medication will go a long way. Using epinephrine can be scary, but not using it is way scarier.

As you can see, managing life with food allergies truly affects more than just what you put in your mouth. An emergency plan always needs to be in place, and one that takes a lower traumatic

toll on those with food allergies would be a game changer. Additionally, administering an emergency injection can be quite intimidating to most of us that don't have medical training. I can just imagine how much less stressful giving a nasal spray to one of my children would be versus holding them down and injecting them.

Please consider my family and our story as you decide on approving nasal epinephrine. We need more options for addressing anaphylactic reactions that do not add to the already huge burden allergic individuals and their families face on a daily basis. Thank you for your time and consideration.

DR. AU: Thank you very much.

Speaker number 20, please unmute and turn on your webcam. Will speaker number 20 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have three minutes. Thank you.

DR. WALLACE: Good afternoon. I am Dr. Dana Wallace, and I have served on the advisory board for ARS and Brian companies who have developed

intranasal epinephrine devices. As a community-based allergist for over 40 years, I have diagnosed and treated thousands of patients who have had or are at risk for anaphylaxis, and I can assure you that this is the diagnosis that drives fear into the hearts of both patients and physicians.

As past president of the American College of Allergy, Asthma, and Immunology, I have both planned and delivered anaphylaxis educational programs for allergists, primary care physicians, and patients. As a member and co-chair of the Joint Task Force on Practice Parameters for over 15 years, I have authored three anaphylaxis guidelines, the most recent of which will be published this year.

These guidelines provide an update on risk factors, triggers, prevention, and diagnosis of anaphylaxis, but the use of epinephrine as first-line treatment has not changed. We have consistently identified the major gap in anaphylaxis management as the failure to properly

administer epinephrine at the onset of a serious allergic reaction.

For most people, anaphylaxis is an infrequent event, occurring when they least expect it. It is impossible to always avoid the trigger even if you know what it is. Most of all, patients have been advised to carry their epinephrine autoinjector wherever they go, to use it at the start of a serious allergic reaction, and not to rely upon antihistamines. We know the delayed administration of epinephrine is associated with severe anaphylaxis, prolonged ED visits, and an increase in biphasic reactions, hospitalizations, and mortality.

Let's imagine a teenage girl anaphylaxis free for two years. She's going to a party with a friend. She's carrying a small bag into which her autoinjector just does not fit and not wanting her friends to know about her peanut allergy. She isn't even sure if she remembers how to use the autoinjector, and besides she hates shots. Yes, it is likely that she'll drop a Benadryl in her purse

and leave for the party, knowing that she is taking a risk. Consider if an alternative intranasal epinephrine delivery device such as neffy were available. Our teenager could drop neffy into her purse -- it's small -- she knows how to use it, and her friends will not ask questions, even if they see it.

Studies have shown that 82 percent of patients prefer using intranasal epinephrine over and autoinjector. I have had the privilege of reviewing the efficacy and safety data on neffy, and feel very confident that this new product will provide a first-line treatment option for anaphylaxis that is equivalent to an epinephrine autoinjector, and more importantly, it will be more effective because it's more likely to be carried and used at the onset of anaphylaxis. Thank you for your attention.

DR. AU: Thank you very much.

We have one more speaker. Speaker number 21, please unmute and turn on your webcam. Will speaker 21 begin and introduce yourself?

Please state your name and any organization you are representing, for the record. Thank you.

DR. GUPTA: Sure. Yes. I'm so sorry. I had an emergency, and I'm driving, but I hope you can hear me okay. My name is Ruchi Gupta. I am a pediatrician. I have studied food allergies for the past 18 years, and I am a mother of a child with food allergies. I have no financial association with ARS.

I guess if I'm last, I feel like everyone has said what I was going to say, but I would love to summarize it. I can tell you when I started in this field 18 years ago, we didn't have prevalence numbers, and part of what our lab does is study the public health food allergies. We know now that 1 in 13 kids have food allergies and 1 in 10 adults. We know and you've heard the data around carrying is poor.

Number one, all the barriers you've heard today, there is needle fear and a pretty significant population. It's difficult for a layperson, even a trained person, to always feel

comfortable using an autoinjector; then you just heard how difficult it is, especially when you become a teenager or young adult, to always carry it in your pocket. It's not easy, and many, many people forget it. Even in our lab, we've had students, many who have food allergies, and we are so careful. But two have had accidental ingestion, and they know the importance of it, and they had both forgotten it, and we had to rush them to the emergency room.

Number two, I just want to point out what everyone has, that innovation is so critical, and we need choices of administration. When I entered this area of food allergies, we only had one choice. We're fortunate now to have multiple options for autoinjectors, but the next phase is so important and a game changer, as you've heard, to have different administration options, and then let people choose and decide what is more comfortable to them.

Finally, I just want to say that my real dream is for my patients, my own child, and all the

amazing parents who are here speaking to you, all their children, and then to all the adults out there, and so many young adults in college and working, whether or not with many precautions, for all of them to have options for administration, ease of carrying so that when they need epinephrine, it is there for them, and they can use it right away, and decrease morbidity, and feel safe. So with that, I'll end, but strongly encourage the approval of this device and many others to come to help all our population of 32 million with food allergies.

Clarifying Questions to the FDA

DR. AU: Thank you very much.

I believe this concludes the open public hearing session. I want to thank all the presenters and speakers who are contributing to this discussion.

I think what we're going to do now is pivot back to take clarifying questions for the FDA presenters. For the committee, please use your raise-hand icon to indicate that you have a

question, and remember to lower your hand by clicking the raise-hand icon after you've asked your question. When acknowledged, please remember to state your name, for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and then end your follow-up question with, "That is all my questions," so that we can move on to the next panel member.

Let me take a look for raised hands. Sorry. Give me one second here. I see a number of raised hands.

Dr. May, can we start with you, please?

DR. MAY: Yes. Susanne May, University of Washington. I have a question regarding slide 104 probably for Dr. Lan.

In slide 104, that was the three graphs, and it indicated the concentration levels were lower

within the first 10 minutes for neffy. So I'm wondering, given the chance that this might be administered earlier rather than for an EpiPen, would that alleviate the concerns with regard to that in the first 10 minutes, the concentration was lower?

DR. PATERNITI: This is Miya Paterniti from FDA. We're working on pulling up that slide, but in the meantime, I wanted to give you a response to your question, which I think was, do we think that potential earlier administration of ARS-1 would potentially alleviate our concerns for the lower concentration within the first 10 minutes that was seen in EPI 15.

DR. MAY: Yes.

DR. PATERNITI: At this point, we would say that the early administration of a nasal epinephrine spray is really hypothetical. We don't know if patients really would use it. We think that it's possible, but we really are interested in the committee's opinion on the data at hand, given that this is what we know about epinephrine nasal

spray compared to epinephrine injection products, and we are very interested in your opinion. If you want to consider potential early administration in your deliberations, that would be for your consideration, but we do emphasize that that is hypothetical. Thank you.

DR. MAY: Another question that I had was are there any concerns -- I was thinking what can go wrong -- that children might put this in their mouth rather than their nose with regard to safety, et cetera, or if friends, they're unlikely to take a needle to themselves, but they might play around with it and use it when they don't need it. Are they any safety concerns regarding either of those?

DR. PATERNITI: This is Miya Paterniti, FDA. We have not looked at that specifically. The studies that were conducted to look at the use of the device are based on the instructions that are provided, and I can turn it over to our Office of Surveillance and Epidemiology colleagues to see if they have any further comments on if that was assessed within the validation studies.

Just give us a moment because he's going to come up to the podium, and this is Mr. Barlow.

DR. MAY: That was my last question, so after this answer, that would be it for me.

MR. BARLOW: Good afternoon. This is Matthew Barlow, human factors expert and safety evaluator with the Division of Medication Error Prevention and Analysis. In further report and validation studies conducted by the applicant, we did not note any wrong route of administration or use issues related to that medication error in this study by any of the participants. Thank you.

DR. MAY: Thank you. That was it.

DR. AU: Thank you.

Dr. Kelso?

DR. KELSO: Yes. Although we often say that the plural of anecdote is not data, it turns out that the --

DR. AU: Would you mind introducing yourself, for the record? I'm sorry.

DR. KELSO: Yes. John Kelso, allergy, Scripps Clinic, San Diego. We often say that the

plural of anecdote is not data. It turns out the person who originally said that, said that the plural of anecdote is data. But in any case, do we have any real-world data -- I did hear the one public commenter talk about compassionate use, but do we have any other data from any source of patients actually using this product for an actual anaphylactic episode and what the response was?

DR. PATERNITI: This is Miya Paterniti, FDA. At this point, the only real-world use we are aware of is the patient that you heard about today, so we will defer that response to the applicant to see if they have any additional comments.

MR. LOWENTHAL: Yes. I'm sorry. This is Richard Lowenthal; not in anaphylaxis because, again, we've been careful about doing more compassionate use, although that may be an option, but we do have, as I said, controlled clinical trials in urticaria, which we believe is representative. They're placebo controlled, and they show a very rapid response.

Dr. Bernstein is here. He can even speak to

you; that he's one of the major investigators in this study, so we could put that up if you want it.

DR. BERNSTEIN: Hi. My name is Dr. David Bernstein. I'm emeritus professor of medicine, University -- College of Medicine. I've been a practicing allergist and clinical researcher for over 40 years, and we've been one of the sites that have been involved with this study of urticaria or patients with severe urticaria, dosed with neffy or epi.

As you can see from the preliminary data shown on this slide, we can see that after dosing and over time, we see, really, I think very good responses in terms of the reduction in itch severity. We see reduction in pain associated with urticaria in patients with severe urticaria, and we see that there's reduction from baseline in the erythema and the investigator's assessment of the extent of urticaria.

Actually anecdotally, I can say in our practice -- this was a single blind study -- we did see it, and of all our patients who were treated,

there was a rapid decline in urticaria that we could see within the first 10 minutes. So the patients were impressed, our coordinators were impressed, and I was impressed. I think this adds on some additional clinical information that one could extrapolate and say that urticaria is one of the important signs that we see in systemic allergic reactions or anaphylaxis, and this at least provides some additional reassurance that the drug is being absorbed and is systemically available enough to result in reduction of urticaria at least in this study. Thank you.

DR. KELSO: Okay. Yes, thank you.

The only other thing is about the packaging. We see this picture of the device here, and we saw the little zip thing that it comes in. I believe the Narcan version of this is in some sort of a enclosed container that you have to peel open to get the device out. Is that the case with this or what sort of packaging does it come in?

MR. LOWENTHAL: Yes. When you first buy it, it is in a blister similar to Narcan, but it's just

because that's pharmaceutically necessary in packaging in the pharmaceutical plant. The stability of neffy and the device itself has been tested as the device without any packaging. The stability is always done with the device itself.

This has been filed to FDA as a secondary packaging, which we would supply at no cost with the prescription so that people could take them out of the blister and carry them more easily. We're very conscientious that if it's in the blister that comes from the production plant, people may not carry it as easily, so this has been sent to FDA for review as a promotional piece, essentially. But it would come in a box with all the labeling and everything; no sprayers, but it would come separately, and we would just give that with each prescription to facilitate carrying.

DR. KELSO: I guess my concern would be the other direction, where somebody rather than taking it out of the blister pack and putting it in this carrying case, would just throw one of them in their pocket as an even easier way to carry it

around, and the chance of it accidentally being dispensed in their pocket.

MR. LOWENTHAL: Yes. That is very, very unlikely that they accidentally dispense. I actually carry one in my pocket all the time and never had one go off, and we know from Narcan and other things, that's done all the time. We can't promote that, and we don't want to promote that. We want to give them a safe carrying case, but it's done all the time with other products with the sprayer.

The sprayer, this doesn't activate that easy. It's easy enough if you push it, but you have to push it with some firm force. I know it would in newtons, but I can't translate that easily, but it's 20 to 25 newtons of force, so it's not going to fire in your pocket easily, and it's pretty sturdy. This is a tough little device.

DR. KELSO: Okay.

MR. LOWENTHAL: We still suggest you put it in the package we're going to provide, but nonetheless, people might put in their pocket. We

don't deny that.

DR. KELSO: Okay. And that's all it requires, is pushing. There's no cap, or twisting, or you just push.

MR. LOWENTHAL: No. There's nothing to activate this. There's nothing to take off the cap. It's your nose, so even if this is a little lengthy, it's fine, and you just fire it like that. That's it, just like Narcan.

DR. KELSO: Okay. Alright. Thank you.

MR. LOWENTHAL: And it's been exceptionally effective with Narcan, and you know that with treating people.

DR. KELSO: Great. Thank you.

DR. AU: FDA?

DR. PATERNITI: Hello. This is Miya Paterniti, FDA. I just want to circle back, Dr. Kelso, on a few responses provided by the sponsor. FDA has not reviewed the urticaria study, so just to keep that in mind. Also, I wanted to comment about the carrying case that has been shown in the slides this morning and also was just shown

again. FDA has not reviewed that carrying case. The human factors studies did include the device within the blister pack. So I just wanted to clarify that the carrying case has not been reviewed. Thank you.

DR. AU: Can I ask just in follow-up, do we have an image for the device in the blister pack?

MR. LOWENTHAL: Yes. Hold on. We can get one. But again, we did file this for review, the packaging. It hasn't been approved yet, but we have filed it to FDA.

(Showing packaging)

MR. LOWENTHAL: This is the blister pack. It's hard to see, but it has the instructions on the back of the blister, what we call the Quick Reference Guide, and it's essentially the exact same package that Narcan comes in because it's coming from the exact same production line and production plan. This is made at the same place as Narcan nasal spray, so it's the exact same package as Narcan nasal spray.

DR. AU: Thank you very much.

Dr. Troendle?

DR. TROENDLE: Hello. This is James Troendle from the National Institutes of Health. My question is about the bracketing strategy. You mentioned that there was a bracketing strategy, and you didn't actually explain what exactly that means, in particular about the timing of what that means. As you may recall, I asked the applicant, and they interpreted it to be the area under the curve from 0 to 20 minutes and 0 to 45 minutes, so I'm referring to the normal subject peak pharmacokinetic data from EPI 15.

DR. PATERNITI: Thank you for that question. This is Miya Paterniti from the FDA, so you're asking about the EPI 15 data for the bracketing, to provide further details. We can do so. I'm going to call on Dr. Yunzhao Ren from the clinical pharmacology team to provide a response.

DR. REN: I would like to show slide 137. Meanwhile, let me explain a few thoughts about this PK bracketing. It's quite a journey to collaborate with ARS with their intranasal product. There are

a lot of surprises during their program, and the thinking is evolving all the time.

This bracketing strategy, two injectable products was not the initial thought at the very beginning because at the very beginning, we think, okay, there are two dosing levels approved, 0.3 and 0.5, and maybe bracketing by two dosing levels may be unreasonable.

We also considered, because subQ and intramuscular PK are different, maybe bracketing by intramuscular and subQ could be a path, but eventually we landed on this idea because the intramuscular injection is the most popular injection and administration path. And we noted significant PK variabilities between different injectable products by different brand names, so we eventually landed up on this.

