FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC) MEETING

Virtual Meeting

Thursday, June 8, 2023

9:30 a.m. to 4:43 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Jankowski, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

Lindsey R. Baden, MD

(Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical & Translational Science
University of Pittsburgh School of Medicine
Division of Infectious Diseases
Director, Antimicrobial Stewardship & Infection Prevention
Co-Director, Transplant Infectious Diseases
Children's Hospital of Pittsburgh Pittsburgh, Pennsylvania

W. David Hardy, MD, AAHIVS

Attending, Rand Schrader (HIV) Clinic
Adjunct Clinical Professor of Medicine
Division of Infectious Diseases
Keck School of Medicine of University of Southern California
Los Angeles, California

Sally A. Hunsberger, PhD

Biostatistician

Biometrics Research Branch

National Institute of Allergy and Infectious Diseases (NIAID)

National Institutes of Health (NIH)

Rockville, Maryland

Ighovwerha Ofotokun, MD, MSc

Professor of Medicine

Division of Infectious Diseases

Emory University School of Medicine

Infectious Disease Specialist

Grady Memorial Health System

Atlanta, Georgia

Nimish Patel, PharmD, PhD

Professor of Clinical Pharmacy

Skaggs School of Pharmacy and Pharmaceutical Sciences

University of California San Diego, Division of Clinical Pharmacy

La Jolla, California

Federico Perez, MD, MS

Infectious Disease Physician

Louis Stokes Cleveland VA Medical Center

Associate Professor of Medicine

Case Western Reserve University

Cleveland, Ohio

George K. Siberry, MD, MPH

Senior Clinical Advisor to the Director

Office of HIV/AIDS

Bureau of Global Health

United States Agency for International Development

Washington, District of Columbia

Roblena E. Walker, PhD

(Consumer Representative)

Chief Executive Officer

EMAGAHA, INC.

Mableton, Georgia

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Richa S. Chandra, MD, MBA

(Industry Representative)

Clinical Development Head

Communicable Diseases

Global Health Development Unit

Novartis Pharmaceuticals

East Hanover, New Jersey

TEMPORARY MEMBERS (Voting)

Mary Cataletto, MD, MMM

(Retired February 2023)

Clinical Professor of Pediatrics

NYU Langone School of Medicine

Pediatric Pulmonologist

NYU Health

Mineola, New York

Douglas S. Diekema, MD, MPH

Professor of Pediatrics and Bioethics & Humanities

University of Washington School of Medicine

Director of Education, Treuman Katz Center for Pediatric Bioethics

Seattle Children's Research Institute

Seattle, Washington

Peter L. Havens, MD, MS

Professor Emeritus, Pediatrics

(Infectious Diseases)

Medical College of Wisconsin

Children's Wisconsin

Milwaukee, Wisconsin

Rohan Hazra, MD

Director, Division of Extramural Research

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NIH

Bethesda, Maryland

Mary Anne Jackson, MD, FAAP, FIDSA, FPIDS

Dean and Professor of Pediatrics

Children’s Mercy, Kansas City

University of Missouri-Kansas City

School of Medicine

Kansas City, Missouri

Karen L. Kotloff, MD

John A. Scholl, MD and Mary Louise Scholl, MD
Distinguished Professor
Head, Infectious Disease and Tropical
Pediatrics, and Associate Director Clinical
Research
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland

Steven Krug, MD

Professor of Pediatrics
Northwestern University Feinberg
School of Medicine
Prior Head, Division of Emergency Medicine
Ann & Robert H. Lurie Children's Hospital of
Chicago
Chicago, Illinois

Tamorah Lewis, MD, PhD

Division Head, Clinical Pharmacology & Toxicology

Staff Neonatologist

The Hospital for Sick Children

Associate Professor, Department of Paediatrics

University of Toronto Temerty Faculty of Medicine

Toronto, Ontario

Meredith McMorrow, MD, MPH

CAPT, US Public Health Service

Acting Branch Chief

Surveillance and Prevention Branch

Coronavirus and Other Respiratory Viruses Division

National Center for Immunization and Respiratory Diseases

U.S. Centers for Disease Control and Prevention

Atlanta, Georgia

Stacey Stokes, MD, MPH

Assistant Professor, Pediatric Hospital Medicine,
George Washington University
Medical Director of Informatics, Children's
National Hospital
Washington District of Columbia

Jasmine Shackleford Thomas

(Patient Representative)
Patient Advocate
Lupus and Allied Diseases Association, Inc.
Waldorf, Maryland

Benjamin Wilfond, MD

Professor, Divisions of Bioethics and Palliative
Care & Pulmonary and Sleep Medicine,
Department of Pediatrics, University of Washington
School of Medicine
Seattle, Washington

FDA PARTICIPANTS (Non-Voting)

John Farley, MD, MPH
Director
Office of Infectious Diseases (OID)
Office of New Drugs (OND), CDER, FDA

Yodit Belew, MD
Associate Director for Therapeutic Review
Division of Antivirals (DAV)
OID, OND, CDER, FDA

Melisse Baylor, MD
Clinical Reviewer
DAV, OID, OND, CDER, FDA

Justin Earp, PhD
Pharmacometrics Reviewer
Division of Pharmacometrics
Office of Clinical Pharmacology (OCP)
Office of Translational Science (OTS)
CDER, FDA

Neha Gada, PharmD, BCPS

Cross Discipline Safety Advisor

Office of Pharmacovigilance and Epidemiology

Office of Surveillance and Epidemiology

CDER, FDA

Anna Kettermann, Dipl.-Math, MA

Statistics Reviewer

Division of Biostatistics IV

Office of Biostatistics

OTS, CDER, FDA

Yang Zhao, PhD

Clinical Pharmacology Reviewer

Division of Infectious Disease Pharmacology

OCP, OTS, CDER, FDA

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

(9:30 a.m.)

Call to Order

DR. BADEN: 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 currently displayed.

My name is Dr. Lindsey Baden, and I will be chairing this meeting. I will now call the June 8, 2023 Antimicrobial Drug Advisory Committee meeting to order. Dr. Jankowski is the designated federal officer for this meeting and will begin with introductions. We'll first start with the standing members of the AMDAC Committee?

Introduction of Committee

DR. JANKOWSKI: Thank you, Dr. Baden.

Good morning. My name is She-Chia Jankowski, and I am the designated federal officer, DFO, for this meeting. When I call your name, please unmute yourself and turn on your camera. Please introduce yourself by stating your name and

affiliation for the record.

We'll first start with AMDAC voting members.

Dr. Baden?

DR. BADEN: I'm Dr. Lindsey Baden. I'm an infectious diseases specialist in Boston at Brigham and Women's, Dana-Farber, and Harvard Medical School. Thank you.

DR. JANKOWSKI: Dr. Green?

DR. GREEN: Good morning. My name is Michael Green. I am a pediatric infectious disease specialist at the UPMC Children's Hospital Pittsburgh, University of Pittsburgh School of Medicine. Thank you.

DR. JANKOWSKI: Dr. Hardy?

DR. HARDY: Good morning. My name is Dr. David Hardy. I am an attending physician at the LA County USC Medical Center here in Los Angeles, and I apologize; my camera's not turning on for some reason, but I am here.

DR. JANKOWSKI: Great.

Dr. Hunsberger?

DR. HUNSBERGER: Good morning. I'm Sally

Hunsberger. I'm a biostatistician at NIAID at NIH. Thank you.

DR. JANKOWSKI: Dr. Ofotokun?

DR. OFOTOKUN: Good morning, everybody. My name is Igho Ofotokun. I am an adult infectious disease specialist at Emory University School of Medicine, Atlanta, Georgia. Thank you.

DR. JANKOWSKI: Dr. Patel?

DR. PATEL: Good morning, everyone. My name is Nimish Patel. I am a full professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California San Diego. I'm an infectious diseases pharmacist and pharmacoepidemiologist.

DR. JANKOWSKI: Dr. Perez?

DR. PEREZ: Good morning. I'm Federico Perez. I'm an adult infectious diseases specialist at Case Western Reserve University and at Northeast Ohio Veterans Healthcare Administration System in Cleveland, Ohio. Thank you.

DR. JANKOWSKI: Dr. Siberry?

DR. SIBERRY: Good morning. I'm George

Siberry, pediatric infectious disease physician and chief medical officer at the Office of HIV/AIDS, United States Agency for International Development. Thanks.

DR. JANKOWSKI: And Dr. Walker?

DR. WALKER: Good morning. I am Dr. Roblena Walker, chief executive officer for EMAGAHA, Inc., and also the consumer representative in Atlanta, Georgia. Thank you.

DR. JANKOWSKI: Next is AMDAC non-voting member, industry representatives, Dr. Chandra.

DR. CHANDRA: Good morning. I am Richa Chandra. I am working as the clinical development head at Novartis for infectious diseases, and today I am representing industry on this advisory committee meeting. Thank you.

DR. JANKOWSKI: Then we have temporary voting members.

Dr. Cataletto?

DR. CATALETTO: Good Morning. My name is Mary Cataletto. I am recently retired from NYU, Long Island School of Medicine after 34 years of

clinical practice. I retired as full professor of pediatrics, and I'm very happy to be here. Thank you.

DR. JANKOWSKI: Dr. Diekema?

DR. DIEKEMA: Good morning. I'm Doug Diekema. I do pediatric emergency medicine and bioethics at the University of Washington and Seattle Children's Hospital.

DR. JANKOWSKI: Dr. Havens?

DR. HAVENS: I'm Peter Havens, recently retired from pediatric infectious diseases at the Medical College of Wisconsin and Children's Wisconsin in Milwaukee.

DR. JANKOWSKI: Dr. Hazra?

DR. HAZRA: Good morning. I'm Rohan Hazra. I'm a pediatric infectious disease physician by training and the director of the Division of Extramural Research at the Child Health Institute at NIH.

DR. JANKOWSKI: Dr. Jackson?

DR. JACKSON: Good morning. I'm Mary Anne Jackson. I'm a pediatric infectious disease doctor

at Children's Mercy Hospital and a professor of pediatrics at the University of Missouri, Kansas City School of Medicine.

DR. JANKOWSKI: Dr. Kotloff?

DR. KOTLOFF: Good morning. I'm Karen Kotloff. I'm head of pediatric infectious disease at the University of Maryland School of Medicine and associate direct the Center for Vaccine Development.

DR. JANKOWSKI: Dr. Krug?

DR. KRUG: Hey. Good morning. My name is Steve Krug. I'm a pediatric emergency medicine specialist. I work at the Ann & Robert H. Lurie Children's Hospital of Chicago, and I'm a professor of pediatrics at the Northwestern University Feinberg School of Medicine.

DR. JANKOWSKI: Dr. Lewis?

DR. LEWIS: Good morning. I'm Tamorah Lewis. I'm a neonatologist and pediatric clinical pharmacologist at Sick Kids in Toronto, Ontario.

DR. JANKOWSKI: Dr. McMorrow?

DR. McMORROW: Hi. I'm Dr. Meredith

McMorrow. I'm a pediatrician and epidemiologist at the U.S. Centers for Disease Control and Prevention in the Coronavirus and Other Respiratory Viruses division.

DR. JANKOWSKI: Dr. Stokes?

DR. STOKES: Good morning. I am Dr. Stacey Stokes. I am a pediatric hospitalist at Children's National in Washington DC and an assistant professor of pediatrics at GW University.

DR. JANKOWSKI: Ms. Thomas?

MS. SHACKLEFORD THOMAS: Hi. My name is Jasmine Thomas. I'm a patient representative with the Lupus and Allied Diseases Association based out of Verona, New York.

DR. JANKOWSKI: And Dr. Wilfond?

DR. WILFOND: Good morning. I'm Ben Wilfond. I am a pediatric pulmonologist at Seattle Children's University of Washington. I'm also an investigator at the Treuman Katz Center for Pediatric Bioethics, and my clinical practice is focused exclusively on children's chronic lung diseases of prematurity.

DR. JANKOWSKI: Thank you.

Finally, we have FDA participants, non-voting.

Dr. Farley?

DR. FARLEY: Good morning. I'm John Farley, director of the Office of Infectious Diseases in the Office of New Drugs, Center for Drug Evaluation and Research, FDA.

DR. JANKOWSKI: Dr. Belew?

DR. BELEW: Good morning. My name is Yodit Belew. I'm the associate director for therapeutic review in the Division of Antivirals, Office of Infectious Diseases, CDER, FDA.

DR. JANKOWSKI: Dr. Baylor?

DR. BAYLOR: Good morning. I'm Melisse Baylor, clinical reviewer in the Office of New Drugs, Division of Antiviral Products.

DR. JANKOWSKI: Dr. Earp?

DR. EARP: Good morning. I'm Justin Earp. I'm the pharmacometrics division team lead and I'm the pharmacometrics reviewer for this application.

DR. JANKOWSKI: Dr. Gada?

DR. GADA: Good morning. I'm Neha Gada. I work in the Office of Surveillance and Epidemiology as a cross-discipline safety advisor.