The prior NDA meeting that we had with ARS back more than two years ago, it was a non-canonical pre-NDA meeting because usually at the pre-NDA meeting, the applicant already completed their dedicated or necessary studies, and

just discussed the potential submission. But two years ago, none of these 15, 16, and 17 studies, the results have been available. Actually, it was a discussion how to carry their product forward, the program forward, and does FDA agree with the 15 study design, 16 study design, and 17 study design.

At that time, with very limited data, we were impressed by the Adrenalin PK variabilities because from some early studies, we do see that in some studies, the Adrenalin PK shows a considerably higher second peak. So that's why the ARS asked which AUC FDA would like to focus on, and we just said you should explore all of them. We didn't say no to early, which is that you should also explore the later time points as well.

As you can see, this is the bioequivalence assessment, the traditional BE evaluation regarding the PK results from EPI 15. As you can see, the AUC 0 to 10, it's not bracketed by the traditional 80 percent, 125 percent of the 90 percent confidence interval of the geometric mean ratio.

So as I said, the comparisons of PK profile

and the parameters, it's always a totality, and at the pre-NDA meeting we haven't seen any data yet.

DR. TROENDLE: You're saying from this table -- it's not so clear what you just said. Can you explain that, the area under the curve --

DR REN: Oh, okay.

DR. TROENDLE: -- from 0 to 10.

DR. REN: Yes. You're talking about bracketing. As you may notice, we have two columns. The right column is compared to ARS 1 to 2 milligrams to that of EpiPen. As you can see, the values are consistently lower.

Oh, okay. You can say it's bracketed per boundary, but then you look at lower boundary. Adrenalin is considered lower boundary, and if you applied the FDA traditional BE analysis, which we define, the bioequivalence is established if the 90 percent confidence interval is within 80 percent and 125 percent. But clearly, you can see 0 to 10, it's outside of the boundary. It's lower than the boundary

DR. TROENDLE: Okay.

DR. REN: We acknowledge that these are totality. Everything is based on totality.

DR. TROENDLE: Okay. Thank you very much higher. That's all I have.

DR. AU: Thank you so much.

Dr. Le?

(No response.)

DR. AU: I'm sorry for mispronouncing your name.

DR. LE: Yes. Hi. This is for the FDA. For the pharmacodynamic --

DR. AU: Sorry. Could you introduce yourself?

DR. LE: Sorry. Jennifer Le from UC San Diego, clinical pharmacy, pediatric infectious diseases.

So for the pharmacodynamic target of 100 that was selected, picogram per mL, what is the clinical implication of this target? Was it in relation to resolution of hypotension, hypoxia, or rash? Because that could be very helpful to infer potential clinical efficacy for serious Type I

reactions.

DR. PATERNITI: This is Miya Paterniti from FDA. Again, as we elaborated in the briefing document, those thresholds were based on continuous IV data from healthy volunteers, but I will turn this to Qianni Wu, who is going to provide additional background detail. Thank you.

DR. WU: Hi. This is Qianni Wu. I'm the clinical pharmacology reviewer from FDA. Can I please call slide 139?

Just like in my presentation, I specified the 100 and 200 picograms per mL was arbitrarily selected based on the published literature for healthy adults following continuous IV infusion with fixed rates. I believe this literature was also cited by the applicant in their presentation.

This publication demonstrated noticeable vital sign changes occurred at around 100 and 200 picograms per mL, based on the IV infusion data in healthy adults. We do not know the clinical meaning of those values in anaphylaxis patients, using either intramuscular or intranasal products.

The reason we select this arbitrarily selected threshold is to assist our PK profile comparison. Given that there's a high PK variability we noted, we just want to do some proportional analysis to see if there's any unbalanced number of subjects who had different numbers of subjects with low PK at various time points. So this is just to assist our PK profile comparisons, and there's no clinical meaning. I hope I answered your question.

DR. LE: Yes, you did. The study was published in 1980, and given that epinephrine has been on the mark for a while, I thought there would be some clinical linkage. For the non-serious infections, I'm less worried about, but I'm just trying to wrap my head around more of the serious anaphylaxis without any clinical data that we have for this. Thank you, though. That's all I have.

DR. AU: Thank you, Dr. Le.

Dr. Jones? They also ask you to announce yourself, for the record, please. Thank you.

DR. JONES: This is Dr. Bridgette Jones. I think my question is for the FDA or the sponsor, or

both. It was mentioned, I believe, in the FDA's presentation that there was one participant, I believe, in the pediatric studies who had non-detectable PK levels for the drug.

Can you comment at all on this in regards to demographic characteristics of the participant or were there any extenuating circumstances that could have led to the undetectable levels?

MR. LOWENTHAL: Yes. This is Richard Lowenthal, ARS. The samples were mishandled and destroyed at the site, so the acid was not added. To stabilize epinephrine in the PK sample, you have to add acid or large amounts of metabisulfite, and it was not done, and they were exposed to extreme heat. It was in Tampa, so that was the problem. The samples were destroyed, basically, and that was the problem.

DR. JONES: Thank you.

Then I have one other question about the patient instructions for use. I don't see where it's covered in regards to if an additional dose is needed. If a second dose is needed, what are those

recommendations as far as giving the medication in the same nostril or the other nostril?

MR. LOWENTHAL: Based on the data that you've seen from EPI 15 -- and we have not discussed this with FDA yet because we haven't got to labeling discussions until after this ADCOM. So if there's a recommendation to approve, we'll have those discussions. But based on the EPI 15 study, as you saw, there's no difference between spraying twice in one nose or once in each nose, so we prefer not to specify.

We believe that patients will do what's the most comfortable. If your dominant hand is right, you tend to go to the right nose, and to cross over to the other nose could lead to more dosing errors, so we would prefer that people do what's comfortable and not confuse them, and provide more detail that could just confuse them by saying opposite nose. And given the PK profile was not that different between those two approaches, we felt it was better just to not specify either way.

DR. JONES: Okay. Thank you.

DR. AU: Thank you so much.

Dr. Dowling, I feel like you've been waiting for hours now. Dr. Dowling, please introduce yourself.

DR. DOWLING: Thank you. Tom Dowling, pharmaceutical sciences, Ferris State University. My question relates to the Cmax values and the bracketing process that's been proposed here. I wonder if we could pull up slide CO-30 from the applicant, and it shows a PK profile; yes, that's it.

Our discussion about bracketing, I think Mr. Lowenthal made a comment about the upper bracket being 350 picograms per mL and the lower bracket, it looks like about 190. I wonder if we could clarify that. I don't know if I fully understand maybe the communications between FDA and the applicant on what the brackets mean and what does this bracket really refer to. Thank you very much.

MR. LOWENTHAL: Yes. This figure is just referring to the Cmax, so the Cmax of EpiPen is

much higher, and Tmax is also faster. Then the lower bracket is the Cmax of IM. FDA also notes in their meeting package that subQ is an approved effective therapy, and that they would consider also, but it was not considered in any of the reviews. We have dose subQ early in our program, and that's the black line, roughly the same as IM. But that was the definition of the bracket originally. And this is just the peak of the mean curve, by the way, not the Cmax because Cmax is calculated differently. But this is just looking at the curves and the peak of the curve, just to clarify.

DR. DOWLING: I wondered if maybe the FDA could comment on that. Obviously, Cmaxes are taken from the PK plot.

MR. LOWENTHAL: No, no. The Cmax is calculated from the mean of the individual Cmaxes. The PK figures, PK figures are misleading compared to data. Figures are the mean at each time point for all the subjects, but Cmax is calculated as the mean of the Cmaxes, so it's a different number.

You won't get the same number.

DR. DOWLING: Thank you. And I wondered if maybe the FDA could comment on whether these brackets were taken into consideration with the bracket review and whether they met the criteria for the bracketing in terms of a decision making from the FDA. Thank you.

DR. PATERNITI: This is Miya Paterniti from FDA. I'm going to turn to our clinical pharmacology team to provide a response.

DR. REN: Hi. This is Yunzhao Ren again. When we walked through the ARS-1 program with ARS at the IND stage, especially before the pre-NDA meeting, we realized that it's almost impossible for ARS-1 to match every concentration at every time point because as everyone sees, the EpiPen just delivers the drug faster and higher. Therefore, since FDA raised the bracketing strategy all the time during the drug development, what will be the lower boundary and what will be the ideal scenario to bracket the ARS-1 PK?

Here, we acknowledge that the study will not

be able to power enough to have bracket concentrations at every time point or bracket every partial AUC at every time point. That's impossible; therefore, I can only give you an ideal case. Ideally, we are looking for the PK profile and the time concentration profile is reasonably bracketed between Adrenalin and EpiPen, all the way to 60 minutes. That's the ideal case. But of course, sometimes time could be a little bit off, and that's why we put the totality review on this issue.

DR. PATERNITI: This is Miya Paterniti again from FDA. I just want to add that one of our questions to the committee is about which parameters you think are critical. So your question relates to Cmax, but we also encourage you to think about the PK profile over time in the different parameters and how you may assess that in the benefit-risk. I just wanted to make that comment. Thank you.

DR. AU: Thank you. No follow-up, Dr. Dowling?

(No response.)

DR. AU: If not, let's go to Dr. Holquin.

DR. HOLQUIN: Yes. Thank you. Fernando Holquin, University of Colorado. My question is mostly a clarifying question to the FDA, which is really to understand what is the rationale of putting so much emphasis on the PK data within the first 10 minutes when, in fact, we don't really know whether these data by themselves really relate to any clinical efficacy of epinephrine? Thank you.

DR. PATERNITI: This is Miya Paterniti, FDA. Thank you for your question. At this time, this is the data that we have. We absolutely appreciate your point, that we don't have clinical efficacy trials to discuss today, so the data we're discussing is the data at hand, which is limited at this time to PK/PD data. The differences for Adrenalin compared to ARS-1 in the first 10 minutes is something that we're interested in hearing the committee's opinion on, but we're also interested in hearing the committee's input on the rapid

decrease in the nasal allergen challenge study and what that might mean for interpreting what this could do in a clinical efficacy perspective.

So this is a really great question, and we're limited to discuss the data we have at hand, but whether you think clinical efficacy studies would be required to support the efficacy for ARS-1 is something we're very interested in hearing from the committee. Thank you.

DR. HOLQUIN: So we could safely say that those boundaries are set rather arbitrarily, given the limitation of the data at hand.

DR. PATERNITI: Yes, we would agree.

DR. HOLQUIN: Thank you. No further questions.

DR. AU: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Hi. Mark Dykewicz, St. Louis University. In reviewing the PK results of the ARS versus the IM adrenaline, the point has been raised that there's been high inter-subject variability with the administration of IM adrenaline, a

confounded comparison. There is literature that suggested that for patients with higher BMI and more adipose tissue, the needle used for attempted IM injection may not be sufficient to accomplish good IM delivery. Needle length of course would not be an issue with intranasal administration.

So my question to either the agency or the sponsor is that in the pivotal studies, were patients excluded from the study who had higher BMIs, and if not, was there any assessment made or analysis made of possible relationship between BMI and the PK IM pharmacokinetics?

MR. LOWENTHAL: I can answer that question. It's Richard Lowenthal, ARS Pharmaceuticals. Because these are clinical pharmacology studies -- and we're well aware of the issue with BMI; it's in some of the published studies we put up from EpiPen, especially where there are fairly dramatic differences with EpiPen PK based on BMI. But in our studies, because they're clinical pharmacology studies, we actually limit the BMI so we will not take obese people into a PK study.

Now with that said, neffy nasal administration is not impacted by BMI, where IM injection is. So we actually bias the study against us in a way if you take a real population across all people, and we could put up the data from our PopPK. With neffy -- this is with neffy -- there's actually no effect of BMI on the pharmacokinetics with intranasal, which you can imagine there's not much rationale for that, but in our studies, we actually limit the BMI, which does favor the IM injection because then you have less issue with the possible subcutaneous injection.

It's also why in our slide with all the studies kind of mimicking the same thing -- FDA did over the first 20 minutes -- we included the data we have on subQ injection, which is always lower than neffy and always lower than IM; subQ injection in the first 20 minutes is quite slow, but it's quite effective.

We actually have Dr. Spergel here from CHOP who uses subQ all the time in the clinic and finds it very, very effective, if you want to hear him

give any comment on that. But that's subQ at the bottom in the black, and obviously subQ is always below neffy or IM, especially in that first 10 minutes, and very similar to some of the IMs after that.

The only other comment I'll make on this is that the FDA briefing book does say subQ is an approved route of administration because sometimes autoinjectors can be subQ, and it is approved in the clinic use, so they use a subQ, and that they would consider going forward, but then there was no consideration of the subQ data.

DR. DYKEWICZ: Thank you.

DR. AU: Dr. Nelson?

DR. M. NELSON: Thank you. Michael Nelson, University of Virginia.

As a committee, we are asked to address whether data presented provides confidence that the benefits outweigh the risks for both safety and efficacy, and for all indicated populations. Accordingly, I strongly believe we should attempt to identify any subpopulations that may be at risk,

either from a safety or efficacy standpoint, with the life-threatening consequences of anaphylaxis. So I have two questions that both the sponsor and FDA may want to weigh in on.

For question number 1, we can either pull up the FDA slide 105 or the sponsor briefing slide 49. So thus question number one on the safety side, second dose proportionality and higher plasma concentrations have been highlighted as both a benefit and a concern by both parties.

Is there data, animal or human PK data, that would provide some reassurance for use in patients at higher risk from epinephrine exposure, such as those with comorbidities, including coronary artery disease. I'm sure in the moment, the benefits of use will outweigh the risk, but it would be reassuring at this point in the approval process if there's such reassuring data in hand.

DR. PATERNITI: This is Miya Paterniti from FDA. I don't know if the applicant wants to start by responding.

DR. CASALE: Sure. This is Tom Casale.

Thanks for the question, Mike. I think, as you pointed out, we don't think that there's a big risk in using epinephrine because of the catastrophic effects of anaphylaxis and the reason for using it, but you would expect that people that are older, like myself, might have coronary artery disease. I hope not, but I think it's reasonable to assume that these levels that are achieved have not provided any adverse consequences in the patients that were studied.

What were the oldest patients that we had in the studies? Yes, they were up to 55 years of age, so I'm pretty confident that the risk-benefit ratio would still favor using this no matter what the age of the patient, but we don't have the data.

DR. M. NELSON: Yes. I think the interesting piece of this particular slide is the proportionality piece, with the second dose being much higher than we see with the injectable second dose. So is this the cap? I know it's outside of the scope of today's conversation, but you can envision that multiple doses beyond two might

occur. Does that proportionality increase? Did you see that in your dog models, for example?

DR. CASALE: It's never been studied --

DR. M. NELSON: Understood.

DR. CASALE: -- the doses. And then the other issue would be, in the patients that have severe anaphylaxis that don't respond, IV epinephrine is sometimes used to treat patients without any significant adverse consequences.

DR. M. NELSON: Great.

Does FDA have a comment or do you want me to go to question two?

DR. PATERNITI: Yes. This is Miya Paterniti from FDA. I just want to state that, at this point, one of the limitations is that the safety data that we have is based only on the studies that were conducted, which if you were to compare it to large clinical efficacy trials, is limited. These were patients who did not have risk factors for cardiovascular comorbidities, and those were excluded from the trial. So the data is just limited, but we do think that the concern about

safety is something we'd be interested in hearing the committee discuss today. Thank you.

MR. LOWENTHAL: Yes. We'd just like to add one more point. We've provided this analysis in our NDA also, but this is an analysis of what's called the a ceiling effect with epinephrine, and this is published in other publications as well.

Epinephrine, as it goes up in concentration, does reach a ceiling effect where blood pressure does not go up more, and this is also true for heart rate, where it levels off, and your body has compensatory mechanisms to prevent blood pressure from going too high.

The only time that you go through this ceiling appears to be when you have an IV bolus injection. That's known in the literature. We have also seen it in our clinical trials, where we've had Epipens inject. In fact, this is one case that was published. It's a published case that was published back in 2022 by Ebisawa, the current president of the World Allergy Organization. This was in his study in Japan, and

this is an IV bolus injection with EpiPen that occurred in one of our studies, and you can see the red line is the pharmacokinetic data, and it went very high, almost to a theoretical maximum blood level if you gave an IV bolus, if we calculate it. You could see the blood pressure change, which we only measured at 4 minutes. It may have been higher before that, but it was a 104-millimeter increase in blood pressure, millimeter mercury and systolic blood pressure. This is not possible, obviously, with neffy, but this has been observed in some of our clinical trials with autoinjectors.

DR. M. NELSON: Very helpful. That was the ceiling or plateau effect, that reassuring data I was looking for.

Switching gears quickly, this question's a lot briefer I think. Acknowledging enhanced single-dose PK and PD results for EPI 16 and 17 in the dog models for the allergen challenge and anaphylaxis, respectively, does the sponsor or FDA have any comments or experience with other intranasal product approvals that might shed light

on the predicted PK/PD and efficacy in patients who are on chronic intranasal treatment such as nasal steroids and antihistamines, very common in the allergic population?

MR. LOWENTHAL: This is Richard Lowenthal. We can only speak to acute products of FDA and if they they have evidence from chronic use products that they've experienced. But at least with the other emergency medicine products, I've been involved and I'm aware of single-dose types of emergency use, including migraine medications.

Nobody has ever been asked to do as many studies as we have. Nobody has ever done congestion, so we don't know what happens with Narcan or any other product when people are congested. And again, it's not just congestion. FDA keeps talking about congestion, but we're very clear there are two things going on here, congestion, which accelerates absorption, and if you run this study without the rhinorrhea, if you run a study and the only induced congestion without running nose, you'll probably get higher

absorption, more rapid and high absorption like we saw in the dogs. The fact that we get lower absorption is probably more related to the runny nose and the drug draining out of the nose more quickly.

Resonance time of your ciliary movement, as you know, is 20 to 30 minutes to clear your nose. That's why the Tmax of nasal sprays is always around 20 minutes to 30 minutes. And when you have rhinorrhea you're going to get more rapid drainage. So that's the cause of this. We did not allow the people to blow their nose. We really ran this as a worst-case scenario to find out what's the worst thing that could possibly happen, and we content that it will probably be exceptionally rate that that would ever happen, but nonetheless, the blood levels were effective levels and, again, we believe the systolic blood pressure shows that the data is sustainable and durable, and lasts as long as IM injection.

DR. M. NELSON: Thank you.

DR. PATERNITI: This is Miya Paterniti, FDA.

I have my clinical pharmacology colleague, Dr. Ren, who would like to provide additional feedback. Thank you.

DR. REN: Hi. This is Yunzhao Ren again. That's a very interesting question. We acknowledge the nasal condition could be different under, let's say, anaphylaxis -- it's more like edema -- or under the nasal allergen challenge, including both edema and nasal congestion. The applicant also conducted a common cold study, which the inflammation conditions are suspected to be different. As you can see, all these conditions are subtly different.

From the FDA's perspective, we saw this a lot, and the closest pathologic condition we can think of to mimic the nasal edema condition under an anaphylaxis attack is probably the nasal allergen challenge study. Interestingly, the applicant raised the rhinorrhea effect on PK, and we actually have some subgroup analyses.

Please go to slide 166, and Dr. Wu will explain in detail.

DR. WU: Hi. This is Qianni Wu from FDA. We're aware that EPI 16 has this question to assess multiple nasal conditions, including not only congestion but also rhinorrhea, itchiness, and such and such. There are four elements into it. One of the elements is rhinorrhea, so we did a subgroup analysis to see how rhinorrhea could impact PK because just like the applicant is thinking, we might think rhinorrhea may affect the nasal clearance of the drug. So we did an exploratory subgroup analysis by grouping the subjects with no post- rhinorrhea versus people with post-dose rhinorrhea. The post dose is after those patients received ARS-1 treatment.

Among these 7 patients who did not have any post-dose rhinorrhea symptoms, as you can see, their PK curve is similar or even slightly lower than those patients who were still experiencing post-dose rhinorrhea. Again, this is a subgroup analyses with a limited sample size, but this shows that the impact with rhinorrhea might be small on the PK in this case. Thank you.

MR. LOWENTHAL: But that is post-dose, so is there a predose? The predose rhinorrhea is the issue when you dose the drug. Post-dose, I'm not sure I understand how that would impact or what that would mean. Predose before you dose the drug, if you have a runny nose, I can understand the impact, but I'm not sure I understand the impact of if the rhinorrhea resolves because 73 percent of the people when they dose, the rhinorrhea resolves because the first dose -- epinephrine cures rhinorrhea and congestion.

So you presented the opposite way; 27 percent of the people didn't resolve, but 73 percent did resolve after post-dose. But predose rhinorrhea is what we're looking at because predose congestion and predose rhinorrhea is what impacts absorption.

Just one more comment, it's one of the reasons also we believe the dog model is very informative because they have also congestion. They get edema of the face just like humans, in the nose, and we believe that's very informative of

what happens with just congestion. Based on the totality of the studies we've done -- which FDA knows we've done a lot more studies with pollen-induced rhinorrhea and other rhinorrhea studies, but based on the totality of data, we know the congestion alone is probably going to accelerate and increase absorption. It's the rhinorrhea we believe that is really causing the more rapid clearance. And that makes more sense than saying congestion causes rapid clearance because congestion makes the membrane more permeable.

So we think it's a little bit more complex than that. And again, it depends on how you run this study, because if you ran this NAC study and let people recover and blow their nose, it would be a totally different outcome than if you run the study and dose right away when they haven't been able to blow their nose and clear the rhinorrhea out of their nose. We ran it as a worst-case scenario, so we believe it's really the worst thing you can see.

DR. M. NELSON: Thank you both.

DR. PATERNITI: This is Miya Paterniti, FDA. Sorry. I just wanted to comment that this is the analysis that we thought was most clinically relevant, but we'll leave it to the committee to discern. Thank you.

DR. M. NELSON: Thank you both for highlighting these complexities. In the interest of time, Dr. Au, I yield to my colleagues. Thank you.

DR. AU: Thank you so much.

I've been asked to remind participants not to speak unless called on by the chair, please, just to try to keep a little bit of order.

We're going to try to truncate this discussion at 35 after, which does not leave us a lot of time. I would like to recognize a couple of people we've not heard from today. I'd also like to see whether or not there are any points of discussion that are not directly related to emphasis around or discussion around the PK levels in particular. I feel like we've heard a fair

amount about that.

So acknowledging the time limitations and the like, I'm going to call Dr. Bacharier. I'm sorry if I mispronounced your name.

DR. BACHARIER: Thanks. Leonard Bacharier, Vanderbilt in Nashville. I apologize if this feels like we're going back to the PK, but it's a different perspective than I think we've touched on, which is the use of adrenaline that would effectively provide the lower bracket for nearly every assessment that has been made. And I was struck by how different it really is than the clinically, widely used EpiPen.

Part of the concern is that they're using very different clinical situations. The EpiPen is used in the field by parents, children, individuals, and epinephrine is given in, generally, a medically supervised setting. So maybe we tolerate a little bit less from it because we know there's immediate medical assistance, but using that as the lower bracket, it makes me wonder if that's really the most appropriate lower

bracket; and had one of the other commercially available comparators been used, would this have all turned out differently? Does that really matter? I'd be interested in the FDA's thought on methodology and why and how that lower bracket agent or delivery approach was chosen, and what impact that might have. Thank you.

DR. PATERNITI: This is Miya Paterniti from FDA. I'm going to turn to Dr. Qianni Wu to provide a response to your question, Dr. Bacharier.

DR. WU: Hi. This is Qianni Wu again from clinical pharmacology, FDA. I'd like to call slide 141.

With regard to selection of Adrenalin at the lower boundary, based on the data we received about EPI 11b and Study EPI 15, EPI 11b was a dose-ranging study that compared ARS-1 with Symjepi, which is an approved prefilled syringe product used in a community setting, and Adrenalin is obviously in the medical setting. The two study results show that the comparison results are kind of similar when comparing ARS-1 to Adrenalin or

comparing ARS-1 to Symjepi.

Our other thoughts is whether Adrenalin is appropriate in this case also because I think it's mainly based on the study EPI 15 and EPI 11b with the Symjepi comparison results, and Adrenalin comparison results are similar. That's why we think at that point Adrenalin is an appropriate lower boundary for PK bracketing.

In this slide, I'll also present this overlay of ARS-1 PK profile among all the products, which includes Symjepi, Adrenalin, and EpiPen. As you can see, within the first 10 minutes, the PK profile of ARS-1 is bracketed by all Adrenalin, however, if you look at EpiPen and Symjepi, the first 10 minutes seems to be slightly lower for ARS-1 compared to either Symjepi or EPI 10.

At that time, we think it's still reasonable using Adrenalin given that Symjepi and EpiPen, they were also approved for another administering route just like the applicant mentioned, which is a subcutaneous route. The PK profile will mimic like Adrenalin those lower PK profiles you see in

Adrenalin. So in that sense, the subcutaneous route is also proven to be effective in use, so we think using Adrenalin as the lower boundary is a reasonable PK bracketing approach.

DR. BACHARIER: Great. Thank you so much. No further questions.

DR. AU: Thank you so much.

Dr. Butler?

DR. BUTLER: Yes. Thank you very much. I have a question to the sponsor. It's related to the comment made about the ceiling effect with epinephrine. Especially with regards to children, if there is a situation where there is an uninitiated person around, like a teacher or a relative who has not dealt with the condition, is the ease of use a potential problem that they may give multiple doses, which is unlikely with an injection, and do we have any animal or otherwise data of what happens to the levels if multiple doses greater than the intended doses are used?

MR. LOWENTHAL: [Inaudible].

DR. AU: Sorry. I can't hear the sponsor.

(Pause.)

DR. AU: Can anyone else hear the sponsor?

DR. BUTLER: No. I am also unable to hear.

(Pause.)

MR. LOWENTHAL: Can you hear now?

DR. BUTLER: Yes.

MR. LOWENTHAL: I apologize. We're having a little technical difficulty. I'll repeat the whole thing very quickly.

First of all, labeling is for two sprayers only just like EpiPen or other community-used products. If a third is needed, you're supposed to go from emergency help. So that's one thing.

Two, unlike a multi-dose sprayer, this is a single sprayer, single shot, only one shot. So to give two of these is probably the same as giving two injections because you would have to go and get the second one, intentionally put it up the nose, and fire it. So this was a multi-dose sprayer.

By the way, there is a multi-dose unit available, and we intentionally did not want to use it for that reason because if there were 2 sprays

in one device, it would be too easy to overdose. And FDA, from day one that we spoke to them, was very concerned about too much epinephrine, especially more than the EpiPen, being over EpiPen. So we didn't want to take any risks of exactly what you're talking about, and it's one of the reasons why we only use the single-dose sprayer like Narcan, although they've tried to use a multi-dose sprayer, and it doesn't work, but that's a different discussion. But the single-dose sprayer is the best option, we believe, for this particular indication, and that would prevent too much epinephrine as well. So we did take that into account very much.

DR. BUTLER: Thank you.

DR. AU: Thank you. I know I'm going to leave four of my colleagues, and myself makes five of us, hanging in terms of being able to ask questions, but I do feel like in the interest of the time, we should move on.

What I'm going to propose we do is move to the discussion section to receive our charge, and

then after we hear the charge, we have a scheduled break that I think we can take for five minutes. So why don't we go ahead, and we'll now proceed to the charge to the committee with Dr. Paterniti.

Thank you, Dr. Paterniti. Thank you, Dr. Paterniti. The committee will now turn its attention to the task at hand, the careful consideration of the data before the committee, as well as the public comment.

We will now proceed with the questions to the committee and panel discussion. I would like to remind the public observers that while this --

DR. STEVENSON: Hi, Dr. Au. I am so sorry to interrupt. If you want to go to the charge, could you please go to number 15?

DR. AU: Number 15. I apologize. I am sorry if I got this out of order.

DR. STEVENSON: No problem.

DR. AU: I'm looking at 15. It says we will now proceed to the charge of the committee from Dr. Paterniti.

DR. STEVENSON: Correct.

DR. AU: Yes. Okay.

DR. STEVENSON: And then you can stop, and we can proceed to Dr. Paterniti's presentation.

DR. AU: My apologies.

DR. STEVENSON: No problem. Thank you so much.

(Pause.)

DR. AU: I think this is a hint that we should take our break now, for five minutes.

(No response.)

DR. AU: Why don't we do this? Why don't we take a break for five minutes, come back at 3:45, and then we will receive the questions to the committee, if that's okay. It will give us a little time to reorganize a little bit. I know this has been a little bit out of order.

(No response.)

DR. AU: No dissent, I going to assume that's an affirmative.

Great. Thank you so much. I'll see everyone at 3:45.

(Whereupon, at 3:40 p.m., a recess was taken,

and meeting resumed at 3:45 a.m.)

DR. AU: Welcome back, everyone. I hope you enjoyed that quick five minutes. I think we're ready to proceed.

We'll now proceed to the charge to the committee with Dr. Paterniti.

Charge to the Committee - Miya Paterniti

DR. PATERNITI: Thank you so much. This is Miya Paterniti, FDA. Before I get started, I really want to take a moment to extend our gratitude to the committee for your thoughtful and robust discussions already today. I'd also like to thank those who spoke at the open public hearing and who submitted public comments with regards to this advisory committee. I will now turn to close the presentation portion of this meeting with the formal charge to the committee.

As we move into the next part of this meeting and prepare for further discussion and voting, I'd like to take the next few minutes to review the regulatory framework upon which our decision making is based; provide a brief overview

of the issues and results; and review the questions to be discussed and voted on.