DR. JANKOWSKI: Dr. Kettermann?

DR. KETTERMANN: Good morning. My name is Anna Ketterman, and I'm a statistician in the Office of Biostatistics in CDER, FDA.

DR. JANKOWSKI: And Dr. Zhao?

DR. ZHAO: Good morning. I'm a clinical pharmacologist in the Office of Clinical Pharmacology, CDER, and I'm the clinical pharmacology reviewer for this BLA. Thank you.

DR. JANKOWSKI: Thank you, everyone.

Now back to you, Dr. Baden.

DR. BADEN: Thank you. I'd like to remind panel members to turn off their cameras and microphones when they are not speaking.

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 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 the 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 please refrain from discussing the meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. JANKOWSKI: Thank you, Dr. Baden.

The Food and Drug Administration, FDA, is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, 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 biologics license application, BLA, 761328, for nirsevimab, a long-acting respiratory syncytial

virus, RSV, F protein inhibitor monoclonal antibody for intramuscular use, submitted by AstraZeneca AB. The proposed indication is prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. This is a particular matters meeting during which specific matters related to AstraZeneca's BLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Lindsey Baden and Ighovwerha Ofotokun.

Dr. Baden's waiver covers his employer's license for patents used for a competing product. Dr. Baden is not aware of the funding amount being provided to his employer for this license. Dr. Ofotokun's waiver covers his employer's license for proprietary RSV technologies used for a

competing product. Dr. Ofotokun is not aware of the funding amount being provided to his employer for this license.

The waivers allow these individual to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-267.

To ensure transparency, we encourage all standing committee 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. Richa Chandra is participating in this meeting as a non-voting

industry representative, acting on behalf of regulated industry. Dr. Chandra's role at this meeting is to represent industry in general and not any particular company. Dr. Chandra is employed by Novartis Pharmaceuticals.

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 other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

Back to you, Dr. Baden

DR. BADEN: We will now proceed with the with FDA opening remarks from Dr. John Farley.

Dr. Farley?

FDA Opening Remarks - John Farley

DR. FARLEY: Good morning. I am John

Farley, and I'll be giving the FDA opening remarks. Today the FDA is convening this advisory committee to discuss whether the available data support an overall favorable benefit-risk assessment for the use of nirsevimab for prevention of respiratory syncytial virus, or RSV, lower respiratory tract disease in neonates and infants born during or entering their first RSV season, as well as in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Nirsevimab is a monoclonal antibody directed against the prefusion conformation of the RSV fusion, or F protein, which is required for cell entry. The mechanism of action of nirsevimab is passive immunity. It is not a vaccine and it is being regulated as a drug. The proposed indication is prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, as well as children up to 24 months of age who remain vulnerable to severe RSV disease through their

second RSV season. The proprietary name is Beyfortus, which has been conditionally granted.

The proposed dosing for the first RSV season is a single 50-milligram intramuscular, or IM, injection for infants weighing less than 5 kilograms, and a single 100-milligram IM injection for infants weighing 5 kilograms and greater. For children less than 24 months of age, who remain at increased risk for severe RSV disease in their second RSV season, the proposed dose is a single 200-milligram IM injection. For the purposes of today's discussions, we will define an infant as a child not more than 12 months of age.

In terms of other drugs or biologics for prevention of RSV disease in the U.S., palivizumab is an FDA-approved monoclonal antibody for prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. It is indicated for use in infants with a history of premature birth that is less than or equal to 35 weeks gestational age; children with chronic like lung disease of prematurity; and

children with hemodynamically significant congenital heart disease. It is administered monthly during the RSV season. There are multiple RSV vaccines currently in clinical development for both maternal immunization and for immunization of infants and children.

We'll be discussing three major clinical trials today. The first is Trial 03, a double-blind, placebo-controlled trial, which evaluated the safety and efficacy of nirsevimab for the prevention of medically attended respiratory syncytial virus lower respiratory tract infection -- so we will abbreviate that MA RSV LRTI -- and infants born at greater than or equal to 29 weeks to less than 35 weeks of gestation, who were born during or entering their first RSV season.

Trial 04 was a double-blind, placebo-controlled trial, which also evaluated the safety and efficacy of a single dose of nirsevimab for the prevention of MA RSV LRTI. Trial 04 enrolled infants born at greater than or equal to

35 weeks of gestation who were born during or entering their first RSV season.

Trial 05 is a double-blind, active-controlled trial, which compared the safety of nirsevimab versus palivizumab in infants at high risk of severe RSV disease; the premature infants born at less than 35 weeks of gestation; infants with chronic lung disease of prematurity; or hemodynamically significant congenital heart disease.

I'd like to highlight two regulatory considerations this morning. The first is data pooling. Trial 04, which enrolled infants born at greater than or equal to 35 weeks of gestation, had an enrollment pause related to COVID-19 after enrolling approximately 1500 children.

In addition, the agency had requested a safety database of approximately 3,000 children considering all trials. Patients enrolled prior to this pause are referred to as the primary cohort. Patients enrolled after the pause are referred to as the safety cohort. The statistical analysis

plan for Trial 04 prespecified the primary analysis for efficacy would be conducted in the primary cohort. While analyses pooling the primary cohort and safety cohort may be helpful for subgroup analyses, the agency regards such analyses as exploratory.

Relevant to Trial 05, extrapolation of efficacy is an explicit authority granted to the agency in the pediatric setting. It was first introduced in 1994. Regulations describe the evidence needed for extrapolation of efficacy based on adult studies as follows: pediatric use statement may also be based on adequate and well-controlled studies in adults provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients.

Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage and additional pediatric safety information must

also be submitted. The Pediatric Research Equity Act of 2003 addressed extrapolation of efficacy from one pediatric age group to another, utilizing the same principles and stating that a study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group.

We'll be asking the committee to address four questions today. The first is a voting question. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season?

The second is a discussion question. We'll ask you to comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Please discuss the population or subpopulation for whom nirsevimab administration in the first RSV season would be most appropriate.

The third question is a voting question. Is

the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season?

And the last question is a discussion question. In the context of potential, future availability of maternal RSV disease to protect infants from RSV disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who received RSV vaccination?

I want to conclude by thanking the committee for the time you took to prepare for this meeting and for the advice that we'll receive today.

Back to you, Dr. Baden

DR. BADEN: Thank you, Dr. Farley.

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 the AstraZeneca 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 upon 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 AstraZeneca's presentations. Dr. Villafana will lead the presentation, and I assume, Dr. Villafana, that you will choreograph the different presentations for the applicant.

I will give you the floor.

Applicant Presentation - Tonya Villafana

DR. VILLAFANA: Good morning. Yes, and I confirm that I will choreograph the presentations from the sponsor.

Good morning, members of the advisory committee, FDA, and guests. I'm Tonya Villafana, global franchise head in Vaccines and Immune Therapies at AstraZeneca. We are grateful for the opportunity to present our data today in support of the positive benefit-risk of nirsevimab. We will describe the strong efficacy and safety profile of nirsevimab across infant populations, from healthy term and preterm infants, to those who are most vulnerable for serious outcomes due to RSV disease.

With many others at AstraZeneca, I have had the privilege to lead the development of nirsevimab for the past decade. Nirsevimab has been authorized for use in Europe, Great Britain, and Canada, and is currently under review globally, including in Japan and China.

RSV is a major unmet public health need in

infants and children globally. It comes in seasonal epidemics in the Northern Hemisphere and is the most common cause of acute lower respiratory tract infection in infants and children. In addition to the outpatient burden, RSV is the major reason for hospital admissions in infants and young children globally, regardless of national economic status.

Premature infants and those with underlying lung or heart disease are at highest risk of severe illness. For those infants, the only approved prophylaxis is palivizumab, which requires monthly dosing to provide protection through a season. Importantly, most medically attended RSV cases occur in otherwise healthy term infants for whom there is no effective RSV prevention licensed in the United States.

The pyramid on this slide illustrates the significant burden of RSV disease in the U.S. in the first year of life, which is when the disease is of primary concern. Every year in the U.S., there are over 500,000 medically attended RSV

infections, which lead to approximately 400,000 office or clinic visits. Approximately 150,000 infants will be seen in the emergency department and 33[000] to 80,000 will be admitted to the hospital. This creates a significant burden on hospitals and families, particularly during the height of the RSV season, which typically overlaps with the influenza season in the winter months.

Because those infants generally receive excellent supportive care, the number of deaths is small compared to the rest of the world, and sadly the majority of deaths occur in infants at highest risk of severe RSV disease. It's important to remember that almost three-quarters of hospitalizations and two-thirds of ICU admissions for RSV occur in healthy term infants in their first year of life.

Also, the most vulnerable infants with certain conditions, such as congenital heart disease and chronic lung disease of prematurity, remain at significant risk in their second year of life and need protection. Last, the burden of RSV

is exemplified by the most recent RSV season, where we saw many hospitals overburdened by RSV and ICUs at full capacity.

It has been a long road to developing an effective prevention to address the unmet medical need in a broad infant population. RSV was first discovered in the 1950s, and the first RSV vaccine trial of a formalin-inactivated vaccine was conducted in the mid-60s. However, that vaccine caused enhanced disease in seronegative children who were subsequently exposed to RSV and resulted in the death of 2 infants, which dramatically impeded subsequent vaccine development of active immunizations directly to the infant.

In the mid '80s, the first studies demonstrating passive immunization with an antibody were completed, and this led to the development of RSV-IVIG and its approval in 1996. Next came the approval of palivizumab in 1998, which targets the RSV F fusion protein. In 2013, the conformational mapping of the prefusion F protein by Jason McLellan and Barney Graham's group at the NIH

revolutionized the field, identifying important epitopes on prefusion F, including site 0, which nirsevimab targets. The first clinical trials of nirsevimab began in 2014.

Nirsevimab represents our commitment to finding a solution for RSV prevention in all infants and builds on our 25-year history of development in this space, including palivizumab, which has been given to millions of infants worldwide. We have demonstrated that passive immunization with a monoclonal antibody is a safe and effective approach to preventing RSV disease.

Nirsevimab was made possible by advances in technology, including the ability to isolate highly potent neutralizing antibodies from human B cells; select conserved epitopes through mapping of the crystal structure; and extending the half-life of antibodies. Those advances have translated into a product profile with potential advantages, including rapid onset of protection, coverage for an entire RSV season with a single fixed dose, and well-defined levels of neutralizing antibody.

Nirsevimab meets the desired product profile. It is a highly potent, recombinant, human IgG1 kappa monoclonal antibody that targets site 0, a highly conserved epitope on the prefusion RSV F protein, and it has a prolonged serum half-life. Nirsevimab binds to site 0, locks the F protein in the prefusion conformation, thereby inhibiting the essential membrane fusion step in the viral entry process. It directly neutralizes RSV and blocks cell-to-cell fusion.

Importantly, regardless of when the infant is born, nirsevimab directly administered to the infant provides the opportunity for flexible, rapid, and sustained protection throughout the entire RSV season, with a single fixed intramuscular dose of a potent monoclonal antibody.

The key regulatory milestones for nirsevimab are illustrated on this slide. We conducted a comprehensive and thorough clinical development program in close collaboration with the FDA and other regulatory authorities. We've also had extensive interactions with the Advisory Committee

on Immunization Practices, shown by the gold triangles on the slide, and nirsevimab received fast-track and breakthrough therapy designations.

There are 4 main studies in the nirsevimab clinical development program supporting licensure, three pivotal studies and one supportive. We conducted two randomized, placebo-controlled efficacy studies, Trial 03 and Trial 04, in healthy preterm and term infants. These studies differ only in the infant populations that were studied. They had similar designs and they evaluated similar endpoints.

We also conducted a randomized study in infants with significant underlying medical conditions who were eligible for palivizumab called Trial 05, and an ongoing open-label, single-arm, phase 2 study in immunocompromised children called Trial 08. For these studies, efficacy extrapolation was based on PK. Taken together, these studies span the entirety of the infant population. In addition, we have an ongoing real-world study in Germany, France, and the UK

called HARMONIE, which looks at prevention of hospitalization due to RSV.

A clinical development program supports the proposed indication we are seeking for nirsevimab. We are proposing nirsevimab for the prevention of respiratory syncytial virus lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and in children up to 24 months of age who remain vulnerable to RSV disease through their second RSV season.

Nirsevimab can provide direct protection of infants through their first RSV season regardless of the time of year they are born. Infants born outside of the RSV season, such as April through October, would receive nirsevimab at the beginning of the season during a routine well-baby visit in the pediatrician's office. Infants born during the RSV season, such as November through March, would receive nirsevimab at birth before discharge from the hospital.

This simple vaccine-like implementation strategy, which delivers a 50-mg dose to infants

less than 5 kg and a 100-mg dose for infants greater than or equal to 5 kg, provides protection to all infants with a single intramuscular injection, and this strategy offers an advantage to palivizumab-eligible infants. For infants who remain vulnerable to RSV disease entering their second season, a 200-milligram dose prior to the start of the season will deliver protection.