ARS submitted an NDA utilizing the 505(b)(2) regulatory pathway, which permits FDA to rely on previous findings of safety and effectiveness of an approved epinephrine injection product. To support this reliance, a scientific bridge must be established between ARS-1 and an approved epinephrine injection product. Due to the high variability of epinephrine and clinical trial feasibility barriers, this scientific bridge was established by PK bracketing of ARS-1 to Adrenalin and EpiPen with PD support. The approach to PK bracketing included focusing on the first hour, based on the clinical course of anaphylaxis, and as epinephrine can be used as single and repeat doses, the clinical pharmacology program assessed both single and repeat doses in healthy adults.

In order to address potential local differences during anaphylaxis, ARS also conducted a trial with single doses of ARS-1 administered to patients with allergic rhinitis before and after a

nasal allergen challenge. A repeat-dose nasal allergen challenge was not conducted. Additionally, due to difference in shape, size, and surface area of the nasal cavity in children compared to adults, ARS conducted a clinical pharmacology study in pediatric subjects to assess the PK/PD and safety of ARS-1.

In my next few slides, I will review the results of these clinical pharmacology studies that were conducted to establish a scientific bridge from ARS-1 to epinephrine injection products with a focus on topics for the discussion for the advisory committee. I would like to start by highlighting the different epinephrine trends of ARS-1 compared to Adrenalin and observed during the first 10 minutes across Trials EPI 15, 16, and 17; the PK for a single dose of ARS-1, shown in red, compared to Adrenalin, shown in dark blue, in EPI 15 and 16, and shown in green in EPI 17.

In EPI 15, ARS-1 was lower than Adrenalin, in EPI 16, ARS-1 was similar to Adrenalin, and in Epi 17, ARS-1 is higher than Adrenalin. The agency

believes that these differences are due to the variability seen with Adrenalin. After 10 minutes, the PK for ARS-1 was bracketed by Adrenalin and EpiPen in EPI 15 and was higher than Adrenalin 0.3 and 0.5 milligrams in EPI 16 after 10 minutes. PD responses for ARS-1 were similar or higher compared to Adrenalin and EpiPen from baseline. The significance of the lower exposure of ARS-1 in the first 10 minutes in EPI 15 and the available data across studies and potential implications for efficacy in the setting of anaphylaxis is a topic for AC discussion.

Clinical pharmacology studies were also conducted in subjects with allergic rhinitis to assess the PK and PD in subjects with altered nasal mucosa to mimic nasal mucosal changes during anaphylaxis. In subjects who received a single dose of ARS-1 post-nasal allergen challenge, shown in the red curve, the PK was initially higher but then demonstrated a rapid decline at 10 to 20 minutes compared to Adrenalin 0.3 milligrams, shown in dark blue, and

0.5 milligrams shown in light blue. The PD responses that are not shown but they did follow a similar pattern, nasal congestion in subjects continued to be reported in about 30 percent of subjects who received ARS-1 post-nasal allergen challenge, suggesting that nasal congestion may persist if a second dose is administered. The PK and PD with repeat doses of ARS-1 under the nasal congested state have not been studied.

Since patients with anaphylaxis may require a second treatment with epinephrine, and since the PK and PD declined rapidly 10 minutes after ARS-1 administration in the nasal allergen challenge study, repeat doses of ARS-1 may be needed. Since repeat-dose studies have not been performed in the nasal allergen challenge model, there is residual uncertainty in the PK PD response following a repeat dose, and thus uncertainty about ARS-1 efficacy in the treatment of anaphylaxis. Whether additional dose ranging or repeat-dose nasal allergen studies would be necessary is a topic for AC discussion.

Today we have heard discussion that has primarily focused on the 10-minute delayed or lower epinephrine concentration in the first 10 minutes for EPI 15, and we would really like to hear the committee's input on the implications of the rapid decline in the nasal allergen challenge study as seen here.

PK/PD data was ascertained based on an uncontrolled single-dose study. Pediatric study patients who weighed 30 kilograms or more received a single dose of 1 milligram, shown in orange or 2 milligrams, shown in blue, of ARS-1. Cross-study comparison to PK and PD data from adults, while not ideal, was used due to lack of an approved epinephrine injection product as a comparator in this trial. Based on this cross-study comparison, pediatric subjects who weighed 30 kilograms or more and were treated with 2 milligrams of ARS-1 had similar epinephrine PK compared to that of adults treated with the same dose for the first 15 minutes, as shown in green. After 15 minutes, the PK curve in pediatric subjects was higher.

Conversely, the pediatric PD responses, which included systolic blood pressure and pulse rate, were slightly lower compared to adults. The significance of the lower PD compared to adults and potential implications of efficacy in the setting of anaphylaxis is a topic for AC discussion.

For a drug to be approved for marketing in the United States, the FDA must determine that there is substantial evidence of effectiveness and that the benefits outweigh the risks to patients. A benefit-risk assessment for ARS-1 requires careful consideration of the evidence and uncertainties about the benefits and risks. While we acknowledge that availability of a noninjectable epinephrine product could address certain barriers to use of epinephrine injection products, the evidentiary standard for ARS-1 must be met.

Based on the severity of the indication and the availability of approved safe and effective products, the agency expects that there is confidence that efficacy of epinephrine administered by this novel route of administration

has been established, and residual uncertainties should be minimized. Due to clinical trial feasibility barriers, the benefit-risk assessment relies on PK/PD studies in healthy subjects and subjects with allergic rhinitis. Uncertainties for establishing benefit of ARS-1 are primarily based on the challenges in establishing a scientific bridge via PK with PD support, based on the high variability of the PK/PD of epinephrine injection products and the uncertainty in whether PK/PD of epinephrine in healthy subjects will translate to the PK and PD in subjects undergoing anaphylaxis.

Additional uncertainties were identified in the clinical pharmacology studies which demonstrated different PK trends between ARS-1 and Adrenalin for the first 10 minutes and lack of PK sustainability in subjects who received a single dose of ARS-1 after allergen-induced nasal congestion.

There are also uncertainties in establishing the risks of ARS-1. Although the AE profile for ARS-1 did not result in unexpected AEs, as the

trials were small and only a few subjects received 2 doses, the systemic safety primarily relies on available data from epinephrine injection products, and there is limited local safety data for ARS-1.

We ask the advisory committee to consider whether the benefit of ARS-1 is sufficiently understood to support a favorable benefit-risk for ARS-1 for the treatment of anaphylaxis, particularly when considering the uncertainties in efficacy for an emergency treatment for a potentially fatal condition.

This brings us to our questions. The first question to put forth to the advisory committee panel members is a discussion question and is as follows. We ask the committee to discuss the PK/PD approach for establishing efficacy for ARS-1 epinephrine nasal spray for the emergency treatment of Type I allergic reactions, including anaphylaxis, specifically the PK bracketing approach using approved epinephrine injection products; 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 the lack of data from repeat dosing under allergen-induced nasal congestion conditions, and the different PK comparisons for single-dose ARS-1 and Adrenalin in the first 10 minutes for EPI 15, EPI 16 without allergen-induced nasal congestion, and EPI 17.

We also ask the committee to discuss 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 efficacy data is needed.

The next two questions are voting questions. We ask you to vote whether the PK/PD results support a favorable benefit-risk assessment for ARS-1 in adults for the emergency treatment of Type I allergic reactions and anaphylaxis. If you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus

the risks of ARS-1.

Finally, in question 3, we ask you to vote on whether the PK and PD results support a favorable benefit-risk assessment for ARS-1 in children less than 18 years of age and weighing 30 kilograms or more for the emergency treatment of Type I allergic reactions and anaphylaxis. If you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus the risks of ARS-1.

That ends the FDA presentation. Thank you again for your time and attention, and we look forward to your thoughts and discussion.

I will now turn the podium back to the chair to begin the discussion.

(Pause.)

DR. AU: [Inaudible].

DR. STEVENSON: Good afternoon. One moment while we reconnect Dr. Au.

Dr. Au, can you hear us? This is Takyiah Stevenson speaking.

DR. AU: I'm sorry. My telephone just

dropped for some reason. I don't know why. I just connected via computer. Can everyone hear me okay?

DR. STEVENSON: Yes, we can. Thank you so much.

I was asking the committee when I dropped off how much they could hear Dr. Paterniti's presentation because I couldn't hear much of any.

MALE VOICE: I heard it just fine.

Questions to the Committee and Discussion

DR. AU: Okay. Great. I think we can proceed.

Thank you, Dr. Paterniti.

The committee now will turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Question 1 is a discussion question and

reads as follows. Discuss the pharmacokinetic/pharmacodynamic approach for establishing efficacy for ARS-1 for the emergency treatment of allergic reactions, 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 indications, 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 a single dose of ARS-1 and Adrenalin in the first 10 minutes for Studies EPI 15 and EPI 16, and EPI 17.

Lastly, the uncertainty of the 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.

Are there any questions about the wording of these questions?

Dr. Kelso, you have your hand up. I just want to know if that's in context of the questions or whether or not it was up previously.

DR. KELSO: I guess it's actually more the discussion of the question rather than the wording.

DR. AU: Okay.

Why don't you go ahead and ask your question now?

DR. KELSO: John Kelso, allergy, Scripps Clinic San Diego. There's been a lot of attention about this bracketing process relative to the PK variables, but since we've learned that there's not a very good correlation between the epinephrine levels and the clinical response, depending on the route of administration, was there any sort of bracketing process done relative to the PD parameters, the clinical response, in terms of what was considered an acceptable comparison of the intranasal route versus the other routes in terms

of PD or clinical response?

MR. LOWENTHAL: Is that a question to the sponsor or FDA?

DR. KELSO: I think to the FDA.

DR. AU: Yes.

DR. PATERNITI: This is Miya Paterniti from FDA. When we first were looking at these programs, we were primarily focusing on PK, so that's why the bracketing approach is really focused a lot on the PK. PD was also captured, but we consider this supportive. But I will turn to Dr. Ren to provide additional details.

DR. REN: There's a concept when this IND was first submitted. It's like how do we deal with it, whether we rely more on PK, or more on PD, or the general concept. Eventually we landed on to a general concept because the treatment of anaphylaxis by epinephrine is considered a systemic treatment, and mostly it occurs within the circulation system. So therefore, the drug concentration, if you would measure the drug concentration and compare between different

products, that has clinical meaning because it directly reflects the epinephrine levels in the blood.

The different PD response, as the applicant proposed, could be due to the dilation of the blood vessels in the injection site of the skeletal muscle; however, there's no dedicated study or experiment to prove this hypothesis. On the other hand, early in the day we heard some committee members propose another method, which could be through the central nervous system. Of course, it's also a hypothesis; no proof.

So therefore, as you can see, if you compare the PD, there are a lot of uncertainties. There's some mechanism of action, which cannot be explained, but on the other hand, PK is there. The concentration no doubt is a direct comparison endpoint of the epinephrine products.

DR. KELSO: Okay. Of course what we really want to know -- although I understand that and the precision of measurement of the blood levels and what not, what we're interested in is the clinical

response. And I understand that since there's this disconnect, that we don't have that same maybe confidence in the PD data.

The particular circumstance where it seems to be in greatest question is this issue in the nasal allergen challenge model, where both the PK fell off quickly, but I thought I saw different slides from the FDA and the sponsor regarding the PD in that situation. So I'd like to know what the FDA thinks about the PD falling off in the nasal allergen challenge model and what the sponsor has to say about that.

DR. AU: Actually, can I interrupt for one second?

DR. KELSO: Sure.

DR. AU: Why don't we try to redirect this back to the questions that we're trying to address directly. In that context, I guess I would ask the FDA to clarify how they would like us to incorporate the slides that Dr. Kelso -- or how you would like us to include the discussion around the PD -- it is in question B, but I just wanted to

clarify -- or actually, do you think we need clarification, or do you think we can just proceed on with the discussion? How about that?

DR. PATERNITI: This is Miya Paterniti from FDA. We'd like to provide additional feedback on that statement. We would like to hear the committee's opinion about the difference in the PK profile for the nasal allergen challenge compared to the PD profile. We did show a slide where the PK declined around 10 to 20 minutes, but the PD sort of follows a similar line to the Adrenalin line, and it sort of follows the same trends but maybe doesn't have as big of changes as the PK.

The slide that we shared, I don't think we need to show it again, but we are very interested in the committee's opinion about how they're interpreting PK versus PD for the nasal allergen challenge study.

DR. AU: Okay. Let's do this.

MR. LOWENTHAL: Can we provide --

DR. AU: I'm sorry. Who's speaking?

MR. LOWENTHAL: Sorry. This is Richard

Lowenthal. I thought they asked for our clarification as well.

DR. AU: Actually, let me --

MR. LOWENTHAL: Go ahead.

DR. AU: -- I'm going to ask you to hold on that.

Let me ask if the committee has any other questions around the wording in particular, and then I'm going to open this up for discussion.

(No response.)

DR. AU: Great.

So if there is no other concern around the wording of the questions, let me go ahead, and I'll start calling on people by the order that I have on my list.

DR. GREENBERGER: Can you hear me?

DR. AU: Yes.

DR. GREENBERGER: I have a few points. First of all is regarding 1C, and this is slide 125 of FDA. I don't think Dr. Paterniti wanted it up there again, but at 20 minutes, I caution against overinterpretation of what that means.

100 picograms per mL, concentration is at 20 minutes. That may be well above the effect of dose, the effect of concentration that's required because perhaps 50 picograms per mL is sufficient, and that is seen in the first few minutes after the sponsor's product occurs. So I would caution against overinterpretation of that drop-off, especially when, as I said, in 20 minutes it goes down to 100 picograms per mL.

The other point is I believe that the sponsor's data from the nasal allergen challenge is quite important because having personally done a lot of nasal allergen challenges with cat dander in a tezepelumab study -- and by the way, people had to have a total nasal symptom score of 8 to continue in that study, not 5 like this. The person has congestion and rhinorrhea, and we're seeing increased absorption presumably for more capacity to absorb epinephrine. To me that's favorable for the patient and for the resolution of the anaphylaxis.

That gets me to this point, which is for the

sponsor and the FDA. I'm seeking out optimal absorption characteristics in pharmacodynamics to resolve the anaphylaxis as soon as possible. We talked about the intranasal route compared to IM, but I'm bringing up again the supine position, and I would like to know what kind of data we have, if any, on the absorption characteristics of this sponsor's product in the supine position since, indeed, that may be the favorable position of the body to receive the intranasal ARS product.

Can someone answer this so we actually get optimal characteristics for using this --

MR. LOWENTHAL: Yes.

(Crosstalk.)

DR. GREENBERGER: -- [indiscernible] device. Thank you.

MR. LOWENTHAL: Yes. Sorry.

This is Richard Lowenthal from ARS Pharmaceuticals. Early in the program with the 1-milligram dose, we did do some studies with semi-supine. We believe the absorption is slightly better, and certainly with other programs, it was

done semi-supine as well.

When we presented our 1-milligram data in a pre-NDA meeting early on, FDA specifically said that they want us to do it sitting up because they felt that was the worst-case situation for nasal. But certainly, I think there is evidence, not only from our product but other intranasal products, that if you're semi-supine or supine, it would actually be better because there's less risk of any nasal drip.

DR. GREENBERGER: My point is in treating anaphylaxis, when people are third-spacing, it's well known that sitting up sometimes in people who are dehydrated leads to collapse.

MR. LOWENTHAL: We agree.

DR. GREENBERGER: So it may be the most favorable position for administration would be supine.

MR. LOWENTHAL: We agree that if somebody is severe and maybe hypotensive, they shouldn't be sitting or standing, yes.

DR. GREENBERGER: But I mean from the

regulatory point of view, to get it right in my view would be to determine the favorable position of the body to receive --

DR. AU: I'd like this to be a discussion of the committee, so I'm going to ask the sponsor, again, to please refrain unless called on specifically by me.

Dr. Greenberg, I appreciate the comment. Is there any additional follow-up that you have, or would any members of the committee want to comment on that?

(No response.)

DR. AU: Great.

The next person on my list is Dr. Bacharier.

DR. BACHARIER: Thanks. Len Bacharier. I'd be interested in the committee's view because we've seen a ton of data today, and I think everybody is struggling with the multiple, for lack of a better word, inconsistencies. The PK doesn't replicate the PD, one wasn't doesn't reflect the other. At one time point, one is better; at one time point, one may look less good.

I mean, we're really struggling here with figuring out where are the most salient aspects of these data; what are really important; what are fine points that have theoretical value but may or may not impact patients. We heard many families and other groups remind us of the space that they live in and the value that such a product would bring to them. And as I hear this, and as we talk about this, I really struggle with the idea that doing one more study with 45 patients under any set of circumstances will clarify any of it.

We spend our lives doing clinical trials of the disease of interest, and here we're not studying the disease of interest; we're studying multiple surrogates, be it PK or PD. And we understand why we can't study it in this setting of acute anaphylaxis for all the appropriate reasons that were laid out there.

So I guess my real question is, what more can we reasonably legitimately expect, and if that turned out exactly the way we wanted it, would we have that much greater confidence than where we sit

now? I'm just not sure of that. I think there's just so much inherent variability with this type of drug and all the issues we've discussed, that I just worry that a couple studies of 40-50 patients are not going to give the most black and white of answers, and I think we have to make our best judgment based on the type of data that has been shared with us today.

So I'll stop there, but I'd be interested if folks see it in a more clear fashion than I've been able to.

DR. AU: Let me ask if the committee members have -- let's circle around this topic for a moment because I think this deserves actually a fair amount of light.

Is there anyone on the committee who would like to speak to this?

DR. HOLQUIN: Yes, Dave. Fernando Holquin, University of Colorado. I second what Len Bacharier is saying, I think fundamentally, to me, the frustration is we're being asked to evaluate parameters; by those I mean, primarily, the PK

level data for which there is just not data to support any clinical correlate. I am more convinced in supporting the use of this application by the PD data, although the FDA considers it to be more supportive. But I agree with Len that if you do a similar size study, I think you're going to end up with the same type of variability. Thanks.

DR. AU: Can I press on our committee members? Earlier we've heard that studies were not ethically appropriate, which I agree with in terms of the consideration of placebo. There's also the opportunity, though, for different studies that provide convergence kind of information, information that might be surrounded around comparative effectiveness, or studies in relation to -- well, comparative studies, comparative effectiveness studies, or efficacy studies, and then the other issue that I really understood was that it was not feasible because of issues around modeling or acquisition.

I don't know if anyone has an idea of how long it would actually take to do one of these

studies; what the relevant endpoint might be; why could we not do this in something like around food allergy or the like. So if any one of the committee members has a frame around that, I would appreciate it, because I think it gets back to directly what was being discussed earlier.

DR. BUTLER: May I make a comment, Dr. Au?

DR. AU: I'm sorry. Who's talking?

DR. BUTLER: Javed Butler.

DR. AU: Sure. Absolutely. Sorry. It's hard to tell.

DR. BUTLER: Javed Butler, cardiologist. I have a question related to your comment about what other ways we can get some idea and some clarity, and I wonder if there's a disease expert here who knows whether there's a post-approval for the existing marketed therapies.

Are there any post-approval data on both the safety and efficacy, i.e., how many times that 2 doses did not work and people had to go to the emergency room, or how many times older people ended up getting a myocardial infarction, or

something like that, that we can correlate the bracketed PK/PD with the post-approval clinical outcome. Granted, it's not the best way, but at least get some idea of correlation of PK/PD with clinical outcomes of the existing therapies that we can then extrapolate to this novel therapy.

DR. TRACY: Can I just add something also, Dr. Au?

DR. AU: Yes. Please, I don't -- is that Dr. Tracy?

DR. TRACY: Dr. Tracy.

DR. AU: Let me just say that the committee can speak freely. I'm sorry. I just wanted to make sure that we had some control of the meeting.

DR. TRACY: Allergist/immunologist, University of Nebraska. I've been mulling this thing over for weeks like everybody else, and Leonard's kind of already touched on some of this stuff. I sometimes think we're looking at this thing a little bit wrong.

When you go back to the original PK [indiscernible - audio garbled] on the EPI 5, and

we talked about the 10-minute element, the agency goes back about variability with the epinephrine, I think it's just variability of the device. I went back and actually did a little homework on the EpiPen. The EpiPen has a 22-gauge needle. If you're actually in a clinic, most people are getting their EpiPen subcutaneously or IM with a 25-gauge needle, which is considerably different. That alone may be sufficient along with the length of the needle. So that's the first thing.

The second thing that kind of popped into my head, tied into that point is how would you study this? I'm part of a very large allergy group, and before I actually begin utilizing this product, I probably would get someone in my office, and if I had shot reactions, I'd see how people did with that. It's obviously hardly blinded, but it might give me some of the confidence to actually give this to a 5 year old or an adult with allergies because, ultimately, if we approve this or recommend approval, there is a certain wish and a prayer here that goes with it. So ultimately, if

it is approved, then it's going to play out in real life with real people. Thank you.

DR. AU: Thank you. I appreciate that.

DR. AMIRSHAHI: Dr. Amirshahi. May I make a comment?

DR. AU: Please. Thank you.

DR. AMIRSHAHI: My disclaimer is I'm an emergency medicine physician, and we treat anaphylaxis all the time. One of the things that gives me pause, number one, is the uncertainty. Number two is the pharmacokinetics in the first 10 minutes, and I think this is something that we need to think about critically because these patients are not in a healthcare setting in the first 10 minutes. It takes that long or longer for EMS to arrive. So when you have a life-threatening condition and you're managing it out of the hospital, those first 10 minutes may really matter. If it doesn't work, this is really going to end badly for the patient.

So what I might suggest as an emergency medicine researcher is perhaps we want to get more

data, and we want to study this, and I think clinical outcomes are more important than necessarily PK/PD data because, once again, that data is limited and variable. Perhaps people like myself could hold compared studies in a control setting where there is a backup, where there is capacity to resuscitate and administer additional medications that we could compare this with EpiPen. In fact, many of the EDs and hospitals are using EpiPen and pulling it up in vials. So this would actually be something that would be really easy to do, and I think it would give us some [indiscernible] because letting this go with so much uncertainty in an out-of-hospital setting for a life-threatening condition, I just think we need more information, and that might be a way to study it.

DR. LEE: Dr. Au?

DR. AU: Yes. Thank you.

Yes?

DR. LEE: This is Dr. Janet Lee from Washington University, and thank you so much for

all of this robust discussion, and the presentations by Dr. Tanimoto from neffy, as well as Dr. Wu from the FDA.

I just would like to contribute to the discussion related to the actual question at hand, and that's the PK bracketing approach as a scientific bridge to establish efficacy. And while there is, admittedly, great uncertainty of how this translates in terms of meaningful clinical outcomes, as many of our colleagues have spoken to, I think we have to also consider the three studies that we have been presented here, the EPI 15 with a PK/PD; the EPI 16, the nasal allergen challenge; in addition to the EPI 17, the self-administration challenge. I think the other thing that we do need to consider as well are the two points that the FDA has brought up about the diminished PK/PD sustainability in subjects with allergen-induced nasal congestion, as well as the different PK comparisons of the single dose, and the Adrenalin for studies EPI 15 and EPI 16.

I think one thing that I was struck by, and

I think one of the other advisory committee members has discussed was nasal congestion will increase delivery. That I think was very unexpected, I would say, data, but it does make sense after thinking about it and hearing the presentations.

I think the other thing that I really appreciate is the open public hearing about filling a great unmet need with this needle-free delivery system, and the other aspect that we really need to consider is time to dosing. So even though that first 10 minutes we have uncertainty based upon the data that's presented, time to dosing I think with this method, we need to consider and take that into the full discussion. I just want to stop there.

DR. AU: Thank you, Dr. Lee.

DR. LE: Dr. Au, I'd like to provide some comment.

DR. AU: Yes, please.

DR. LE: Hi. Jennifer from UC San Diego. I'm trying to put all of this in perspective. I'm trying to look at the bigger picture here. I do PK modeling. I was part of the national guideline for

vancomycin, and coming from the pediatric point of view, it's not uncommon for us to see a little bit of a lag of the pharmacodynamic effect after the PK. There's never -- well, I shouldn't say never, but there are instances where it won't always align up, and the PD will not always perfectly match with the PK. An example of this is antifungal agents, where despite having MIC, still the clinical side, correlating the PK side is not always there. So it's not unusual to see this in other disciplines, in other infections.

But I do appreciate the FDA taking a very unique and, I think, innovative approach with the PK bracketing to really try to make use of PK/PD data because we do that all the time in pediatrics. We're not going to have outcomes data necessarily, and for the vancomycin that we have, in terms of our recommendations to go with AUC, it was largely on adult data, and it was not the best of full-blown clinical trials. I actually was impressed by the effort made by the sponsors here with a different EPI 15, 16, 17, totaling

600 patients, which is informative to me in terms of that.

So I realize that when I use this and put it in the full scope of Type I reactions, yes, I am only concerned about the anaphylaxis side, but there's also the spectrum of patients without anaphylaxis who may greatly benefit from this. So I think it's hard, especially for the voting. I'm trying to figure out the voting side because it does bring in allergic reaction Type I and anaphylaxis, but I would err more towards looking at this as a whole and having some faith in that PK/PD data. Granted, there's no clinical trials out there, but that's what we've had historically. So I'm just wondering is there a double-standard if we were to introduce and require that if we were to go towards asking for more clinical data.

DR. AU: Great.

Can I follow up on that? I went off video just to stabilize my audio. I guess I wonder a little bit how much -- I mean, the data that we're comparing to was based in the early 1900s, and is

that an acceptable standard now in 2023? Should we be using equivalency or PK and PD data based on comparators that actually have no efficacy data?

Let me pose that to the FDA to the FDA. I see the FDA has had their hand raised as well.

DR. PATERNITI: Miya Paterniti from FDA. We just wanted to circle back to Dr. Le's comment about the indication, and just to clarify that the indication is really intended for anaphylaxis, and the inclusion of Type I allergic reactions is there because sometimes epinephrine may be used slightly before you technically meet anaphylaxis criteria. So it's more of an all-encompassing indication, but the intent is really for treatment of anaphylaxis. So I just wanted to clarify that.

In terms of Dr. Au's question about making inference on PK/PD for epinephrine injection products for which we have no efficacy data, I think that is something that FDA also struggled with, but we do rely on the clinical experience and literature support for epinephrine for treatment of anaphylaxis. So we are relying on that conclusion,

and using the data that we have at hand. I hope that helps to clarify.

DR. SEYMOUR: Dr. Au?

DR. AU: Yes? I'm sorry.

DR. SEYMOUR: This is Sally Seymour from the FDA, too. I think we are really interested in the committee's thoughts about gaps with data here, and that would include whether you think clinical data are needed and if a clinical study is necessary or appropriate. So really, I think that's one of the questions -- it's under C -- whether clinical data are needed. So we'd love to hear what you all have to think about that.

DR. AU: Thank you so much. I started my video again. I hope my audio will last.

Let me go to the committee. People have their hands up, and I want to know if there are different topics they would like to bring up as well. There are a lot of hands up, so I'm just going to start with Dr. Nelson, and I'll just run my list.

DR. L. NELSON: I assume you mean Lewis

Nelson. That's me. Thank you.

DR. AU: Yes.

DR. L. NELSON: Because it's two of us here today. I'm Lewis Nelson. I'm from Rutgers New Jersey Medical School in Newark, New Jersey. I don't even know which question to answer anymore, so I'll just go through them in my head.

I just first want to say that I really want this product to work. We definitely benefit from a needleless means of delivering Epi, and I think the sponsor's done a nice job trying to find that balance. That said, I think we're using weak surrogate data to assure ourselves that we could be confident in our ability to successfully treat one of the scariest clinical syndromes that we see in the public, and in the ED, and where I work. As Dr. Amirshahi mentioned before, it's a devastating illness when you see it. I know many people in the public session have commented on that.

I think the bracketing approach makes sense, but we are comparing apples and oranges to some extent, and I think the FDA and the sponsor

understand this and tried to show equipoise between the various data sets, but I don't really think we've done that sufficiently to make a clinical judgment that these devices will prove as successful as we see with the other forms of epinephrine that we use, particularly because we've really only used healthy patients or simulated ill patients. We really have not studied patients with disease that we're interested in.

I do think that the most important part of the treatment trajectory that we deal with, particularly for the sick patients, as Dr. Amirshahi said also, is the first 10 minutes. So the idea that showed that this device works quickly in this patient population with swollen mucosa is very encouraging, but as I mentioned in my comments earlier, or my question earlier, I don't know that we can equate slowing mucosa with anaphylaxis. I mean, I could see where there's some relationship, but it's clearly two different diseases. One is a weak surrogate for the other.

One can seek medical care pretty quickly,

whether it's EMS through an emergency department, or whatever, and patients can always redose. And I know there are some questions about how functional that will be in a swollen mucosa, which I assume we are thinking about somebody with anaphylaxis. So the rapid fall in Epi concentrations don't concern me that much, although I obviously would rather not see that.

To answer the clinical question, the clinical data question, I strongly believe that we need some clinical data to support this product. I do think that it's feasible to perform a study. It's hard, but we study stroke, we study MIs, we study cardiac arrest, and we do all kinds of pre-hospital studies that involve very sick patients, and from what we heard in the public session, there are millions, potentially, of patients who could be enrolled in the study, and we could identify those patients proactively, get them enrolled in a trial where they might have a rescue medication or a fail-safe mechanism in case this drug failed to reverse the anaphylaxis with the

initial dose. But I really would hate to learn, without some better clinical data, that we recommend approval of a product on the basis of surrogate data that's inconsistent and somewhat confusing, and ultimately because of that, patients are harmed. So I do think we need to have more data, clinical data. I just don't think surrogate data is going to be adequate to allow this indication, to support this indication. Thank you.

DR. AU: Thank you very much.

In the interest of time as well, I think we should try to wrap up by or 4:45 or so Eastern Time because we're still going to have a number of discussions and a number of voting questions that come after.