This slide outlines what you will hear today. Dr. Amanda Leach from AstraZeneca will cover the clinical efficacy of nirsevimab. Our data demonstrate that nirsevimab achieved clinically meaningful efficacy across the spectrum of disease severity in a broad range of infants, and the data showed that a single dose is efficacious for a minimum of 5 months.

Dr. Manish Shroff will present the clinical safety data, which shows that the overall safety profile of nirsevimab is favorable across the populations studied. Dr. William Muller from Northwestern University will provide his clinical perspective on the unmet need and his view that the

data support the use of nirsevimab for all infants entering their first RSV season and high-risk children in their second RSV season. And finally, I will summarize the benefit-risk of nirsevimab in the proposed indication, based on the totality of the data, which shows that nirsevimab provides consistent rapid and durable protection from RSV LRTI with a single dose and a favorable safety profile.

In addition to the presenters, the individuals shown here will be available today to respond to questions, and now I will turn it over to Dr. Leach.

Applicant Presentation - Amanda Leach

DR. LEACH: Thank you, Dr. Villafana.

I'm Amanda Leach, global clinical head for nirsevimab at AstraZeneca. Today, I'll review the clinical development program and efficacy data for nirsevimab from the placebo-controlled trials in healthy infants, and followed by the extrapolation of efficacy to vulnerable populations based on PK data.

The efficacy profile of nirsevimab was evaluated in two double-blind, randomized, placebo-controlled trials in healthy preterm and term infants. Trial 03 was a phase 2B trial conducted in infants who were born from 29 up to 35 weeks gestational age. The sample size was 1,500 infants. Trial 04 was a phase 3 conducted in infants who were born term and late preterm from 35 weeks gestational age. It was intended to enroll a total of 3,000 infants.

Apart from the gestational age at birth, both studies had near identical designs. Infants were randomized 2 to 1, nirsevimab or placebo, and dosed prior to the onset of their first RSV season. Efficacy was established over the 5-month period of the RSV season. Safety, PK, and ADA were assessed through day 361.

In addition, in Trial 04, children were monitored for RSV disease through their second season without re-dosing. These two studies were also similar with respect to case definitions, disease surveillance procedures, and statistical

methods of analysis. This was done from the outset to allow comparison of results between studies.

Here is the primary case definition of medically attended RSV LRTI, which was specific and represents significant clinical disease. It was developed in consultation with leading experts in the field and was discussed and agreed with the FDA. Every case was presented for care by their parents or guardians, and this is the medical attendance component of the definition. The case should be RSV positive by a central laboratory PCR assay and have a sign of low respiratory tract involvement on chest auscultation. In addition, there should be at least one sign of disease severity present, as is listed on this slide.

The secondary endpoint was RSV LRTI with hospitalization. The attending physician made the decision which cases needed to be hospitalized in line with the local or national guidelines. These guidelines were evidence driven and broadly similar across sites. They required evidence of significant respiratory distress, hypoxia, or

reduced capacity to feed.

We also introduced another case definition, very severe RSV LRTI. This was added as an exploratory endpoint in response to regulatory authorities' requests for definition of severe disease, applying objective criteria. Very severe disease corresponds to the subset of hospitalized infants who required supplemental oxygen or IV fluids. Efficacy analyses were done according to the intention-to-treat principle using a Poisson regression model with robust variance. This slide summarizes our statistical approach.

Next, I'll focus on the results of Trial 03. This trial enrolled preterm infants born from 29 up to 35 weeks gestational age. The infants were otherwise healthy and were not eligible to receive palivizumab under local practice guidelines. In total, 1,453 infants were enrolled. All demographic factors were balanced between placebo and nirsevimab arms.

You can see there was good representation across the gestational age range. Fifty-three

percent were less than or equal to 3 months of age at randomization and the arms were balanced for sex. Approximately 70 percent of the study was white and 20 percent were of Hispanic or Latino ethnicity, and approximately 60 percent weighed less than 5 kilograms.

Moving now to the results of Trial 03, the primary endpoint was met. Efficacy was estimated to be 70.1 percent with a lower bound of the confidence interval above 50 percent and a highly significant p-value. For the secondary endpoint of medically attended RSV LRTI with hospitalization, the efficacy estimate was 78.4 percent, which was again highly statistically significant. For very severe RSV LRTI, the estimate was consistent at 87.5 percent.

The subgroup for analysis of medically attended RSV LRTI in the Trial 03 ITT population showed clinically meaningful estimates of efficacy across subgroups that were consistent with the overall results, which is shown at the top of the slide. However, we observed a trend to lower

efficacy in the subgroup weighing 5 kilograms or more at dosing, so we conducted a post hoc exposure-response analysis and observed a trend towards lower efficacy in infants with the lowest nirsevimab serum exposures. Nirsevimab serum exposure is correlated with body weight, and as you can see in this figure, infants weighing 5 kilograms or more had substantially lower exposure to nirsevimab after receiving a 50-milligram dose.

Therefore, the decision was taken to optimize the dose for infants weighing 5 kilograms or more by increasing their dose to 100 milligrams, and this is the basis for the weight-banded dosing strategy, which was evaluated in all studies going forward.

We reanalyzed efficacy in the cohort of infants in Trial 03 who were less than 5 kilograms at randomization, and therefore was considered adequately dosed. We termed this the proposed dose cohort. In this exploratory analysis, the efficacy estimates for medically attended RSV LRTI was

86.2 percent, with similarly high efficacy estimates against hospitalization and very severe RSV disease.

Now, I'd like to turn your attention to Trial 04. Trial 04 was the phase 3 trial conducted in term and late preterm infants. Enrollment began in the Northern Hemisphere in 2019. Shortly afterwards, the COVID-19 pandemic was declared at the beginning of 2020, and the onset of the pandemic led to several operational challenges and a decline in RSV incidence; therefore, we took the decision to pause enrollment to the trial.

We were faced with difficult choices. It was a period of uncertainty, and we sought to protect the primary endpoint of the trial. We consulted with the FDA, and agreement was reached to analyze the primary endpoint based on the first 1,490 infants enrolled at that time. This was termed the primary analysis and the primary cohort. We began to enroll the remainder of infants to the safety cohort in the Southern Hemisphere by the 2021 season. By this time, the restrictions

associated with the COVID-19 pandemic were being eased, and RSV transmission was occurring, albeit with some atypical seasonality. Of note, both cohorts were conducted in a fully double-blind manner.

So here are the demographics for Trial 04 primary cohort. All the demographic factors were balanced between placebo and nirsevimab arms. Approximately 85 percent of the infants were born at term. Fifty-eight percent of infants were less than or equal to 3 months of age at randomization, and the trial was racially diverse. Approximately 50 percent were white, and a quarter were black or African American, and about 10 percent of infants were Hispanic or Latino ethnicity.

Shown here is the primary analysis conducted on the primary cohort. Trial 04 met its primary endpoint, demonstrating 74.5 percent efficacy against medically attended RSV LRTI, with a lower bound of the confidence interval close to 50 percent and a significant p-value. However, due to the extraordinary circumstances of the pandemic,

the secondary endpoint was impacted by the reduced sample size and the low number of events.

For RSV LRTI with hospitalization, there were only 8 events in the placebo arm and 6 events in the nirsevimab arm. Remembering the 2 to 1 randomization, this translated to a point estimate of 62.1 percent efficacy, but the confidence interval was broad and overlapped zero. The analysis did not meet statistical significance. The exploratory endpoint of very severe RSV LRTI was similarly impacted by the low number of events.

Here's the subgroup analysis for medically attended RSV LRTI. Shown at the top is the overall result showing 74.5 percent efficacy, and although we did see some heterogeneity, we observed clinically meaningful efficacy across subgroups consistent with the overall result.

Now, if I may, I'd like to consider what information on efficacy is available from the safety cohort, and first to look at the demographics. As you can see, they were similar between the two cohorts with gestational age at

birth, age, and sex. The difference in racial and ethnic breakdown reflects that for the safety cohort, we enrolled from Latin America but not South Africa.

Now looking at the comparison of the results from the safety cohort with those in the primary cohort, you'll notice similar disease incidence of medically attended RSV LRTI in the placebo arm of both cohorts being 5 percent and 5.7 percent, respectively. The estimates of efficacy against medically attended RSV LRTI are very similar, which strongly supports the consistency of effect and the validity of analyzing the two cohorts together.

There were 14 cases of hospitalization observed in the primary cohort and an additional 15 in the safety cohort. The point estimates are 62.1 percent and 86.2 percent, respectively, and the confidence intervals of both include the estimate effect of the other. Sites enrolling in both cohorts followed formalized local criteria for admitting children with RSV LRTI.

The hospitalization rates of cases of

medically attended RSV LRTI were similar between cohorts, being around 30 percent of cases admitted. Therefore, the observed differences in point estimates may be explained by the small number of events that occurred in each of the cohorts. Here now, combining the two as the all subject analysis, we see an estimate effect of efficacy of 76.8 percent against RSV LRTI with hospitalization, with a confidence interval extending from 49 to 89 percent.

I'd like to take a moment to explain why we believe this exploratory data showing efficacy against RSV hospitalization in term infants is of high relevance for healthcare providers. The COVID-19 pandemic was an exceptional situation, and we did everything we could to ensure safety of participants and robustness of data. This was one trial that was divided in two by the pandemic.

The all subject data is the trial as it was originally designed and is the largest data set for the analysis of less frequent events. There was robust data collection in both cohorts in a

double-blind manner. We've seen that the populations were consistent and admission practices to hospital were consistent between the two cohorts, and the results of the all subject analysis are highly consistent with Trial 03, which looked at preterm infants. There is no biological mechanism to presuppose efficacy would be different in term and preterm infants, so we believe that the all subject analysis provides important information for healthcare providers and for families.

This shows the duration of efficacy over 150 days in Trial 03, ITT on the left and the primary and safety cohorts of Trial 04 on the right. The takeaway from these, that the curves diverge over the full-time period of observation, leading to a conclusion of consistent efficacy over 150 days. And shown here are the results of efficacy against medically attended RSV LRTI for RSV subtypes A and B in Trial 03 ITT and Trial 04 all subject cohorts. As you can see, there was consistent efficacy demonstrated against both subtypes.

Finally, I'd like to briefly touch on another important exploratory endpoint that we assessed in the placebo-controlled trials all-cause respiratory illness. In Trial 03 ITT cohort and Trial 04 all subject analysis, there is a demonstrably efficacy both against all-cause medically attended LRTI and respiratory illness with hospitalization. We have shown the consistent strong efficacy of nirsevimab against RSV disease, and now this evidence of effect against all-cause disease is strongly reassuring of the overall benefit of nirsevimab.

Turning now to high-risk infants and children who remain vulnerable to RSV disease in their second season, as agreed with the FDA, efficacy in vulnerable populations may be established through a PK bridge to the clinical efficacy studies.

This shows the design of Trial 05. Prior to their first RSV season, preterm infants and infants with CHD or CLD were randomized 2 to 1 to nirsevimab or palivizumab. In the second season,

children with CHD or CLD who received nirsevimab in the first season received a repeat dose in the second season. Those receiving palivizumab in their first season were re-randomized to either nirsevimab or palivizumab in the second season, and the second dosage was 200 milligrams. The primary endpoint for the study was safety. PK was a secondary endpoint to support the efficacy extrapolation. Safety, PK, and ADA were assessed through day 361 in both Season 1 and Season 2.

This slide shows the PK results of Trial 05. These graphs show mean serum concentrations over time, with Season 1 on the left and Season 2 on the right. For efficacy extrapolation, we are focusing on serum concentrations at the end of the season, day 151.

Here you can see the nirsevimab serum concentrations at day 151, focusing on the subgroups of interest and directly comparing them to the concentrations in the efficacy Trial 04, which is represented by the shaded bar going across. All subgroups achieved similar serum

exposures compared to Trial 04 in Season 1 and slightly higher exposures in Season 2. Based on these results, efficacy against RSV disease is expected in the Trial 05 study population.

The study was not designed to estimate efficacy, but cases of medically attended RSV LRTI were captured in a systematic manner. In the first season, there were a small number of cases which were balanced by group. In the second season, when children were older and there were only 262 children in the CHD/CLD cohort who remained under surveillance, no cases were observed in either recipients of palivizumab or nirsevimab.

In further support of the efficacy, we can also look at RSV neutralizing antibodies. In the nirsevimab group, the peak level of neutralizing antibody at the first measured time point day 31 is approximately 150 times higher than baseline levels. At day 151 they're still 50-fold higher than baseline levels. In fact, at all times measured post-dose, nirsevimab recipients had higher levels than palivizumab, which are shown in

gray, and here are the results from Season 2.

You'll recall that infants who received palivizumab in Season 1 were re-randomized in Season 2. Nirsevimab provides high and sustained RSV neutralizing antibody levels throughout the season, which compared very favorably with the palivizumab comparator arm. So in summary, first based on PK levels, which are comparable to those in the efficacy studies and supported by clinical cases, which are balanced to the palivizumab group, and in addition, high levels of neutralizing antibody associated with nirsevimab, we've established the efficacy of nirsevimab in high-risk infants and vulnerable children in their second season.