Let me ask the committee, we've heard a lot of opinion about the idea of the linking between PK and PD and clinical efficacy outcomes and clinical relationships. We've also heard about issues around the desire and the other concerns around timing, the desire for this device to work, as well as the context of the open public hearing.

Are there other comments that the committee members would like to make that augment that or are separate to that? I would take preference over the separate because I think we've heard some pretty robust discussion around the former.

DR. PEDEN: I have a question. This is Dave Peden. In the event this drug were approved -- and I'm just speculating -- given that there's no clinical data, what is the agency going to propose to monitor how effective this is? Is there going to be post-approval surveillance, and is there going to be some kind of recordkeeping of failure rates, or how many times the 2 doses of epinephrine given with this device not work?

To me, frankly, I didn't see a ton of difference, overall, between the Adrenalin and the data I saw for ARS-1. I didn't, but that's with loss of in-confidence [ph] intervals, I'll call them, surrounding those data. I was actually more compelled with the PD than the PK, but that's just me talking. But I would be curious with how the agency would surveil the outcomes with this.

That's kind of a black box. I mean, if we approve it, does it just go off into the ether, and we always assume -- like we did with all the other epinephrine agents -- that this is going to work?

DR. EVANS: This is Scott Evans. Can I just add on to that real quick?

DR. AU: Please?

DR. EVANS: I am very tightly aligned with Dr. Peden's comments just now. That's why I wanted to springboard off of that. The sponsor was able to provide data about how often we need second dosing with the available agents. That tells me we can track this carefully and look at it closely, so I am very anxious to hear the agency's response to that. And also -- just because I'm so probably aligned with Dr. Peden's comments -- I agree that I find the PD data much more compelling than the PK data. It was just commented that these are weak surrogates. That seems likely a closer physiologic surrogate to me than the PK data. I'll stop there. Thanks.

MS. SCHELL: Hi. This is Karen Schell,

University of Kansas Medical Center, respiratory therapist. I want to step back and go back to the patients and their advocation during the public hearing. We heard from them that they are in need of something that they can provide quicker to their patients. So with all the variability of how long it takes to get this medication to the patient, I think that we can't forget how important it is to them to have something in hand that they can work quickly. That's our whole image, is for them to get it into their patient quickly, or their loved one quickly, and it seems like there's been a delay with the pen.

I agree that clinical is real important because when we look at patients as a respiratory therapists, they're all different, and they all react differently to the medication. So if we could approve the medication at this point and do some clinical studies of those that are involved giving it, I think it would be more beneficial. I appreciate the studies that were provided but, again, to me, I can't see not giving it to a person

and letting them try it and study it. Those are just my thoughts. Thank you.

DR. AU: Can I ask the FDA to go back and comment on the previous two points, please.

DR. PATERNITI: This is Miya Paterniti from FDA. I'm going to turn to Dr. Jennifer Lan to provide a response about what would happen if this product was approved in terms of safety monitoring post-approval.

DR. LAN: Hi. This is Dr. Jennifer Lan. I'm the clinical reviewer in DPACC. For all post-approval drugs, we do have the FAERS database, which is the FDA Adverse Event Reporting System, which does have some limitations with respect to assessment of drug effectiveness. There's no way to tease out that it's due to epinephrine being ineffective and not the device or another reason of why it would be ineffective. I hope that answers your question.

DR. HOVINGA: [Indiscernible - audio garbled].

DR. STEVENSON: Hello. This is Takyiah

speaking, the DFO. I'm sorry. Dr. Hovinga, I think your audio is going in and out.

Can anyone else hear what he was saying?

MALE VOICE: It's all so garbled.

FEMALE VOICE: No. We can't hear.

DR. HOVINGA: [Indiscernible].

DR. AU: Dr. Hovinga, I'm going to stop you because I think the committee can't actually hear you or understand you. I heard a little bit about how would we adequately power a study such as that, but I'm sorry. We really couldn't hear you.

DR. STEVENSON: Dr Hovinga, this is Takyiah speaking. I would recommend if you could just hold your comments. Please don't lose your comments. We're going to address this technical issue with your audio. If you could please just hold on to them while we address the technical issue. Thank you so much. Sorry about that.

Thank you, Dr. Au. Back to you.

DR. AU: Yes. Thank you.

Actually, I don't think we've heard from Dr. Schwartzott, so I'm going to call on

Dr. Schwartzott.

MS. SCHWARTZOTT: Hi. Well, I'm the patient representative.

DR. AU: Oh, I'm sorry.

MS. SCHWARTZOTT: I'm not a doctor.

DR. AU: I promoted you. I'm sorry.

MS. SCHWARTZOTT: I have different perspectives, but I also agree with what some of the other doctors have said. I've been through this. I have used my EpiPen way more than once. I've had serious anaphylaxis reactions. Time is of the essence; there's no doubt about that one.

In regard to the studies that have been done and the PK, the PD, I know there are lots of uncertainties. I understand there are a lot of questions about the design and limitations and what is possible, but like Dr. Schell said and like Dr. Lee said, this is a very serious unmet need. I'm not afraid of injecting, but other people are. It's very difficult to be able to afford the EpiPen. It's difficult when people are afraid of the EpiPen. I have nieces that are small, and they

need it. They have severe allergies.

So I really think that this is a way of getting the medication to the patients, and I think that the benefits outweigh the risks in this case. I also do think, though, that further data needs to be collected, but not necessarily what's already been done. I have serious concerns about seniors and cardiac patients. I also have concerns about young children. I think it was Dr. May that brought up the possibility of inappropriate use, and I can see that happening. Some of these smaller children are used to asthma inhalers. They put things in their mouth. I would like to see what the data is for the safety if they get this in their mouth, and what's going to happen to them on that. But for the population that's been studied for this trial, I think that the data that's shown, the benefits outweigh the risks and that this is something that is so serious, that it's worth it to get it out and study it in the population, in the community, with the doctors prescribing it and with the emergency rooms.

Yes, it's not always perfect in that first 10 minutes, but it's better than nothing, and maybe it'll buy time to get them further care if necessary. That's my opinion on that; that it's that important, and there's enough data here, in my opinion. But again, I'm not a doctor, but I would be willing to take the risk.

DR. STEVENSON: Thank you.

Anyone want to touch that? Otherwise, I'm going to move on to Dr. May.

DR. MAY: Yes. I just want to make a quick comment. Susanne May, University of Washington. I wanted to make a quick comment with regard to the clinical data and the likelihood of obtaining the right information. I do not think that we can get around a leap of faith, to some degree. I've been involved in a lot of emergency medicine clinical trials in the out-of-hospital setting and the ED setting as well. We do not get to the patient quickly enough to really answer the question of how fast and good it works when it is done immediately when they have the symptoms. Once they're in the

ED, it's already far down the line. Even when the medics arrive, it's far down the line.

But we could not rely on patients randomly picking either the spray or the EpiPen, so I think, really, even if we were to say we need clinical data and it would be good to have clinical data, I don't think it will be clear-cut. There is no study design that will answer the question with regard to that it's feasible and with regard to really early administration of this. That was my comment.

DR. AU: Thank you.

Does the committee have any follow-up with that? Is there a scenario that they could see, where they could actually see in clinics; for example, a trial that's done within the clinic setting or the like?

DR. JONES: This is --

DR. AU: Dr. Jones?

DR. JONES: Sorry. I'm trying to get my camera on. I wanted to make comments somewhat relevant to that. I think in the study design,

with the attempt to model allergic response with allergen induction, with the nasal allergen induction, I think that model is not reflective, in my mind, of what happens when you have a systemic reaction. So I think there definitely is a need to do clinical studies.

I think, for one, in that model you have direct allergen exposure to the nasal mucosa, so that likely alters the epithelial component there, as well as the direct allergen response, so it's not surprising that the absorption may be a little bit better; where I don't know if you could necessarily say that that would happen with a systemic reaction.

So I do think there's a need to do clinical setting type studies. I think there is an opportunity with the more wide use of oral immunotherapy. Part of that procedure is getting patients to the induction of anaphylaxis to find their dose, or close to, or having allergic symptoms. I think that provides an opportunity to maybe do a type of rescue type study. I think it

was also already mentioned that in allergist offices, we give allergy shots every day. Patients have anaphylaxis to allergy shots, and that would also provide a more controlled setting to use a rescue type model.

I believe, based on our current data, there's not enough there to say that this medication is beneficial and meets the need, and I do think that there's room for more clinical studies.

DR. AU: Thank you.

I want to go back to Dr. Hovinga because I do believe he is back [indiscernible].

(No response.)

DR. AU: Maybe.

Dr. Hovinga?

DR. HOVINGA: Sorry. I was muted.

DR. AU: There you go.

DR. HOVINGA: Can you hear me?

DR. AU: Yes. We can hear you great now.

DR. HOVINGA: Yes, I was muted, essentially.

Many of the comments that I was going to

make sound like they've been mentioned. I do think that the closest example to a feasibly operational study might be what's done in food allergy or allergen testing and whatnot, where anaphylaxis is induced. I still think this will be a significant delay in giving this treatment to families. I also wonder, not using the FARE route, but would there be a pathway for a postmarketing requirement where we could look at this versus put it into a traditional clinical trial. I think, given what we've heard from families, this is an important intervention for them and wonder if there's a route that might make the drug more accessible to patients earlier. Thank you.

DR. AU: Can I ask the FDA to comment on that? Is there an opportunity or once this drug is out of the barn, it's is out of the barn?

DR. PATERNITI: This is Miya Paterniti, FDA. Based on the proposed use of ARS-1, we would consider that the evidence that is provided to support that proposed use would be sufficient. If there is additional safety concerns, that could be

considered in the postmarketing space, and we would welcome discussion regarding that. However, if you have concerns that would require additional efficacy data postmarketing, we would like to hear why you would want that and what additional data would support the proposed use and would be sufficient to support efficacy based on what the sponsor has proposed.

DR. AU: Thank you.

[Indiscernible - audio garbled.]

So hopefully that answers your question.

DR. STEVENSON: I'm sorry. Dr. Au, I cannot hear you. I'm not sure if anyone else is also having difficulty hearing Dr. Au.

FEMALE VOICE: Yes. I can't hear him either.

DR. STEVENSON: Okay. One moment, please.

(Pause.)

DR. AU: I think I've lost my audio again. Can anyone hear me?

FEMALE VOICE: Yes.

DR. STEVENSON: Yes, we can. Thank you.

DR. AU: Sorry. This is the life of Zoom.

If feel like we've had a pretty robust discussion, and I was hoping to be able -- unless there's anything more, I was going to try to succinctly summarize the discussion.

Is that okay with everyone?

DR. KELSO: Can I just add one more?

DR. AU: Sure.

DR. KELSO: John Kelso, Scripps Clinic. Yes, it would be nice to have clinical data from any kind of a study, whether it's randomized or not, but I think those studies, I agree, they would be very difficult to do, given the fact that you should intervene with this drug early, and then it prevents the progression of the condition. I think it would be very difficult to design those studies.

Even though I would like to see that data, I think one thing for us to consider is given the PK/PD data that we have, is it biologically plausible that this would not work? What explanation can we come up with that would say when you squirt this into your nose, it leads to an

increase in the level of the drug in your bloodstream, and it leads to clinical consequences of increased blood pressure and heart rate? What scenario can we describe where that would not translate into effective treatment of anaphylaxis? And I can't really think of any. So even though we don't have clinical data we'd like to have, I can't picture why it would not work.

DR. AU: Great.

DR. JONES: I'll just comment, for me, I wonder are we studying the right dose? I know it was mentioned briefly earlier that there were safety concerns with going higher, but we're not meeting the PK, at least within the 10 minutes, and I feel like that's a very critical period. We don't really know exactly when epinephrine is acting in anaphylaxis, but we've heard multiple times that it's very important to get it on board early. So if we're not able to show systemic absorption within the brackets within the first 10 minutes, I think that's really concerning, and maybe there's a need for a higher dose if you're

administering in the nose versus an injection.

I think the other component is looking at the PD as well, even though, overall, there's an increase in systolic blood pressure. But that's still somewhat delayed when you compare it to what I would consider the gold standard for community use with an autoinjector, and there's a delay of about 10 minutes of meeting that increase in systolic blood pressure. I think the other component that could be explored is the dosing, and you kind of need to go back and see if higher doses may be needed if you're administering it in the nose.

DR. AU: Thank you.

MALE VOICE: I also would like to comment, if I may.

DR. STEVENSON: I'm so sorry. This is Takyiah speaking.

Dr. Jones, could you please just restate your name, for the record, please.

DR. JONES: This is Bridgette Jones.

DR. STEVENSON: Thank you so much. You can

continue, sir. Sorry for the interruption.

DR. AU: It's 5:00 p.m. Eastern, so let me take the opportunity to actually pause this conversation and see if I can summarize. I think we've had a pretty robust discussion. Even though new things may come out, I think the bulk of the tensions are laid out to bear.

Those are, there is a public need. It is clear there's a public need; that patients themselves have all sorts of consequences related to injection and route of epinephrine, and those cross multiple domains of patient well-being. So I don't think there's any question that this committee wants to have faith and this committee wants this device to work.

I think where we are is the use of surrogate data or surrogate markers and whether or not those surrogate markers lead to actual clinical outcomes. There was inconsistency, or consistency -- there were just differences in how the PK data can be interpreted and whether or not the PK data was actually the right surrogate endpoint versus

whether or not we had more faith in the PD data, and that the PK data and the PD data followed somewhat, but then they're not consistently suggesting comparability, at least in certain contexts, and in particular around nasal allergies, the inducement of allergy [indiscernible] symptoms.

I think the large issue is whether or not we can make this leap, and I think it's not a hyperbole to say make a leap of whether or not PK/PD data then translates into clinical outcomes, which I think a number of the committee members expressed concern about. Then in subsequent downstream effects or downstream questions is how could that information be collected?

I think everyone noted that the studies would be challenging to some degree, and maybe not done in the emergency room, as Dr. May pointed out, but maybe done in allergy clinics, as Dr. Jones had illustrated. But then we would actually have to come to some consensus around what the outcome of choice would be and what would be the primary outcome and what would be the number of people that

would need to have those studies performed, as well as the time lag in terms of how long it would take to accrue that population overall.

So I think, overall, what we're left with is a foundation that was rooted in decision making or the way the rules were set back in the 1900s, and we're left asking the committee to opine around whether or not we can make clinical efficacy endpoints or clinical efficacy assumptions around the use of PK and PD data.

Let me pause there and ask the committee if I've missed anything of substance.

(No response.)

DR. AU: Great. Hearing none, maybe we can move on to the first voting question. Is that okay with everyone?

We will now move to the next question, which is a voting question. Dr. Stevenson will provide the instructions for the voting.

DR. STEVENSON: Thanks, Dr. Au.

This is Takyiah Stevenson, DFO. Questions 2 and 3 are voting questions. Voting members will

use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson has read the voting questions into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select the radio button that is a round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the submit button, you will not be able to change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room. Next, the vote results will be displayed on the screen. I will

read the vote results from the screen into the record. Thereafter, the chairperson will go down a list and each voting member will state their name and their vote into the record. You should also address any subparts of the voting question, which includes the rationale for your vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. AU: Seeing no questions, I will hand it back to Dr. Au, and we can begin.

DR. AU: Question 2 is a voting question, and it reads as follows. 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? If not, what additional data are needed?

Are there any questions about the wording of the question?

(No response.)

DR. AU: If there are no further questions or comments concerning the wording of the question,

we will now begin voting on question 2.

DR. STEVENSON: We will now move non-voting. participants to the breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. The voting results will be displayed.

There are 16 yeses, 6 noes, and zero abstentions, for the record.

I will hand it back to the chairperson. Thank you.

DR. AU: Thank you. We will now go down the list and have everyone who voted state their name and vote into the record. You may also state the rationale for your vote. However, if you voted no, please recommend what additional data are needed.

We'll start with Dr. Holquin.

DR. HOLQUIN: Fernando Holquin, University of Colorado. I voted yes, and the reason is because even though there's uncertainty regarding the PK/PD data, I think, overall, there's more in favor that it will work than it will not, and there's a significant unmet need that this product

does bring to the board. Thank you.

DR. AU: Dr. Evans?

DR. EVANS: This is Scott Evans from MD Anderson. I voted yes. I am reasonably convinced by the PD data. I believe there is biological plausibility of efficacy. I recognize the unmet need, and I have no reason to suspect that there's greater risk of harm than any of the currently approved preparations. Thank you.

DR. AU: Thank you.

Ms. Schell?

MS. SCHELL: This is Karen Schell. I voted yes mostly because I wanted to get it into the patient's hands quickly and see the results from it. Thank you.

DR. AU: Dr. Dowling?

DR. DOWLING: Yes. This is Tom Dowling. I voted no, and the reason I think -- sorry about that. I think we're obligated to the public to have clinical data in this situation. I think, as mentioned, comparative effectiveness data would be important here under very controlled environments

and adequately powered, as mentioned. And really, the main reasons for my concerns are lower PK levels within the first 10 minutes, really not knowing what that minimum effective concentration is -- it's not been defined -- and having a new route of administration for a drug without demonstrated bioequivalency.

DR. AU: Thank you.

Dr. Bacharier?

DR. BACHARIER: Yes. Len Bacharier, Vanderbilt. I voted yes. I think the PK data were consistent enough with what they should have been. It performs at least as well as one of its readily available comparators. The PD data are reassuring to me that there is physiologically active drug after administration, especially in the setting of upper airway disease, and I think that balanced with the unmet need, and in the context of the lack of real clear weight to take the clinical development program forward with any other compelling studies, I voted yes. Thank you.

DR. AU: Great.

Dr. Greenberger?

DR. GREENBERGER: I voted yes. I felt that the PK/PD results do indeed support a favorable benefit-risk assessment in adults, and let's keep focused on the huge unmet need that we've heard about and we know, and that's anything to do to get the epinephrine into people effectively and faster, the better.

DR. AU: Great.

Dr. Kelso?

DR. KELSO: I voted yes because I think that the data showed that the drug gets into the bloodstream and has an effect in a way that's comparable to the injectable products that we're using now, and I have no reason to think it wouldn't have the desired clinical outcome.

DR. AU: Dr. Le?

DR. LE: I also voted yes to approve. Given the benefit I felt was greater than the risk assessment due to the public hearing today, and the numerous public comments posted on the website, I think this needle-free epinephrine spray would

certainly provide an unmet need. However, I do believe that the PK/PD data presented today was informative, and particularly evident to me was similarity between the Adrenalin and the ARS-1, and I believe it can be extrapolated to inform patient response in the clinical setting, as we do see changes in systolic blood pressure and heart rate; although I am concerned about the real-world clinical efficacy, so to ensure safe and effective use, I do recommend a statement in the product labeling, if approved, to emphasize prompt administration of the dose due to potential delay in the clinical effect by 10 minutes after dose administration, and also have some mechanism where patients and healthcare providers should be educated on the consideration to use EpiPen first unless patients don't have access to that or cannot use EpiPen until clinical data become more available.

DR. AU: Great.

DR. STEVENSON: Hello. This is Takyiah speaking. I'm so sorry to interrupt.

Dr. Le, could you please state your full name and your vote, for the record?

DR. AU: I'm sorry.

DR. LE: Yes. Thank you. Jennifer Le from UC San Diego.

DR. STEVENSON: Thank you..

DR. AU: My apologies.

Dr. Peden?

DR. PEDEN: Yes. I voted yes.

DR. AU: Could you state your name, for the record?

DR. PEDEN: I'm David Peden, and I continue to vote yes. I did so because I felt the PK data were reasonably consistent with the Adrenalin. I thought the PD data were better, as showing biological proof of concept that there was epinephrine actions systemically given this dose, not in a disease state. And consequently, I thought the benefit-risk ratio weighed in favor of benefit.

DR. AU: [Inaudible].

Sorry. Can I ask if anyone can hear me?

DR. STEVENSON: Yes, we can hear you.

DR. AU: Okay. Great. Sorry. I was frozen for a little while, so I apologize.

Dr. Amirshahi?

DR. AMIRSHAHI: Yes. Maryann Amirshahi from Washington, DC. I voted no. I recognize that there is a tremendous need for this product, and I would like to see it approved immediately [indiscernible]; however, when we think about what we use clinically, we use EpiPens and not the Adrenalin injections, and in the first 10 minutes, there was a really significant difference in PK parameters. I think that this is really important clinically because the fact of the matter is we are treating out of hospital a life-threatening condition. If we don't have efficacy data, we can't afford to be wrong here. Thank you.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: Dr. Tracy, allergist/ immunologist from University of Nebraska. I voted yes for this. Initially, I was really concerned

about the bracketing. I had some confidence as we progressed through it. I found that the 505(b) strategy, recognizing that actually studying this thing would be really, really challenging, and perhaps maybe even unethical, depending on how it's designed.

Kind of like Dr. Peden, I put a lot of stock in the PD data. I was not encumbered by the PK 10-minute issues at all for things that I've already brought up. I do recognize there is sort of a leap of faith with this, but in the end, I felt that the benefits outweighed the risks.

DR. AU: Thank you.

Dr. Lee?

DR. LEE: This is Janet Lee from Washington University in St. Louis, and I voted yes. And like many of my colleagues, I felt that the PK bracketing approach, in addition to the PD data, was compelling enough for me to vote affirmative, and that the results showed favorable benefit-risk assessments.

I did take a little different take on some

of the things that were previously said. I do think that this needle-free delivery system not only fills a great unmet need, but I do feel like it would reduce time to dosing because of the fact we heard in the open public hearing that this fear of the needle prevented early dosing of this very important drug, so thank you.

DR. AU: Thank you.

Dr. May?

DR. MAY: Susanne May, University of Washington, and I voted yes because I also felt that the benefit-risk ratio was in the direction of approval. I agree with the previous speaker and others who have mentioned that I believe that this is going to be used earlier, probably by more people who need it. I was a little concerned, potentially, that that might not be the right dose, that the dose might need to be stronger, but that could lead to the second dose being used more often, and I did not see any particular risks with that.

DR. AU: Great.

Dr. Jones?

DR. JONES: This is Bridgette Jones. I voted no. I voted no because I felt with the data provided, it did not establish that there was confident scientific bridge criteria that was met. Again, I feel like with the delayed PK, particularly within the first 10 minutes, I think that could potentially put patients at risk even if the drug is used earlier on in the reaction. The PD data also didn't give me much confidence either because, again, even the PD responses seemed to be a little bit delayed in the first 10 minutes.

So because of those two factors, I wasn't able to confidently say that this drug would be effective. I do think that there is potential for feasibility of additional clinical studies, as well as looking at additional dosing.

DR. AU: Thank you.

Dr. Troendle?

DR. TROENDLE: Hello. I'm James Troendle from the National Institutes of Health. I voted yes. I felt, assuming the PK/PD data is

meaningful, and I believe the FDA thinks it is, then the results of the studies were overwhelmingly collaborative of that, and if that is true, that there is likely a clinical effect from this. So I think the risk-benefit ratio is enormously positive.

DR. AU: Thank you.

Dr. Nelson?

DR. L. NELSON: Hi. Lewis Nelson. I voted no. I think we have a good treatment now in the EpiPen, and I think to iterate on that to get a better treatment, the bar is high. Although I do see some benefits to this alternative route of administration, I think that there are some potential limitations in terms of some risks and in terms of its utility. But the single biggest issue that I still struggle with is that even if you believe the PK/PD data to be spot-on, we're still studying them in the wrong disease and the wrong population, and I just don't know that we could apply healthy people data to people with anaphylaxis. It's a disease that's just got so

many pathophysiological aberrations, and I'd like see something that shows that the drug actually is absorbed, at least to the same extent in that population; let alone a true clinical outcome.

As I said earlier, I'm not suggesting it's easy to study, and I'm not sure we need the randomized, double-blind trial to do it, but we don't have even observational data. We have nothing that we've seen that suggest that this drug is safe or effective in the populations it's being indicated to be used on, which are really people with severe anaphylaxis. And I just think that on that basis, without more data, I can't support its approval. Thank you.

DR. AU: Thank you.

Michael Nelson?

DR. M. NELSON: Michael Nelson, University of Virginia. I voted yes, based on the preponderance of evidence presented. I, too, have some concerns and hesitancies, but the basis was the original development plan and jointly planned with the FDA and sponsor, and certainly fulfilling

some of the significant unmet needs.

Short of prohibitive large clinical trials, this bracketing approach gets us probably as close as we're going to get in the way of meaningful evidence of systemic absorption and biological effects that are beneficial to the treatment of anaphylaxis; whereas a taste of clinical efficacy data in some of these other smaller clinical trials might make us feel a little bit better, frankly, I'm not totally convinced we're ever going to get adequately powered study data that would beat the bar to definitively prove efficacy for the wide variety of conditions for which this product will and should be used.

I plead for robust postmarketing surveillance of phase 4 studies to really address this efficacy question and perhaps the dose-response curve in order to better serve the best interest of our patients going forward. On this PD/PK disconnect piece, I don't think we should expect or be surprised that there's a disconnect when we take into account that

epinephrine can have sustained effects on mast cells and mediator release, and doesn't require their continuous receptor stimulation or presence. Thank you.

DR. AU: Thank you.

This is David Au. I voted no. I voted no for similar reasons, in that we have actually no clinical evidence of benefit. We have no idea what the harms profile are. It's not being studied in the population under consideration. I think there are a lot of unknowns, and I agree with Dr. Lewis Nelson that we have a treatment that's not perfect, but we should be able to at least have comparisons to that drug.

I also think that there are ways to approach a convergence of evidence that is not presented here, so I think we were expected to make a leap of faith that I could not take; so for that reason, no.

Dr. Butler?

DR. BUTLER: Hi. Javed Butler. I voted yes for all the reasons that my other colleagues have

already mentioned. But this was a difficult decision, and this is a yes with a very strong recommendation to the regulators that a reasonable, and for some length of time, surveillance program post-approval for both clinical effectiveness and safety should be put in place so that we can get some idea post-approval.

DR. AU: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz, St. Louis, University of St. Louis. I voted yes. In terms of adding to all the previous comments, in terms of the extension, if you will, of the pharmacodynamic data to the applicability to anaphylaxis, I am mindful that in terms of cause of death from anaphylaxis, patients who have anaphylaxis from venom and medications are more likely to die from vasculature collapse and shock; so blood pressure and pulse effects, pharmacodynamically, more tie with, I think, what we would need pharmacologically.

There's no reason to think, I think, that

there would not be a benefit on respiratory status, but if you look at what is the cause of death of anaphylaxis from foods or oral ingestion, it tends to be respiratory; so that's a little caveat. I am still mindful that with Epi, I think it was 14, you had with the EpiPen a much faster spike within the first 10 minutes. And based upon that, I think, still ideally, a risk-benefit alternative would be a preference for using autoinjectable epinephrine, but I also see patients in real life, and I know that the nasal application would be preferred by many people.

The only other thought I had was we had the study looking at post-allergen challenge in allergic rhinitis patients to see what happened with epinephrine PK and PD, but we have to be mindful that in terms of rhinitis, nasal obstruction, at least a third of people who have year-round problems have non-allergic vasomotor rhinitis of some type, and there's a heterogeneity. The issue there is that I don't think there's any evidence that there's increased permeability. It

had some concerns about whether people who have nasal blockage for reasons other than allergic rhinitis would get adequate delivery, so I think a small after-approval study of that would be reassuring. Thank you.

DR. AU:

Ms. Schwartzott.

MS. SCHWARTZOTT: I'm Jennifer Schwartzott, the patient representative. I feel that the data presented was sufficient for the benefits to outweigh the risks. This is a life or death unmet need. I believe that there was more risk at not approving it than of harm coming from the drug. This gives the patients a choice. We can still choose to go with the EpiPen or we can choose to go with this new mechanism.

I would like to see postmarketing studies on the effectiveness and safety out in the real world, but I think that the benefit-risk was sufficient. Thank you.

DR. AU: Thank you.

Dr. Hovinga?

DR. HOVINGA: [Indiscernible - audio garbled].

DR. AU: Dr. Hovinga, I'm afraid we're having issues with your audio again. I'm going to ask Dr. Stevenson if we heard a sufficient amount for record.

DR. STEVENSON: Hi. This is Takyiah speaking. Just give me one moment. I believe we caught bits and pieces, but let me just confirm with our tech team if we captured -- just one moment, please. I'm sorry. Apologies.

(Pause.)

DR. AU: I appreciate the committee's endurance. This has been a long meeting, and a number of us had technical issues, so I appreciate the willingness to stay.

DR. STEVENSON: Dr. Hovinga, could you maybe reattempt one more time, at least to state your name and your vote into the record? I apologize, again, for technical difficulties.

DR. AU: Dr. Hovinga, you're on mute, still.

DR. HOVINGA: Okay. Can you hear me now?

DR. STEVENSON: Yes. Yes, we can. Thank you.

DR. HOVINGA: Okay. I switched to phone.

Collin Hovinga. I said no. I took the question very literally. I think the pharmacokinetics information was very unclear in how to interpret it with respect to its variability. But I ultimately think the dynamic information was and is compelling and suggestive of benefit. I do think if the FDA does continue to encourage approval, I would support some kind of postmarketing commitment for looking at long-term need for redosing or safety. Thank you.

DR. AU: Thank you.

The last voting question, question 3, is a voting question.

DR. STEVENSON: I do apologize, Dr. Au. Could you please summarize the committee's discussion around question 2 before continuing to question 3? A quick summary is just fine.

DR. AU: Sure.

I'm sorry. We were talking about the voting

question. I just want to confirm that, right?

DR. STEVENSON: Yes, that's correct, voting question, question number 2 regarding the results.

DR. AU: Great. I just wanted to make sure because that's not what's displayed right now for me.