And lastly, I'd like to share some of our findings with respect to anti-drug antibodies and monoclonal antibody escape variants. With regard to anti-drug antibodies, the overall incidence of detectable ADA to nirsevimab was low across the clinical program. The incidence was approximately 6 percent in Trials 03, 04, and 05. Importantly,

ADA did not have any discernible effect on efficacy and did not have an apparent effect on the safety profile of nirsevimab. Furthermore, there was no anamnestic ADA response observed in infants who received a second dose of nirsevimab in the second season of Trial 05.

Given the potential for emergence of monoclonal antibody escape variants, we performed genomic analysis of all RSV infections in our clinical trials. We evaluated a total of 267 RSV genomes and sequenced the F protein to identify potential polymorphisms. There were no major variant binding site substitutions in RSV A and only two binding site substitutions in RSV B were infrequently observed. We are characterizing all substitutions observed in the clinical trials and have found that over 99 percent of RSV sequences isolated from these studies were effectively neutralized by nirsevimab.

In Trial 03, there were three substitutions associated with decreased susceptibility to nirsevimab, which occurred in 2 infants.

Importantly, both of these infants had high serum concentrations of nirsevimab. No infant in Trial 04 or Trial 05 had substitutions that impacted susceptibility to nirsevimab. In addition, we've conducted prospective global molecular surveillance studies and confirmed that nirsevimab escape variants are rare that resistance-associated substitutions occurred with less than 1 percent prevalence, results that are consistent with our clinical studies.

In summary, we have robust data from two large randomized, placebo-controlled trials in healthy preterm and term infants, demonstrating that a single dose of nirsevimab was efficacious over a minimum of 5 months, which is consistent with the observation that RSV neutralizing antibody levels remain more than 50 times higher than baseline at day 151.

In these two studies, we observed a consistent level of RSV protection across subgroups and the spectrum of disease severity for medically attended visits to severe cases of disease. I also

showed you data on exposure and neutralizing antibodies that suggests at least similar protection to palivizumab in vulnerable populations through their first and second RSV seasons. And finally, I showed you that the incidence of ADA was low and that nirsevimab escape variants are rare.

Thank you for your attention. I'll now turn it over to Dr. Shroff to review the safety data.

Applicant Presentation - Manish Shroff

DR. SHROFF: Thank you, Dr. Leach.

I'm Manish Shroff, global safety lead for nirsevimab at AstraZeneca, and I will take you through the safety data that demonstrates the overall safety profile of nirsevimab is favorable across the populations studied.

A total of 3,620 infants and children were exposed to nirsevimab in our pivotal clinical trials. Of those, 3,224 received the proposed dosing regimen. In the first RSV season, a total of 3,580 infants were dosed, including 3,184 at the proposed dose. In the second RSV season, 220 children were dosed with nirsevimab. Safety was

monitored to day 361, which represents 5 half-lives of nirsevimab elimination.

As of the data cutoff, the median safety follow-up was 361 days in the first RSV season and 198 days in the second RSV season. The safety database across clinical trials is adequate to assess the safety profile of nirsevimab in the proposed indication, which builds on over two decades of experience with safety of palivizumab.

Safety assessments included treatment-emergent adverse events; serious adverse events; adverse events of special interest; and new onset of chronic disease through day 361 post-dose. No events were solicited. AEs of special interest for the program included, one, immediate hypersensitivity, including anaphylaxis; two, immune complex disease, both of which are based on risks associated with any monoclonal antibody; and three, thrombocytopenia based on postmarketing experience for palivizumab. These reflect important potential risks during clinical development. An external independent data

monitoring committee reviewed the safety data across all studies and did not identify any safety concerns.

Among 3,580 infants who received nirsevimab in the first RSV season, 59 percent received 50 milligrams and 41 percent received 100 milligrams. Among 220 children who received nirsevimab in the second RSV season, 98 percent received the full 200-milligram dose. A few subjects received different doses either due to replacement after cardiopulmonary bypass or medication errors.

Overall, the safety profile of nirsevimab in healthy term and preterm infants was favorable. The data shown here and on the next few slides represent the proposed-dose safety pool of the placebo-controlled trials, including Trial 03 infants who weighed less than 5 kilos at dosing and all infants in Trial 04. These data are based on completed safety follow-up through day 361 for Trial 03 and primary cohort of Trial 04, and at least through day 151 for the safety cohort of

Trial 04.

The incidence of any grade treatment-emergent adverse events, as well as grade 3 or greater severity AEs, SAEs, and deaths, were well balanced across treatment groups. Unfortunately, 9 deaths were reported in the proposed-dose safety pool. Every reported fatal event was reviewed in detail for the cause of death, underlying comorbidities, concurrently reported events, and background rates in those populations. The causes of death were attributed to common causes of infant mortality reported in the region where the infant was enrolled or to underlying medical conditions.

Importantly, none of the deaths were considered related to the investigational product by the investigator or the sponsor, and these conclusions are aligned with the agency's assessment. Based on investigator assessment, 6 infants in the nirsevimab group had an AESI, which I will describe more in detail later in my presentation. New onset of chronic disease was

reported in a few subjects and did not suggest any safety concern.

The most frequently reported all-grade, treatment-emergent adverse events, by preferred term per MedDRA, or Medical Dictionary for Regulatory Activities, were well balanced between the nirsevimab group, shown here on the right in plum, and the placebo group, shown on the left in green. These are mostly related to respiratory and gastrointestinal infections, which is consistent with what is expected in this population of young infants, and the vast majority were mild to moderate in severity and recovered without any medical treatment. Here are the most frequently reported serious adverse events by preferred term. Five of the most common terms were respiratory infections.

Looking at AESIs reported in the safety pool, a total of 6 AESIs were reported by the investigator through at least day 151. There were no reported events of serious hypersensitivity events or anaphylaxis. All reported events were

assessed as non-serious hypersensitivity reactions, and 3 of the 6 events occurred on the day of dosing. There were no AESIs of immune complex disease or thrombocytopenia reported in the safety pool. Overall, the incidence of AESIs was low and the reported events were restricted to non-serious skin and subcutaneous reactions. Close monitoring for these types of events will continue in the postmarketing setting.

Based on prior experience with motavizumab, a different anti-RSV F antibody, events suggestive of immediate hypersensitivity, specifically cutaneous manifestations, were observed. We conducted a comprehensive analysis of post-dose, skin-related adverse events in the nirsevimab studies. These were referred to as skin reactions and collected on a dedicated case report form through day 361 to ensure all potential events of hypersensitivity were adequately evaluated.

In the safety pool, skin reactions, although common in this population, were balanced between nirsevimab and placebo arms. IP-related skin

reactions were reported in the nirsevimab arm, with a low incidence of less than 1 percent. Of these, six were considered IP-related skin hypersensitivity reactions. The remaining were injection site reactions and rash that are not considered hypersensitivity events. Overall, the incidence of IP-related skin reactions and skin hypersensitivity reactions was low. Nearly all were mild to moderate in severity and resolved or recovered without any medical treatment.

Given the proposed indication, an important consideration is the safety of nirsevimab when co-administered with routine childhood vaccinations. Because nirsevimab is a fully human RSV-specific monoclonal antibody that works through passive immunization, it is not expected to interfere with active immune response to routine childhood vaccines.

The available data on co-administration with childhood vaccinations indicate that the safety and reactogenicity profile of the co-administered regimen was similar to childhood vaccines given

without nirsevimab. In addition, palivizumab has been used for more than two decades in infants who also receive routine vaccinations, and to date, concerns related to vaccine efficacy or safety have not been reported, and guidelines, including ACIP, support the co-administration of palivizumab with childhood vaccines.

We also investigated whether nirsevimab could potentially cause enhanced RSV disease in the second season, which is hypothesized to occur in a setting of sub-neutralizing or non-neutralizing concentrations of anti-RSV antibodies. Just as a reminder, infants in Trial 04 only received nirsevimab once prior to their first RSV season, and the same subjects were followed through a second season without additional dosing.

In Season 2, we did not see any increase in cases of medically attended RSV LRTI or increased severity of disease. Notably, there were no reported cases of RSV LRTI with hospitalization or very severe RSV LRTI in Season 2. Results were similar for any cases of medically attended RSV

LRTI due to RSV, either confirmed by central or local tests. Based on these data, there is no evidence to support the theoretical risk of antibody-dependent enhancement of disease with nirsevimab.

Now, I would like to turn your attention to the safety profile of nirsevimab in the populations at higher risk of severe RSV disease studied in Trial 05 and Trial 08. Just as a reminder, Trial 05 enrolls infants at high risk of severe RSV disease who are eligible for palivizumab. This included infants with CHD, CLD, and premature infants. Trial 08 is an ongoing phase 2, open-label study that enrolled children less than 24 months of age with immunocompromised states entering their first or second RSV season and presented here for completeness.

In Trial 05 Season 1, the safety profile of nirsevimab was comparable to that of palivizumab. The incidence of adverse events was fairly balanced between the two arms for both the preterm cohort and the CHD/CLD cohort. Regarding SAEs, the

incidence was higher in the CHD/CLD cohort, in line with their underlying conditions, but the incidence was similar in both treatment groups, and none of these were considered related to the investigational product.

One infant in the preterm nirsevimab group had an AE leading to discontinuation from IP, which was temporally associated with the placebo dose 3 months after the active dose of nirsevimab. There were 5 deaths reported in Trial 05 Season 1 in the nirsevimab group. None of the deaths were considered related to IP by the investigator or the sponsor, and is aligned with the agency's assessment. Two deaths in the preterm cohort included one infant with COVID-19 and the second with bronchiolitis, leading to cardiopulmonary failure, whereas 2 of the 3 events of the CHD cohort died due to cardiac complications, and one subject died due to lower respiratory tract infections.

IP-related skin reactions were reported in two infants receiving palivizumab and 2 infants who

received nirsevimab. Three infants in the nirsevimab group reported AESIs, including one IP-related skin hypersensitivity and two events of non-serious thrombocytopenia not considered related to IP in the CHD/CLD cohort.

In the CHD/CLD cohort that continued to Season 2, the safety profile was also favorable. You can see at the top of the table what each group received in Season 1 and Season 2. Minor numerical differences were observed in the overall incidence of grade 3 or greater severity AEs and SAEs. Those AEs that are cut at a higher frequency in the nirsevimab recipients were primarily due to infections or were related to underlying medical conditions, and none of them were considered related to the investigational product.

There were no clinically relevant trends or safety concerns identified, and when we looked at the events occurring within 30 days after the first dose, there was no imbalance. In addition, there were no SAEs related to IPs, deaths, IP-related skin reactions, or AESIs in Season 2. Overall, we

conclude from these data that nirsevimab demonstrated a favorable safety profile in these vulnerable populations.

Now, turning to safety in immunocompromised infants and children, in their first or second RSV season, based on the open-label Trial 08, the observed safety profile was consistent with what we would expect for the study population. None of the AEs greater than or equal to grade 3 severity or SAEs were considered related to nirsevimab. One death was reported in an infant with underlying pilomyxoid astrocytoma and possible intra-tumoral hemorrhage, not considered to be related to nirsevimab.

Two IP-related skin reactions were reported, including erythema, also considered an AESI, and rash. The AESIs observed in this study were all non-serious hypersensitivity events limited to cutaneous findings of which three were not related to nirsevimab, and none occurred on the day of dosing.

In summary, the overall safety profile of

nirsevimab is favorable in the first and second RSV season across studies and cohorts. The safety profile of nirsevimab in infants at higher risk of severe RSV disease is generally comparable to that of palivizumab. The safety profile in immunocompromised infants and children is consistent with that expected for the study population.

Importantly, the overall incidence of AESIs was low. Hypersensitivity was limited to non-serious skin and subcutaneous reactions. There were no events of anaphylaxis, or serious allergic reaction, or thrombocytopenia attributed to nirsevimab. There were no events of immune complex disease by investigator assessment reported during the trials. Once the product is on the market, we will continue to monitor the safety profile of nirsevimab through a robust global pharmacovigilance system.

This covers periodic and ongoing review of data from several sources, as shown here, including close monitoring of AESIs and ongoing molecular

surveillance studies to monitor escape variants and resistance. Safety is of utmost importance, and we will continue to increase our knowledge of RSV maps, building on 25 years of experience with palivizumab.

Thank you for your attention. Now I will turn it over to Dr. Muller.

Applicant Presentation - William Muller

DR. MULLER: Thank you, Dr. Shroff.

My name is Bill Muller, and I am a professor of pediatrics in the Division of Infectious Diseases at Northwestern University and an attending physician at the Ann & Robert H. Lurie Children's Hospital of Chicago. It's my pleasure to be here today to offer my perspective on the data you've just seen and the potential impact of nirsevimab on public health in the U.S. Note that I am a paid consultant for AstraZeneca, but I have no financial interest in the outcome of this meeting. I also served as a site principal investigator for the studies of nirsevimab that have been discussed.

All of us who have trained in pediatrics are familiar with winter call nights involving multiple admissions of infants with bronchiolitis, some of whom are critically ill. Although this past winter, the RSV surge made national and local news for its effect on children's hospitals, a surge at some level is an annual event for pediatric hospitals and providers. Even though I completed training more than 20 years ago, all we still really have to offer for these infants is supportive care, including suctioning, IV fluids, and oxygen or other respiratory support.

RSV infections in infants lead to tens of thousands of hospitalizations annually, affecting not only these babies, but also their families. As sad as it is to consider a baby in the hospital with difficulty breathing, there are parents stressed about their baby's health who are also missing work and who often have other young children at home, which adds to their burden. By one estimate, the cost of hospitalization for RSV disease in children under age 2 exceeds $1 billion

in the U.S. annually, and that does not even account for the cost of outpatient visits, lost work time, and other effects on families.

From a clinical perspective, there are several aspects of the data presented today that jump out at me. First, you saw the consistency of the efficacy estimates; generally, over 75 percent relative risk reduction for medically attended RSV LRTI, LRTI with hospitalization, and very severe LRTI in the two placebo-controlled studies. These efficacy results were generally consistent across the relevant populations and seem to generally hold across different subgroups, although in certain subgroups the numbers were small.

Importantly, the weight of RSV LRTI in the placebo group of the full Trial 04 cohort was just over 5 percent, with 2 percent requiring hospitalization, which is consistent with rates in the literature and supports generalizability of the study data. In support of this, a real-world phase 3B trial known as HARMONIE was recently reported at ESPID. This study enrolled over

8,000 infants in three countries in Europe who are at least 29 weeks gestational age during or entering their first RSV season, and they were randomized to nirsevimab or no intervention. The study showed 83 percent effectiveness against RSV LRTI hospitalization and 58 percent against all-cause LRTI hospitalization.

From the perspective of the number of infants needed to treat, the data are comparable to or perhaps better than vaccines in similar settings. The Trial 04 data translate to a number needed to immunize 53 infants to prevent one hospitalization for lower respiratory tract infection of any cause. Although it's not completely apples to apples, a 2007 study of influenza vaccine estimated that between 1,000 and 3,000 young children would need to be vaccinated to prevent one hospitalization. So to the extent that these data may be compared, we would expect the benefit of nirsevimab to be at least as great, if not greater, than influenza vaccination, an intervention which is recommended annually.

The levels of neutralizing antibodies observed in Trial 04 and Trial 05 were very consistent over the time period of the trials and significantly above the antibody levels seen with natural infection in healthy term and late preterm infants. It is reasonable to expect that the levels of neutralizing antibodies serve as a surrogate for clinical efficacy, supporting that nirsevimab should provide benefit in the at-risk populations studied in Trial 05.

These neutralizing antibody levels corresponding with efficacy provide optimism that studies in other immunosuppressed populations, such as cancer and transplant patients and those with primary immune deficiencies, could show an additional role for this treatment, and these are the children that I spend the majority of my clinical time caring for.

Regarding safety of nirsevimab, the data presented comprise a large program in pediatrics with good follow-up. These data from the safety pool support that the incidence of adverse events

was remarkably balanced compared with placebo. Combined with the other data presented, the risks were comparable between placebo or palivizumab and nirsevimab recipients. In addition, the phase 3B, real-world HARMONIE study showed a favorable safety profile, consistent with pivotal trials with no safety concerns.

Treatment-emergent AE and serious AE profiles reflected the study population and are comparable between the treatment and placebo groups. The AE of special interest profile was mild and mostly restricted to non-serious skin and subcutaneous reactions and does not raise concern. A theoretical risk of antibody-dependent enhancement was addressed in the trial, and no signal was observed.

Based on our experience with other monoclonal antibodies, there's no reason to expect problems with the co-administration of nirsevimab with routinely recommended childhood vaccines, and in recently published data, there was no interference with the anti-RSV response to natural

infection.

So how would I recommend the use of nirsevimab in clinical practice? I would recommend it for every infant entering their first RSV season, with a timing dependence on the birth month and local RSV epidemiology. I would also recommend using the second RSV season for high-risk infants and children, and I also anticipate a role for nirsevimab in protection of immunocompromised children.

There may be questions about the role of nirsevimab in the setting of maternal vaccination against RSV. This is a question which should ultimately be discussed and addressed by the advisory committee on immunization practices, as there are many considerations, including timing of birth and gestational age at delivery.

There will also be logistical considerations for providers, including whether a maternal dose can be verified at the time an infant would be considered for nirsevimab. My own personal opinion is that the risk of giving nirsevimab is low, even

with high levels of passively acquired maternal antibody, and there is potential for benefit. Ultimately, I would also recommend that the ACIP recommendation be the basis for a discussion of risk and benefit between the caregiver and the infant's provider.

In terms of public health, nirsevimab would be the first RSV prophylactic intervention available for all infants. Use of nirsevimab in babies entering their first RSV season would provide a significant public health benefit. We would see lower demand on hospitals and busy emergency departments and outpatient practices during the winter respiratory season. We would also anticipate fewer secondary infections and less demand for antibiotics, both inside and outside the hospital.

The long half-life of nirsevimab and the convenience of a single injection also confers the potential for an impact on health equity. Because palivizumab requires multiple doses, not all infants receive the full regimen, especially the

ones who are challenged to access healthcare.

Lastly, I would also like to point out the real-world effect that nirsevimab could have on some families. While the data we've discussed support that nirsevimab will reduce RSV disease in infants, as a provider, I will most welcome having fewer parents needing to spend sleepless nights in the hospital, watching their infant children struggling to breathe and worrying about what will happen next.

In summary, I think it's clear that effective interventions that prevent or treat RSV disease would be a major advance in pediatric medicine. Trial data from nirsevimab show a consistent benefit in all infants for clinically significant endpoints, and it's reasonable to extrapolate to high-risk populations.

The safety of nirsevimab is supported by the data presented, showing little difference from placebo and adverse effects consistent with the study populations. The data presented support a proposal to provide nirsevimab to all infants

entering their first RSV season and high-risk children entering their second RSV season. Thank you, and now I will hand it back to Dr. Villafana to conclude.

Applicant Presentation - Tonya Villafana

DR. VILLAFANA: Thank you, Dr. Muller.

I will now summarize our assessment of the benefit-risk profile of nirsevimab in the proposed indication, which should be considered in the context of the unmet medical need.

All infants, including healthy term infants, are at risk for serious outcomes from RSV, but there are no preventive strategies currently available for the majority of infants. Nirsevimab demonstrated clinically meaningful and consistent efficacy across disease severities, with a single dose being efficacious for the entire RSV season for at least 5 months.

The efficacy estimates against medically attended LRTI were 75 percent and 86 percent in term and preterm infants. Efficacy against hospitalization in Trial 04 was clearly impacted by

COVID-19; however, the all subjects analysis, while exploratory, provides a more precise estimate of efficacy against hospitalization. These point estimates are also supported by Trial 03. In addition, infants and children at high risk achieved similar PK exposures to nirsevimab as healthy infants, which allows us to extrapolate efficacy. With regard to safety, nirsevimab demonstrated a favorable safety profile in the infant populations studied.

Going back to the numbers in my introduction, nirsevimab has the potential to have a significant impact on public health and could prevent up to 500,000 medical visits in the U.S. annually. Assuming a hundred percent uptake of nirsevimab, and using a conservative estimate of 75 percent efficacy across disease severity, over 300,000 office visits from medically attended RSV LRTI, 112,500 emergency department visits, and as many as 60,000 hospital admissions with over 40,000 of those being in term infants, could be prevented. This could have significant impact on families and

the U.S. healthcare system. Moreover, nirsevimab is the only intervention that can provide protection to all infants regardless of when they are born, relative to the RSV season and whether they are born full-term or preterm.

Based on the totality of evidence, a single dose of nirsevimab provides consistent, rapid, and durable protection from RSV LRTI for neonates and infants born during or entering their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Therefore, we conclude that the benefits of nirsevimab outweigh the risks in the proposed indication.

On behalf of AstraZeneca and our partner, Sanofi, we would like to thank all the investigators and families who participated and made these studies possible; the independent data monitoring committee; the pediatric advocacy groups; the CDC, and the ACIP, and the committee for your time and consideration today; and finally, the agency for your direction and guidance through

the years. Thank you for your attention, and we look forward to answering your questions.

DR. BADEN: Thank you, Dr. Villafana and team, for an excellent set of presentations on a tremendous amount of data, as pointed out, during extremely challenging times with the impact of COVID.

We will now take a 6-minute break and resume at 11:10. For the committee members, we will have a combined discussion after the agency's presentation, so we will ask clarifying questions of both the applicant and the agency together. So we will be on break, and no discussion among panel members about the meeting topic, and we shall resume at 11:10. Thank you.

(Whereupon, at 11:04 a.m., a recess was taken, and meeting resumed at 11:10 a.m.)

DR. BADEN: We will now resume from break. It is 11:10.

We will now proceed with the FDA presentation from Dr. Baylor.

Dr. Baylor, the floor is yours.

FDA Presentation - Melisse Baylor

DR. BAYLOR: Hi. My name is Melisse Baylor, and I'm going to provide an overview of the agency presentation. The agency presentation will include the following topics. First, we'll discuss an overview of nirsevimab's clinical trials, followed by a discussion of nirsevimab dosing, the efficacy results, and key efficacy considerations, which are efficacy by chronological age and gestational age and efficacy in infants who remain vulnerable to severe RSV disease through their second season.

Then there will be a discussion of safety considerations, including anaphylaxis, rash, and other hypersensitive reactions, and a discussion of the imbalance in the number of deaths between the nirsevimab arm and the control arms. We'll discuss other considerations in our review, and finally we'll discuss our proposed pharmacovigilance strategy if nirsevimab is approved.

You've heard about the three pivotal trials supporting the safety and efficacy of nirsevimab. First, Trial 03 was a randomized, double-blind,

placebo-controlled trial that enrolled infants born at 29 weeks or greater gestational age to less than 35 weeks gestational age. In this trial, 968 subjects received nirsevimab, and the primary endpoint was the incidence of medically attended RSV lower respiratory tract infection.

The design of Trial 04 was similar to that of Trial 03, but Trial 04 enrolled infants born at 35 weeks gestational age or greater. Trial 04 enrolled infants into 1 of 2 cohorts, an efficacy cohort and a safety cohort. A total of 1,998 subjects were enrolled in the two cohorts combined and received nirsevimab. As in Trial 03, the primary endpoint for Trial 04's primary cohort was the incidence of medically attended RSV lower respiratory tract infection.

Trial 05 was conducted in infants who were at high risk for severe RSV disease. Trial 05 enrolled premature infants born at less than 35 weeks gestational age, infants with chronic lung disease of prematurity, and infants with hemodynamically significant congenital heart

disease. While the other two trials were placebo controlled, Trial 05 used palivizumab as the active control. In the two seasons of the study, 654 subjects received nirsevimab, and the primary endpoint for Trial 05 was safety.

As you saw on the previous slide and heard in the applicant's presentation, the primary efficacy endpoint in Trial 03 and the primary cohort of Trial 04 was the prevention of medically attended RSV lower respiratory tract infection. When palivizumab was approved over 20 years ago, the efficacy endpoint was RSV hospitalization; however, the agency also considers medically attended RSV lower respiratory tract infection to be a clinically meaningful endpoint.

The medically attended RSV lower respiratory tract infection endpoint is important because the majority of infants with RSV lower respiratory tract infection are not hospitalized. In fact, infants are much less likely to be hospitalized now than they were several decades ago, and the medically attended RSV lower respiratory tract

infection has a long history of being evaluated in the literature.

In the classic 2009 New England Journal article by Dr. Hall and her associates, medically attended RSV lower respiratory tract infection was discussed. Dr. Hall and her associates conducted a prospective surveillance study of RSV. They looked at both RSV hospitalization and outpatient visits. They documented the increased rate of both emergency department visits and of visits to the pediatrician offices in infants younger than 24 months of age; and as you can see, at that time, the rate of pediatric office visits for RSV in infants younger than 12 months of age was as high as 194 visits per 1,000 children.

Finally, the agency has had extensive internal and public discussion about efficacy endpoints in the trials for the prevention of and for the treatment of RSV. Experts in the field have provided their input to the FDA. The clinical benefit of prevention endpoints, such as medically attended RSV lower respiratory tract infection,

were discussed at an FDA-Duke workshop in 2016. After that workshop, FDA published draft guidance on developing antiviral drugs for prevention and treatment of RSV. This guidance, which is cited on the slide, recommends use of laboratory confirmed RSV lower respiratory tract infection as a primary endpoint in prevention trials.

As we move forward, I want to clarify one of the terms that we'll be using in our presentations today. High risk is a term that's often used in RSV disease, and high risk refers to an increased risk of RSV hospitalizations due to severe lower respiratory tract disease.