We had a split vote, where the committee really did feel like there was a sufficient amount of evidence around the PK/PD data. I'm not sure anyone thought it was the perfect data. The plurality felt that the data was sufficient in lieu of the public need, and I think they are balancing that.

I do think that the people who voted no felt that the disconnect between PK/PD and clinical outcomes was insufficient for approval, and in terms of additional data, I think there was uniformity, either pre- or postmarketing, that there is additional safety data and additional data around subpopulations that need to be examined.

Let me yield back at that point, and see if that's sufficient.

(No response.)

DR. AU: Great.

DR. STEVENSON: Yes. I think that's sufficient. Thank you, Dr. Au.

DR. AU: Great. Thank you.

DR. STEVENSON: You may continue.

DR. AU: So we're in the homestretch, team.

Question number 3 is a voting question, and it reads as follows.

Do the PK/PD results support a favorable benefit-risk assessment for ARS-1 in children less than 18 years of age and greater than 30 kilograms for the emergency treatment of allergic reaction Type I in anaphylaxis? If not, what additional data are needed?

Are there any questions about the wording of this question?

(No response.)

DR. AU: If there are no further questions or no questions or comments concerning the wording of the question, we will now begin the voting on question 3.

DR. STEVENSON: We will now move non-voting participants to the breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. The voting results will be displayed.

There are 17 yeses, 5 noes, and zero abstentions. Thank you. I'll hand it back to the chair.

DR. AU: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also state the rationale for your vote; however, if you voted no, please recommend what additional data are needed.

We will start first with Dr. Stevenson's vote for Dr. Butler.

DR. STEVENSON: Yes. Hello. Apologies. Dr. Butler could not stay on late, and apologies for that. Dr. Butler has voted via email. He has voted yes. Javed Butler has voted yes, for the record. His rationale is he strongly recommends post-approval registry assessing clinical

effectiveness and safety. Thank you.

You can continue down the list, Dr. Au; appreciate it.

DR. AU: Thank you.

I that Ms. Schell has a time issue as well.

MS. SCHELL: Yes. Thank you. I voted yes. Again, I just want to state that I think it's important for this to be into the patients' and their families' hands, and hopefully the results will be more positive for them and that they can get the drug earlier. Thank you.

DR. AU: Thank you so much.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Washington, DC. I voted no for similar reasons. I just don't feel that the efficacy data was robust in the [indiscernible] population being studied. I think that there are ways, although I realize they may not be as robust as a randomized-controlled trial that we can study this particular population, and I do acknowledge that there's a tremendous unmet need for this product, particularly in the

pediatric population, and I would like to see it approved. However, if it does show that it isn't effective, once again, that could be disastrous to patients when we have a known safe and effective agent. Thank you.

DR. AU: Thank you very much.

Dr. Evans?

DR. EVANS: Hi. This is Scott Evans from MD Anderson. I voted yes for reasons previously stated. My only concern is that the number of children studies was relatively low, but there's no signal that suggested there should be a higher rate of untoward events. Thank you.

DR. AU: Dr. Dowling?

DR. DOWLING: Tom Dowling. I voted no. While I may ultimately view the preferred route of administration, in pediatrics, there's still a need for clinical efficacy data and safety data, especially with the lower PD response in the study, EPI 10, a much lower PD response than in adults. So for those reasons I voted no. Thank you.

DR. AU: Dr. May?

DR. MAY: Susanne May, University of Washington. I voted yes for similar reasons as for the adults, just noting that the need for children is even greater than in adults. Thanks.

DR. AU: Thank you.

Dr. Bacharier?

DR. BACHARIER: Len Bacharier, Vanderbilt. I voted yes due to an overall favorable benefit-risk ratio, but do support a robust post-approval surveillance program to further understand the clinical behavior. Thank you.

DR. AU: This is David Au. I voted no for similar reasons as I did with adults. I do think that with children there is potential better indication, especially among those that are needle adverse, but I also thought that the downstream risk or the downstream effects of not having efficacy data would accumulate even more, so there's more lives here lost if we are wrong. So for that reason, and because there's also available treatments, I voted no.

Dr. Peden?

DR. PEDEN: Hello Dave Peden, University of North Carolina Chapel Hill. I voted yes. I felt that the benefit-risk ratios, based on the PD and the PK data, were adequate for supporting this use in children. Thank you.

DR. AU: Thank you.

Dr. Le?

DR. LE: Hi. Jennifer Le from UC San Diego. I voted yes to approve, where I believe the benefits may be significant given the preference for children towards a needleless system. However, to ensure safe and effective use, I do recommend the FDA to not only follow up on safety via the ARS system, but also obtain effectiveness data from the sponsor postmarketing if this is approved, particularly looking into perhaps the need for urgent care visit, ED visit, hospital admissions, for example, as some of the clinical outcomes, along with the resolution of symptoms, obviously.

Now to the applicant, I recommend to complete and share your PK/PD data in children younger than 8 years and less than 3 kilos as soon

as possible, and to also investigate and take a closer look at how to conduct a clinical effectiveness and safety with severe anaphylaxis. Thank you.

DR. AU: Thank you.

Dr. Lewis Nelson?

DR. L. NELSON: Yes. Thank you. Lewis Nelson. I voted no for pretty much the reasons I stated earlier. The data presented on children were much less robust and much fewer. I think that it's a vulnerable population. We have to at least have equivalent data that we have in adults, if not a higher bar than we do. So I just don't think this is ready for prime time yet, and I'd love to see a little bit of clinical research, and even quasi clinical research that will at least give us some suggestions of what this drug would look like in a population of children with the disease of interest. Thank you.

DR. AU: Thank you.

Dr. Troendle?

DR. TROENDLE: Hello. This is James

Troendle from the National Institutes of Health. I voted yes for the same reasons as for adults, although I certainly note that a smaller number of children means the safety's not quite as clear, but I still think the benefit cost ratio is positive. Thank you.

DR. AU: Thank you.

Dr. Kelso?

DR. KELSO: As a pediatrician, I understand that children are not just little adults, but given the data that we were presented and our acceptance of the injectable route for this medication in children, which is also based on collective clinical experience and no clinical studies, I still feel that there's not any reason to believe that this would not also be effective in children.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: James Tracy, University of Nebraska. I voted yes for the reasons previously stated. I would also note that I think that the unmet need in this group is even higher than the

previous group of individuals. I do, however, recognize the relatively lower numbers that we were dealing with, but nonetheless, I think it should go for it. Thank you.

DR. AU: Thank you.

Dr. Jones?

DR. JONES: This is Bridgette Jones. I voted no. I totally agree that there is a need for a non-invasive device for use in children with anaphylaxis, and I do think that this device will help in providing something non-invasive. But I think as far as the additional unmet needs, that's still actually to be determined of whether this device will actually meet that in kids because there would still be the need for the child to carry around a device with them. And we know from experience, for even inhalers, kids don't like to carry around anything with them that would set them apart from other kids.

There's also the question of delay in use and whether this would address that. I get the fact that with administering a needle, that may

delay use, but also there has to be the decision to use the device and recognize the symptoms. So again, I'm not sure that this device would address that concern.

I think based on the PK data that we saw in adults and the similar data in kids, I have the same concerns about the delay, the first 10 minutes of the PK concentrations and potential absorption; then also the PD data in kids for me was concerning. I do recognize that kids overall will have lower systolic blood pressures and heart rates than adults, but we saw when the drug was administered, there was a decrease in those PD parameters in kids, which may have been due to their supine position, but we really don't know that. So that would make this really concerning for me in use in kids.

So I definitely think there needs to be more studies in children in a little bit larger population with a wider variability of age to make sure there aren't any age-related differences that could be impacting effect and, again, considering

clinical type endpoints in the pediatric population.

DR. AU: Great.

Dr. Greenberger?

DR GREENBERGER: I voted yes. I do believe that ARS-1 addresses the logistical issues like delays, hesitancy, and outright refusal in the use of epinephrine autoinjector, and this is extremely important. I do believe there's sufficient PK/PD information to say that, yes, there is a favorable benefit-risk assessment in this population. So I hope that the agency and the sponsor can work to get this product on the market as soon as possible.

DR. AU: Thank you.

Dr. Nelson? Michael Nelson?

DR. M. NELSON: Thank you. Michael Nelson, University of Virginia. I voted yes for the same reasons outlined in the last voting questions. It's been 36 years since the EpiPen and EpiPen Junior initial approval, with no access to other alternative treatment routes. It is my hope that this application and the conversation around it

will serve as a reset, breaking down barriers to access and use that we heard about today, and some that we didn't hear about, particularly disparities of care rooted in social determinants of health.

Whether the drug's approved or not, I think there's a real opportunity here to reset the playing field for all, and I hope the entire medical and regulatory community will take full advantage of it. Thank you.

DR. AU: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: This is Jennifer Schwartzott, the patient representative. I voted yes. The risk of unmet need was even greater in children due to the fear of the needles and just the general naivete of children. The benefits outweigh the risks of harm from the medication.

I would suggest further study for the future application for the younger children, especially in the area of inappropriate use and ingestion, and also further postmarketing studies on the pediatric population along with the adults. I just feel that

they need to keep an eye on this and make sure that we're making the right decisions. I did feel the responsibility of this decision, but I think that this need is just so great. Thank you.

DR. AU: Thank you very much.

Dr. Lee?

DR. LEE: Janet Lee from Washington University in St. Louis. In considering the totality of the data, I voted yes. In terms of the PK/PD bracketing approach and the results, I do believe that it showed favorable benefit-risk assessment. There's no reason to believe that it would be extremely different in children based on the data that was presented.

In addition, I think, like many of my colleagues who stated before, the high unmet need is even greater in the pediatric population, and I also want to echo some of the comments made by Dr. Nelson and Jennifer Schwartzott about increasing access, improving our ability to deliver medication with patient preference in mind, and hopefully the time to dosing would be reduced for

this very important issue; so thank you.

DR. AU: Thank you.

Dr. Holquin?

DR. HOLQUIN: Yes. Fernando Holquin, University of Colorado. I, too, like Dr. Lee mentioned, agree that the data presented supports a favorable risk-benefit ratio and an overwhelming need. Thank you.

DR. AU: I apologize to Dr. Dykewicz.

DR. DYKEWICZ: Mark Dykewicz, St. Louis University. I voted yes. I think all the reasons have been very well stated eloquently. One caveat is that because EPI 10 was only looking at the doses of ARS-1 and not, for instance, a direct comparison to autoinjectable epinephrine, the clinical question that remains in a pediatric population is, is this a reasonable enough alternative? I think it would be helpful, therefore, to do some comparative PK/PD studies with autoinjectable epinephrine. Thank you.

DR. AU: Thank you.

Last but not least, Dr. Hovinga.

DR. HOVINGA: Hello. Collin Hovinga, UT Austin and Critical Path Institute. I voted yes, and it may not sound as intuitive. I think the the risk-benefit for children is actually in favor more of getting this to market. I think it's a bit understated, some of the needle aversion and injury during administration of existing products, and I think that this product in particular has significant advantages over existing treatments.

But I would add to that, I echo the sentiment of others that are on this call. I do think we need to have a postmarketing commitment to look at longer term safety and use of this medication. Thank you.

DR. AU: Thank you.

I think that actually wraps up the voting. I just want to make sure I didn't miss anyone, and I'll summarize it quickly to make sure I didn't miss anyone.

In summary, the discussion was similar but not exactly the same as for adults, which is that the need is perceived to be greater in children,

and that I think led to one more vote going from no to yes. On the voting yes side, there was confidence in the PK/PD data in terms of its translation and its relation to currently existing products around Epi. Along the voting favorable, it included that there are risks associated with using the EpiPen itself, and that doesn't just relate to physical trauma, but emotional trauma as well, and it's not just to the patient, but also to the family. Those are all incredibly important issues and consideration. I think on the side of those who voted no, it was, again, the lack of efficacy data, and even a smaller data set from which to extrapolate from.

So, in totum, I think there's been a very robust discussion around the pros and cons, and I hope we have given the FDA a sufficient amount of information to help in its decision making.

Let me ask if there are any last comments from the FDA, and then I would like just to say thank you to the committee as well.

(No response.)

DR. AU: Are there any last comments from the FDA?

(No response.)

MALE VOICE: Are they still here?

(Laughter.)

DR. AU: That's what I'm wondering, too. We'll give them a minute.

DR. STEVENSON: Hello, Dr. Au. This is Takyiah speaking. I believe their hand is raised.

DR. AU: Okay.

Yes, by all means, FDA.

(No response.)

DR. AU: Well, I'll let FDA have the last word when they're able to come back on.

I just wanted to thank the committee. This has been a very robust discussion on areas that could actually be contentious in terms of clinical outcomes for very important populations. I thought the discussion was respectful and in-depth, and I really do appreciate our service to the public good, and I think that's what we're here for, and I feel like we've achieved that goal.

Let me ask if the FDA is able to comment.

DR. STEVENSON: Dr. Au, could you just give us just another moment before you adjourn. We're just trying to work out some technical difficulties with the review team. I do apologize about the delay.

DR. AU: No, we can make reference to the fact that no Zoom call can go through without dogs jumping into -- like my dog's here, and you can see how ill-disciplined my dogs are by just jumping onto the bed.

DR. STEVENSON: Just one moment. Sorry.

DR. AU: No worries.

DR. STEVENSON: The FDA team may be on mute.

(Pause.)

DR. KELSO: On question 4, I vote to meet in person in the future.

(Laughter.)

DR. AU: It would certainly eliminate some of the Zoom technicalities, although it may mean that some of us would need to fly out the next day.

MS. SCHWARTZOTT: Can I say something for a

minute while we're waiting?

DR. AU: Absolutely.

MS. SCHWARTZOTT: I want to thank everybody. As a patient rep, it's really important that we have the support of all the doctors, and the researchers, the FDA, and the companies. I mean, we need these treatments. It's really, really, really important. I also want to applaud all the patients, the parents, the doctors, and the advocates who spoke earlier. They're very brave people, and they are educated, knowledgeable advocates for themselves, including the kids, and I thought they did a wonderful job.

DR. AU: I couldn't agree more.

DR. STEVENSON: Hello. This is Takyiah speaking. The review division is still having trouble getting their audio to work. Just so we can move on, they wanted me to relay the message just to thank the panel and ARS Pharmaceuticals staff for attending today, and that is it. Thank you so much. Apologies again for the technical difficulties.

DR. AU: This is the world of Zoom.

I want to thank everyone again, and thank you especially for staying so late, especially on the East Coast, and all of us on the West Coast for getting up so early. I'm not sure when we'll see each other again, but for those of you who go to ATS, I hope to see you there.

Alright. Take care.

DR. M. NELSON: One alibi, Dr. Au. With all the thank yous, we didn't get to thank you for your leadership. I've been a former chairman of an advisory committee. Your task was very difficult, and we do appreciate your leadership today.

Adjournment

DR. AU: I appreciate that. Thank you so much.

(Whereupon, at 6:13 p.m., the meeting was adjourned.)