The Centers for Disease Control provides a list of high-risk conditions on their website, and these include all infants, particularly infants younger than 6 months of age; so high risk can mean all infants who are 6 months of age and have an increased risk of lower respiratory tract RSV disease. However, when we refer to high-risk infants in our talks today, we're referring to the infants that are listed in the higher risk group,

and that's infants born prematurely and infants with chronic lung disease and/or congenital heart disease, and that's the population that's enrolled in Trial 05.

Now, I'd like to turn the presentation over to Dr. Zhao to discuss nirsevimab dosing.

FDA Presentation - Yang Zhao

DR. ZHAO: Thank you, Dr. Baylor.

Good morning. I'm Yang Zhao, the primary clinical pharmacology reviewer for this BLA. In the next few slides, I will present the data FDA reviewed to support the proposed nirsevimab dosage. The proposed nirsevimab dosage for neonates and infants born during or entering the first RSV season is based on body weight; a single 50-milligram dose by IM injection if body weight is less than 5 kilograms or a single 100-milligram IM injection for infants whose body weight is 5 kilograms or greater. The dosage for children less than 24 months of age who remain vulnerable to severe RSV disease during the second RSV season is a single 200-milligram IM injection dose.

This is the overall basis for nirsevimab dose determination. For neonates and infants in RSV Season 1, the proposed dosage regimen is primarily supported by the clinical efficacy results of Trial 03 and Trial 04. In Trial 03, a single 50-milligram dose was administered to all infants regardless of body weight. Trial 03 results demonstrated differential outcomes in clinical efficacy and nirsevimab exposure in different body weight groups. In the group with body weight above 5 kilograms, the incidence of medically attended RSV LRTI was higher with lower nirsevimab exposure compared to the group with body weight groups below 5 kilograms.

This result indicates a need to increase the dose in heavier infants, and led to a decision to use the proposed bodyweight band-based dosing regimen in Trial 04 and also in Trial 05 and 08. The body weight band-based dosing regimen is also supported by the flat exposure-response relationship between the area under the concentration time curve, AUC, and the incidence of

medically attended RSV LRTI at the proposed dose.

For premature neonates and infants in RSV Season 1, and also for infants and children with certain underlying medical conditions in both RSV seasons, the proposed dosage regimen was primarily supported by similar nirsevimab serum exposure observed in Trial 05 versus in Trial 04, and additionally supported by descriptive efficacy results in Trial 05.

Pharmacokinetic data supported the proposed nirsevimab dosage. One exposure measure is the nirsevimab serum concentration post-dose at the end of the proposed protection period on day 150. The value of 6.8 was determined based on EC90. EC90 is the concentration for 90 percent effectiveness. The EC90 value was obtained in cotton rat RSV challenge model, and this model was used for dose selection for palivizumab.

Another exposure measure used is the nirsevimab AUC, derived based on individual baseline clearance. A value of 12.8 milligram as a target per day per milliliter was identified based

on the exposure-response efficacy analysis based on all the data from Trial 03 and 04. Above this AUC, nirsevimab efficacy plateaus and no additional benefit was observed when the nirsevimab exposure increased. Also, the same PK measure applied to high-risk infants and children, and these two PK metrics on day 150, nirsevimab concentration and the AUC baseline clearance were used to support efficacy extrapolation to high-risk population. Dr. Earp will elaborate on efficacy extrapolation in a later section.

With the proposed nirsevimab dose of 50 milligrams if body weight is less than 5 kilograms or 100 milligrams if body weight is 5 kilograms or greater in neonates and infants in RSV Season 1, more than 90 percent of the subjects achieved day 150 post-dose nirsevimab serum concentration above the target of 6.8 micrograms per milliliter and additionally achieved exposure above the target AUC 12.8 milligram day per milliliter.

After discussion of the dosing, I would like

to turn your attention to nirsevimab efficacy. Anna Kettermann will present FDA's assessment on clinical efficacy. Thank you.

FDA Presentation - Anna Kettermann

DR. KETTERMANN: Thank you.

Good morning. I'm Anna Kettermann, and I'm a statistician in the Office of Biostatistics in CDER. Today, I'm going to present the FDA statistical assessment of efficacy. I will begin with a brief overview of the general structure of the placebo-controlled trials.

The clinical program included two placebo-controlled trials. One of them was a phase 2 trial; the other one was a phase 3 trial. The trials were conducted sequentially. Both trials were randomized, double blind, and had the same primary and secondary endpoints. The primary and the secondary endpoints were evaluated from baseline through day 150 post-dose. The key differences between trials were study populations, selected doses, and duration of safety follow-up.

The discussion of the statistical assessment

of efficacy will include a brief summary of design and basic demographics for Trials 03 and 04. I will present the primary and secondary efficacy results, then I will discuss the primary endpoint results in subgroups. As a part of my presentation, I'm going to touch on COVID-related interruption in Trial 04 and its impact on prespecified analysis. I will wrap up with conclusions.

Both Trials 03 and 04 had the incidence of PCR confirmed medically attended LRTI events as their primary endpoint. The incidence of hospitalizations among subjects with medically attended confirmed LRTI events was the secondary endpoint. Both primary and secondary endpoints were evaluated through day 150 post-dose.

A Poisson regression model with robust variance adjusted for randomization, age, and hemisphere was used to analyze the primary endpoint. In this analysis, the missing outcome data was imputed using the placebo event rate conditional on baseline stratification factors. To

evaluate the impact of missing data, we performed a more conservative sensitivity analysis. This analysis repeated the primary analysis with an additional assumption that data for all subjects with a missing outcome on nirsevimab will be imputed as events.

Trial 03 was a phase 2B double-blind trial. Subjects were randomized 2 to 1 to nirsevimab or placebo. The randomization was stratified by baseline age: 3 months or younger, 3 to 6 months, or older than 6 months of age. The randomization was also stratified by hemisphere. The primary efficacy analyses were conducted at day 150 post-dose after receiving a single dose of nirsevimab or placebo on day 1. Safety follow-up was 360 days post-dose.

The Trial 03 population comprised of very and moderately preterm infants born between 29 and 35 weeks of gestation. In this trial, all subjects randomized to nirsevimab received a 50-milligram dose regardless of body weight.

Overall, 1,453 subjects were randomized to

Trial 03. All of those subjects were born between 29 and 35 weeks of gestation. Of them, 52 percent were male; 72 percent were white; 18 percent were black or African American; 20 percent of the subjects were from the U.S., and 68 percent were from the Northern Hemisphere. The average age at baseline was 3.3 months. The average weight was 4.6 kilos. Ninety-eight percent of subjects were younger than 8 months.

Here are the results of the primary endpoint analysis of Trial 03. Among 969 subjects on nirsevimab, 25 experienced medically attended RSV LRTI. In contrast, 46 out of 484 subjects on placebo experienced an event. The missing data rates were similar between treatment groups, 2 and a half percent on treatment and 2.3 on placebo. The relative risk reduction estimated by the Poisson model adjusted for baseline age and hemisphere was 70.1 percent with a 95 percent confidence interval between 52.3 and 81.2 percent in favor of nirsevimab. In this analysis, missing outcomes were imputed based on the observed placebo

rate conditional on baseline stratification factors.

To test the impact of missing data, we conducted a more conservative analysis. In this scenario, we repeated the primary analysis with an additional assumption that all subjects with missing data on nirsevimab experienced a medically attended RSV LRTI event. In this case, the relative risk reduction went down to 48.4 percent and the 95 percent confidence interval was still above zero and was between 24.2 and 64.9 percent in favor of nirsevimab, suggesting that the results of the primary analysis were robust

Similar to the primary endpoint, the number of subjects who experienced RSV with hospitalization was smaller among participants randomized to nirsevimab. Eight subjects on treatment and 20 on placebo were hospitalized during the trial. Similar to the primary endpoint, 2 and a half percent of subjects on treatment and 2.3 on placebo had a missing outcome.

The relative risk reduction estimated by

unadjusted Poisson model was 78.4 percent with a 95 percent confidence interval between 51.9 and 90.3 percent in favor of nirsevimab. Similar to the primary endpoint in this analysis, missing outcomes were imputed based on observed placebo rate.

In Trial 03, treatment effects of medically attended RSV LRTI events were consistent across subgroups and with the overall treatment effect. All treatment subgroup results were favorable to nirsevimab and were to the right of the vertical line at mark zero. Because there were only 2 percent of subjects older than 8 months and there was only one medically attended RSV event, the relative risk reduction estimate for subjects older than 8 months of age could not be determined.

Trial 04 was a phase 3, double-blind trial. Subjects were randomized 2 to 1 to nirsevimab or placebo. Randomization was stratified by baseline age, 3 months or younger, 3 to 6 months, or older than 6 months of age. Randomization was also stratified by hemisphere. Similar to Study 03, the

primary efficacy analyses were conducted at day 150 post-dose after receiving single dose of nirsevimab or placebo on day 1. Safety follow-up was 360 days post-dose. Additionally, subjects in Trial 04 had a follow-up from day 362 through day 511 to monitor for medically attended RSV LRTI incidence in the second RSV season. There was no protocol requirement for reporting of safety events during that period.

In this trial, all subjects randomized to nirsevimab were dosed based on their baseline weight. Subjects weighing less than 5 kilos received 50-milligram dose; subjects weighing 5 kilos or more received 100-milligram dose. Originally, this trial was designed to include 3,000 subjects, but it was interrupted because of the COVID-19 pandemic impact on operational aspects of the study. The prespecified primary analysis was based on the data collected before the interruption. We'll refer to this part of the trial as the primary cohort.

After interruption, additional participants

were subsequently randomized to collect more safety data. We refer to this part of the trial as the safety cohort. Randomization, safety monitoring, and efficacy assessment were in the same way in both trials. Combining primary and safety cohorts for the analysis of efficacy was considered exploratory because it was a prespecified exploratory analysis in the applicant's statistical analysis plan.

Overall, 1,490 subjects were randomized to the primary cohort of Trial 04. All of those subjects were born 35 weeks or more of gestation. Of them, 52 percent were male, 53 percent were white, and 29 percent were black or African American; 29 percent of subjects were from the United States; 69 percent were from the Northern Hemisphere. The average age at baseline was 2.9 months and the average weight was 5 and a half kilos. Ninety-seven percent of subjects were younger than 8 months of age.

During review of this application, the agency identified data discrepancy. There were

2 subjects in the primary cohort that were initially marked as non-events in the submitted data set, and subsequently the applicant confirmed the status of those subjects as lost to follow-up before day 150 post-dose. Our analyses are based on the updated data set that includes those subjects as lost to follow-up, and the applicant's analyses are based on the original data set; however, the differences in the primary and secondary analysis results are not large.

Here are the results of the primary endpoint analysis in the primary cohort in Trial 04. Among 994 subjects on nirsevimab, 12 experienced a medically attended RSV LRTI event. In contrast, 25 out of 496 subjects on placebo experienced an event. The missing data rates were similar between the treatment groups, 1.6 percent on treatment and 1.4 on placebo. The relative risk reduction estimated by the Poisson model adjusted for baseline age was 74.9 percent with a 95 percent confidence interval between 50.6 and 87.3 percent, in favor of nirsevimab. In this analysis, missing

outcomes were imputed based on the observed placebo rate.

To test the impact of missing data on the primary analysis results, we conducted a more conservative analysis. Similar to Trial 03, we repeated the primary analysis with an additional assumption that all subjects on nirsevimab with missing outcomes had experienced medically attended LRTI events will be imputed as having those events. In this case, the relative risk reduction went down to 44.8 percent and the 95 percent confidence interval was still above zero, between 6.7 percent to 67.3 percent in favor of nirsevimab, suggesting that the results of the primary analysis were robust.

Similar to the primary endpoint, the number of subjects who experienced RSV with hospitalization was smaller among participants randomized to nirsevimab. Six subjects on treatment and eight on placebo were hospitalized during the trial. Similar to the primary endpoint, 1.6 percent of subjects on treatment and

1.4 percent of subjects on placebo had a missing outcome. The relative risk reduction estimated by an adjusted Poisson model was 60.2 percent and the 95 percent confidence interval was between minus 14.6 percent and 86.2 percent. The result was not statistically significant. Similar to the primary endpoint, in this analysis, missing outcomes were imputed based on the observed placebo rate.

In the primary cohort of Trial 04, treatment effects of medically attended RSV LRTI were consistent across subgroups and with the overall treatment effect. All treatment subgroup results showed trends that were favorable to nirsevimab and the relative risk reduction estimates were to the right of the vertical line. Similar to Trial 03, there were no events among subjects older than 6 months of age and no events among subjects from the Southern Hemisphere. Because of this, no estimate for those subgroups could be determined.

In conclusion, the primary endpoint was met in both trials. Missing data did not impact

conclusion of superiority of nirsevimab to placebo in prevention of medically attended RSV LRTI events. Subgroup analyses for the primary endpoint were consistent across all subgroups in both trials. In the prespecified secondary endpoint, incidence of RSV with hospitalization was met in Trial 03, and it was trending towards efficacy in Trial 04 in infants born at 35 or more weeks of gestation.

Now, I would like to turn it over, back to Dr. Baylor. Thank you.

FDA Presentation - Melisse Baylor

DR. BAYLOR: We will now discuss two efficacy considerations. These considerations are, one, the evidence for the efficacy of nirsevimab for the prevention of medically attended RSV lower respiratory tract infection in the first RSV season across both chronological and gestational age groups. The second is the support for the use of nirsevimab in the prevention of RSV lower respiratory tract disease in children who remain vulnerable to severe RSV disease through their

second RSV season.

First, we will discuss the efficacy of nirsevimab across chronological and gestational age groups. Anna Kettermann already showed you the efficacy results from Trial 03, and this slide depicts efficacy as a scatter plot. The green dots are non events in the subjects who did not get medically attended RSV LRTI, the blue dots are subjects with medically attended RSV LRTI, and the red dots are RSV hospitalizations. You can clearly see the difference in efficacy because there are more red and blue dots or more medically attended RSV lower respiratory tract infection and RSV hospitalizations on the placebo side.

Next, I would like to point out that the X-axis shows chronological age at baseline and the red vertical line on the plot represents 6 months of chronological age. You can see the majority of infants enrolled in the trial were younger than 6 months of age. With this overlay, you can see that there were very few subjects who were older than 8 months of age.

This is another scatter plot of efficacy, and this plot is for the primary cohort in Trial 04. The dots and colors are the same in this slide, with blue representing medically attended RSV lower respiratory tract infection and red representing RSV hospitalizations. In Trial 04, as in Trial 03, you can see nirsevimab efficacy and that there are more blue and red dots or more RSV lower respiratory tract infections and RSV hospitalizations in the placebo arm than in the nirsevimab arm.

As you look at efficacy in this slide by baseline age, you can also see that there were few subjects who were older than 6 months of age, and that's the vertical red line, in Trial 04. There was no medically attended RSV lower respiratory tract infection in infants older than 6 months of age who received nirsevimab, and there were few cases of medically attended RSV lower respiratory tract infection in placebo recipients who were older than 6 months of age. You can also see that there were very few subjects older than 8 months of

age and no events of medically attended RSV LRTI in subjects older than 8 months of age.

As these two slides show, the majority of subjects in both efficacy trials were younger than 8 months of age, and while the design of the trials limited the number of subjects over 6 months of age to 500 subjects, the number actually enrolled over 6 months of age was much lower.

The small number of infants older than 8 months of age is not unexpected and is consistent with the epidemiological data regarding age at first exposure to RSV. Age at first exposure is related to when RSV circulates, and RSV circulation varies by climate. The U.S. includes both tropical and temperate climates. In areas with tropical climates such as Florida and Hawaii, RSV circulates year round. In more temperate areas, RSV season starts in the fall, peaks in the winter, and ends in spring. The RSV season typically starts around mid-September to mid-November and ends in April or May, resulting in a 5-month RSV season.

Because of the year-long RSV circulation in

tropical climates, infants born in these areas are exposed to RSV shortly after birth, but in temperate climates, infants may be born during RSV season and exposed shortly after birth, or infants may be born after the RSV season, and will then be exposed to RSV during the next RSV season, and most infants are exposed to RSV by approximately 7 months of age.

These data have shown that efficacy was demonstrated across chronological age in both Trial 03 and in the primary cohort of Trial 04, but there were few infants enrolled in these trials who were older than 8 months of age and there is less need for prevention in this age group.

Infants of all gestational ages were enrolled in the three main nirsevimab trials. While Trial 03 enrolled infants from 29 weeks or greater gestational age to less than 35 weeks gestational age, Trial 04 enrolled late preterm infants and term infants, and the majority of subjects in Trial 04 were term infants. Trial 05 enrolled preterm and term eventsinfants, including

128 subjects who were born at less than 29 weeks of gestational age and who received nirsevimab. As you can see, the majority of subjects in Trial 05 were born from 29 weeks gestational age to less than 35 weeks gestational age.

Anna Kettermann described the results of Trial 03 and the results of the primary cohort of Trial 04, and efficacy was demonstrated in both of those trials. If you look at the next-to-the-last subgroup, infants that were born at 35 weeks to less than 38 weeks of gestational age, the percentage of medically attended RSV lower respiratory tract infection is lower in the nirsevimab arm compared to the placebo arm.

In the last subgroup on this slide, infants born at 38 weeks gestational age and older, and that's term infants, again the percentage of infants with medically attended RSV lower respiratory tract infection in the nirsevimab arm was lower than the percentage of infants in the placebo arm; and thus, efficacy results were consistent across gestational age subgroups in

Trial 03 and in Trial 04.

Trial 05 enrolled premature infants born at less than 35 weeks gestational age. In addition, infants with CLD and CHD enrolled, and those infants were born across a range of different gestational ages. Trial 05 included 196 infants, or 21 percent of the entire study population, who were born at less than 29 weeks gestational age and who received either nirsevimab or palivizumab. Efficacy was the secondary endpoint in Trial 05, and the trial was not powered to show a difference in the incidence of medically attended RSV lower respiratory tract infection between the nirsevimab and the palivizumab arm.

There were only 2 events of medically attended RSV LRTI observed in infants born at less than 29 weeks gestational age. One event was in the nirsevimab arm and one was in the palivizumab arm. Clearly, these numbers are too small to reach any conclusions.

So in conclusion, on analysis of efficacy by chronological age, we observed that few infants in

the efficacy trials -- that's Trial 03 and the primary efficacy cohort in Trial 04 -- were older than 8 months of age, and that most infants in the U.S. are exposed to RSV by 7 months of age; however, we do recognize that there are times when the use of nirsevimab in infants older than 8 months of age is appropriate. There can be infants who present to health care late or infants who are in care but are lost to follow-up and reappear in health care at a later time. In addition, as we've recently seen with the COVID pandemic, there can be an unusual or unpredictable timing of the RSV season.

In our analysis of efficacy by gestational age, efficacy was observed across the subgroups of gestational age from 29 weeks to term in the two efficacy trials, Trial 03 and the primary cohort of Trial 04. Trial 05 was not powered to demonstrate efficacy. Efficacy in this high-risk population, including in infants born at less than 29 weeks of gestational age, was established by extrapolation, and now we'll discuss further efficacy in

extrapolation in Trial 05.

The population in Trial 05, which I've been calling high risk, can be described also as preterm infants, including those born at less than 29 weeks gestational age, as well as neonates and infants with certain underlying medical conditions. Trial 05 was a randomized, double-blind, palivizumab-controlled trial in infants and children at high risk of severe RSV disease. This included infants born at less than 35 weeks gestational age, including those born at less than 29 weeks gestational age. These infants participated in Trial 05 during their first RSV season and were either born during that RSV season or were enrolled prior to entering that first RSV season.

The second population was infants and children with chronic lung disease of prematurity and hemodynamically significant congenital heart disease who were enrolled in their first year of life. These infants were born during the RSV season or received nirsevimab before entering their

first RSV season, and then these study subjects were also followed through their second RSV season. In Trial 05, efficacy was assessed by the incidence of medically attended RSV lower respiratory tract infection as a secondary endpoint, and efficacy in both RSV Season 1 and Season 2 was supported by extrapolation.

This is the Trial 05 design, and as you can see, all subjects, both premature infants and infants with chronic lung disease and/or congenital heart disease, were randomized in a 2 to 1 ratio to receive either nirsevimab or palivizumab. Subjects were then followed for safety, which was the primary endpoint until 360 days post-dose or day 361. Subjects with CLD or CHD could continue the trial into their second year of life. Subjects who received nirsevimab in year 1 also received nirsevimab in year 2, but subjects who received palivizumab in year 1 were randomized in a 1 to 1 ratio to receive either palivizumab or nirsevimab in year 2. All subjects in year 2 were followed for safety for another 360 days. In both

trials, information on efficacy was collected through day 150 or day 151, as you see on this schema.

The total number of subjects who received at least one dose of nirsevimab or palivizumab in Trial 05 was 918, and this included 304 subjects who received palivizumab and 614 who received nirsevimab. A similar percentage of subjects in both arms were born prematurely -- 68 percent and 66 percent -- and approximately one-third of subjects in both arms had either CLD or CHD. Of those subjects, the majority, which is 64 in the palivizumab arm and 138 in the nirsevimab arm, had chronic lung disease. Some subjects, a very few, had both chronic lung and congenital heart disease, and there was one subject with Down syndrome enrolled.

Of the subjects with CLD and CHD in Season 1, the subjects who continued in Season 2 are shown in the box to the right. 85.6 percent of subjects in the CLD/CHD cohort from Season 1 continued the trial and participated in the second

year. Again, the majority of subjects had CLD.

In the first RSV season of Trial 05, the percentage of subjects with medically attended RSV lower respiratory tract infection was low and was similar between the two study arms, with medically attended RSV lower respiratory tract infection reported in 0.6 percent of subjects in the nirsevimab arm and 1 percent of subjects in the palivizumab arm. In the second RSV season, no cases of medically attended RSV lower respiratory tract infection were reported. The second RSV season was conducted in 2020 and 2021, and may have been affected by the COVID pandemic.

Now, I'd like to turn it over to Dr. Earp who will discuss extrapolation of efficacy in this population.

FDA Presentation - Justin Earp

DR. EARP: Thank you, Dr. Baylor.

Extrapolation of efficacy from the population enrolled in Trials 03 and 04 to the population enrolled in Trial 05 is based on the following key principles. First, the disease

etiology and pathophysiology is expected to be the same for each population. Second, as the target of nirsevimab is the virus molecule itself, the mechanism of action for prevention remains the same regardless of the population, and the key therapeutic exposures of the drug should also remain the same. Thus, it is expected that the exposure-response relationships for nirsevimab be similar between the healthy infants and the high-risk population.

This is also supported, in part, from additional data in preterm neonates in Trial 03 and from the low incidence of infections in the 614 subjects that received nirsevimab in Trial 05. Because of these principles of extrapolation, an exposure matching approach was taken to ensure that the dose in the high-risk infants in children would give similar concentrations as those from the proposed dose in healthy infant and neonate trials. The applicant evaluated exposures utilizing the concentration at 150 days post-dose and also utilizing the AUC determined from the patient's

body weight at baseline.

This plot was made for the comparison of concentrations at 150 days post-dose in Trial 05 against those from Trial 04. The Y-axis depicts nirsevimab concentration at day 150. Our point of reference and target range is defined by the experience in Trial 05 [sic - Trial 04], shown in the red box plot on the far left. Immediately adjacent to this box to the right is the summary of concentrations for every subject receiving nirsevimab in Trial 05. Further right are exposures from subsets of patients in Trial 05.

The first two groups in dark blue are congenital heart disease and chronic lung disease in Season 1. The next two panels with the highest exposures are congenital heart disease and chronic lung disease patients in Season 2. Their exposures are higher, as they received the 200-milligram dose in Season 2. The last two groups are preterm neonates less than 29 weeks gestational age, and greater than 29 weeks gestational age without either CHD or CLD.

The pink band behind the boxes is provided for visual reference back to the interquartile range of concentrations in Trial 04, as the doses in Trial 04 are the proposed dosing regimen for labeling and efficacy that are being utilized for extrapolation. The dashed line is an EC_{90} that was identified as an early target exposure from preclinical data. It is clear the exposure profiles for patients in Trial 05 are comparable to the concentrations in Trial 04 and, in general, exceed the target concentration identified in nonclinical development.

The second exposure metric evaluated for extrapolating efficacy is the subject area under the curve, or AUC, of nirsevimab concentrations. AUC is generally considered to be represented as a patient's overall exposure and often correlates closely with concentrations in the elimination part of the pharmacokinetic time course, like those you saw on the previous slide.

The applicant's exposure-response analyses from the clinical efficacy data for the primary

endpoint in Trials 03 and 04 led to the identification of a threshold AUC value of 12.8-milligram days per milliliter. Above this point, exposures fall into the plateau of maximal response for nirsevimab efficacy, and no additional benefit is expected by increasing nirsevimab exposures further.

This table shows the percentage of patients in each subset of Trial 05 that achieved AUC values greater than 12.8. For reference, in Trial 04, 92.5 percent of subjects met this threshold at the proposed dose. This AUC comparison also suggests that the proposed dose in patients in Trial 05 achieved similar exposures to those in Trial 04.

In summary, nirsevimab concentrations and AUC values are comparable between healthy infants and neonates in Trial 04 at the proposed doses and high-risk infants and children in both seasons of Trial 05. This supports extrapolation of efficacy to Trial 05, and the extrapolation is also, in part, supported by overlapping populations of preterm neonates in both Trials 03 and 05 and by

the efficacy data obtained from 614 subjects that received nirsevimab compared to the palivizumab arm in Trial 05.

I will now turn the presentation back over to Dr. Baylor to discuss the safety considerations for nirsevimab.

FDA Presentation - Melisse Baylor

DR. BAYLOR: Hi. First, we'll discuss the safety database, and then we'll discuss some safety considerations. Overall, 3,285 infants and children received the proposed dose of nirsevimab in clinical trials. This included 3,224 who were enrolled in one of the three main trials; that's 03, 04, or 05. The majority of subjects were enrolled in Trial 04.

All subjects in the three main trials of nirsevimab were followed for safety for 360 days post-dose. Subjects in Trial 04 were also followed for an additional time, from day 361 to day 510, to collect information on medically attended lower respiratory tract infections, and this was without further dosing with nirsevimab. At the time of the

BLA submission, safety data from days 361 to 510 in the safety cohort for Trial 04 were not available, and they were not included in the BLA. In addition, safety data for days 150 to 360 in RSV Season 2 of Trial 05 were also not available and not included in the BLA.

The two key safety considerations that we will discuss are anaphylaxis, rash, and other hypersensitivity reactions and the imbalance in the number of deaths in the nirsevimab and control arms. For rashes that may be a manifestation of a hypersensitivity reaction, we conducted two analyses, and these analyses differ from the analyses conducted by the applicant.

First, all skin reactions that were identified from the safety data sets, using a large group of adverse event terms to identify skin adverse events that could be associated with hypersensitivity were used to collect adverse events. Once the skin or adverse rash events were identified, we narrowed the list to those that may have been drug related by omitting rashes with

another clear etiology such as diaper dermatitis. We also omitted rashes that involved a single lesion and chronic skin conditions such as eczema. And finally, we omitted all rashes after day 75 if the rash was judged by the investigator as mild.

The second analysis of rashes that may have been associated with a hypersensitivity reaction was an analysis of rash within 14 days of study drug administration. The 14-day period was used because of the temporal relationship to nirsevimab administration and because that time period includes the time in which subjects have the highest serum concentration of nirsevimab.

In our analysis of anaphylaxis rash and other hypersensitivity reactions, there were no adverse events of anaphylaxis. In addition, no serious skin events such as Stevens-Johnson syndrome were reported. One event developed grade 2 or severe angioedema on day 142 and was hospitalized for observation, and her angioedema may have been related to a change in formula.

There were two adverse events of urticaria,

one on day 7 and one on day 20 after the subjects both received nirsevimab, but both events of urticaria were mild in intensity. A moderate or grade 3 drug eruption was reported in one infant on day 6 after receipt of nirsevimab, and this adverse event was judged as related to nirsevimab. In our second analysis of rash within 2 weeks of receipt of study drug, rash was reported in less than 2 percent of subjects in both the nirsevimab and the control arms, and the majority of rashes were mild and moderate, and were not accompanied by other symptoms.

In conclusion, there were no adverse events of anaphylaxis in the clinical trials of nirsevimab. Skin and mucous membrane adverse events consistent with hypersensitivity reactions were observed at a low incidence in subjects who received nirsevimab and in those who received the control; however, anaphylaxis hypersensitivity reactions in rash have been reported with palivizumab and other monoclonal antibodies. Therefore, postmarketing reports of these events

are likely to be observed in patients who've received nirsevimab if nirsevimab is approved.

The second safety issue that we would like to consider is the imbalance in the number of deaths between the nirsevimab and control arms. There were 12 deaths in subjects who received nirsevimab in the clinical trials that were included in the BLA compared to 4 subjects in the control arms; however, the percentage of subjects who died was low, and the overall percentage was similar in the nirsevimab and control arms in all of the studies. In addition, Trial 08 did not include a control arm, and one subject in the placebo arm of Trial 03 died 6 days after the study end.

The causes of death varied. Most deaths were due to an underlying disease such as cardiac disease or one subject with a tumor in Trial 08. Other infants died of an infectious etiology such as 2 subjects in South Africa who died of gastroenteritis and one infant who died of COVID.

One subject did die of a lower respiratory

tract infection, but that infant's health was compromised by severe protein calorie malnutrition. And finally, 2 infants were doing well when they were put to bed, but died of possible SIDS. One of these infants was previously healthy, and although she had an autopsy, those results were not made available. The other subject had multiple hospitalizations and was thought to have an undiagnosed chronic condition.

In conclusion, in the trials of nirsevimab, the absolute number of deaths was higher in the nirsevimab arms than in the control arms, but the percentage of deaths was low and similar between nirsevimab and control arms. The causes of death varied, and there was no pattern in the cause of death, and the deaths were not all related to a single organ system. And finally, none of the deaths appeared to be related to nirsevimab.

I will end my presentation with a discussion of two other considerations. The first consideration is use of nirsevimab in infants whose mothers received the maternal RSV vaccine. There

are currently several RSV vaccines under development. An advisory committee was recently held for a maternal RSV vaccine on May 18th of 2023, so just last month.

In the clinical trials of nirsevimab, infants whose mothers had received an investigational maternal RSV vaccine were excluded from participation; so as a result, we have no information from clinical trials, and we're left with several gaps in our knowledge, such as does use of nirsevimab in infants whose mother received a maternal RSV vaccine provide added benefit and is there concern for safety that's related to the use of nirsevimab in this setting?

The second question is what happens to children in their second RSV season who received nirsevimab in their first RSV season? Do they get infected with RSV in their second year; and if so, do they have more severe RSV in their second year of life?

Subjects in Trial 04 were followed through their second RSV season; so that's from day 362

through day 511, and they did not receive an additional dose of nirsevimab prior to the second RSV season, and the subjects were monitored for medically attended lower respiratory tract infections. These were the results for the primary cohort, and the results for the safety cohort have not been submitted.

As you can see, the percentage of subjects with a medically attended RSV lower respiratory tract infection, regardless of the test used to diagnose RSV, was low in each arm and similar between the two arms. One subject in each arm was hospitalized for an RSV respiratory tract illness, and the low incidence of medically attended RSV lower respiratory tract illness suggest that there was no shift of RSV burden to the second year of life, and the low number of RSV hospitalizations suggest that there was no increase in severe RSV disease after nirsevimab, potentially secondary to antibody-dependent enhancement of disease; however, the numbers are very small, and we are expecting to have additional data to address long-term safety.

Therefore, it's difficult to reach definitive conclusions.

I'd like to now turn it over to Dr. Neha Gada from the Office of Surveillance and Epidemiology.

FDA Presentation - Neha Gada

DR. GADA: Good morning. My name is Neha Gada, and I work in CDER's Office of Surveillance and Epidemiology. Today, I will discuss FDA's proposed pharmacovigilance strategy for nirsevimab if it is approved, and we are including this in the presentation for the advisory committee today because, if approved, nirsevimab has the potential for widespread use and will be used for the prevention of disease as opposed to for the treatment of disease in a population that includes healthy children, where the risk tolerance for use of an agent is appropriately low.

So first, let's discuss premarketing safety and safety in the overall lifecycle of FDA regulated drug products. Safety is addressed in all aspects of the product lifecycle. Prior to

approval, safety is evaluated throughout the phase 1 to phase 3 clinical trials in conjunction with the dosage and efficacy evaluation. When FDA concludes the benefit-risk balances is positive, a determination may be made to approve the drug product. Although premarketing clinical trials are the gold standard to determine safety and efficacy at the time of drug approval, all trials have limitations, and while nirsevimab has a large safety database from the clinical development program, one important limitation of clinical trials for all drugs is the size of the population studied in trials that are smaller than what would be exposed in the real-world setting.

With this, trials will allow characterization of the safety profile for adverse events that happen frequently, but rare and serious adverse events may not be observed, as it is not feasible to power a study around multiple safety outcomes that rarely occur. As a result, FDA relies on pharmacovigilance as the safety net for monitoring approved drug products after approval to

detect rare but serious adverse events that may not have manifested during the clinical trials.

The benefit-risk assessment does not end with the FDA's approval of a product. FDA considers a lifecycle approach to a drug's benefit-risk assessment, acknowledging that our understanding of both a product's benefit and risk often changes over time as new information about the product becomes available. On the next slide, I will explain how postmarketing reports get to FDA.

The mainstay for pharmacovigilance includes our spontaneous adverse event reporting system. In the United States, spontaneous adverse events are received and entered into the FDA adverse event reporting system, or the FAERS database, or sent to the applicant's global safety database. FAERS is a computerized database of spontaneous adverse event reports for human drug and therapeutic biological products.

This illustration here depicts how voluntary adverse event reports are submitted to FDA. There

are two pathways for patients, consumers, and healthcare professionals to report a suspected adverse event. First, reports can be submitted directly to MedWatch or they can be submitted to the product's manufacturer who is then required to submit all such reports to FDA. Once the manufacturer receives these reports, they are required, under the Code of Federal Regulations, to report to FDA. Note that for serious and unexpected adverse events, the manufacturer is required by law to submit the reports to FDA within 15 days of receipt of such information, and all other reports can be submitted periodically.

From a regulatory standpoint, I want to explain what a serious adverse event means. Those would be adverse events that result in any of these outcomes here: death; life-threatening; inpatient hospitalization; persistent or significant disability; congenital birth defect; or other serious. Also, from a regulatory standpoint, expectedness of an adverse event is based on the product labeling information, so an unexpected

adverse event would be one that is not listed in the product's current labeling.

In the next slide, I will go over how to submit adverse event reports to MedWatch. There are two ways to report to MedWatch, online at the website listed on this slide or the forms can be downloaded from this site, completed, and sent back. When you access MedWatch online to report an adverse event, the website will guide you through an electronic questionnaire. In the next slide, I will go over two types of postmarketing surveillance and then describe FDA's current thinking regarding our pharmacovigilance strategy for nirsevimab if it is approved.

The spontaneous reporting systems are labeled as passive surveillance based on the fact that the reporting center or the manufacturer passively received this information rather than actively seeks it out. In contrast, active surveillance system is a system for the collection of case safety information as a continuous preorganized process.

FDA's pharmacovigilance strategy for nirsevimab, if approved, will include coordination across multiple data sources, and our strategy for nirsevimab, if approved, includes screening of FAERS reports for new safety information for nirsevimab; reviewing the published medical literature using Embase and PubMed on a regular basis, again, for new safety information; and reviewing the applicant's periodic safety report for new safety information. The user required regulatory submissions that are generally submitted quarterly for the first three years, and then annually thereafter.

We are also exploring claims-based data sources, including Sentinel, for active surveillance approaches that can be conducted post-approval. Based on the safety profile for nirsevimab that has been assembled from the clinical development program, expected adverse events of interest include hypersensitivity reactions, as we've heard earlier today. We would also be monitoring for prespecified adverse events

of interest such as injection site reactions and serious cutaneous adverse reactions.

FDA intends to reassess our strategies based on drug uptake and any new safety information that may emerge, and we acknowledge it is critical to review the totality of available data in order to inform any regulatory decisions across the drug lifecycle. And for nirsevimab, we plan to leverage our federal partnerships for the Centers for Disease Control and Prevention to foster information-sharing across the agencies who are collaborating with CDC on the safety data collected, using their near real-time active surveillance encompassing claims-based data from the Vaccine Safety Datalink database for nirsevimab if it is approved.

As the agency or the applicant identifies any new safety information, FDA will work with the applicant and propose regulatory action based on the safety signal as warranted. And as per the applicant's submitted pharmacovigilance plans, the applicant will conduct routine pharmacovigilance.

So how will FDA share new safety information with the public if nirsevimab is approved? FDA has many communication pathways that we use for all drug products to communicate new safety information, and I will bring a few to your attention.

First, we have the FAERS Public Dashboard, which is a highly interactive web-based tool that allows for the querying of the FAER's database. There are many limitations to the use and interpretation of these data, but for the purposes of the advisory committee meeting today, I want to note that one important limitation is the presence of a report is not confirmation that the drug or biologic product caused the event because causation does not have to be proven for a report to be entered into our database.

Second, FDA shares early safety signals, or potential signals, in accordance with Section 921 of the Food and Drug Administration Amendments Act of 2007. On this website here, safety information does not mean that FDA has determined that this

drug has this risk, but rather it may be a potential safety signal under investigation. FDA may also update the prescribing information for the product labeling, and at times, FDA may decide to communicate directly with the public or healthcare professionals using drug safety communications and other communication tools.

I will now turn it back to Melisse Baylor, who will provide an overall summary on behalf of FDA.

FDA Presentation - Melisse Baylor

DR. BAYLOR: In summary, nirsevimab efficacy for the prevention of medically attended RSV lower respiratory tract infection was demonstrated in two adequate and well-controlled trials. Nirsevimab efficacy for the prevention of RSV hospitalization was demonstrated in infants born at 29 weeks or later to less than 35 weeks of gestational age, and there was a trend toward efficacy in infants born at 35 weeks of gestational age or later.

The efficacy of infants less than 24 months of age who remain vulnerable to severe RSV disease

in their second RSV season was established by extrapolation. No major safety concerns were identified. And finally, FDA plans to conduct postmarketing surveillance to further assess nirsevimab safety, if approved, using several data search sources, and that's the end of our presentation.

Clarifying Questions

DR. BADEN: Thank you, Dr. Baylor and colleagues for presenting complex data, reanalyzing, and making it incredibly accessible and digestible.

We will now take clarifying questions for the presenters, AstraZeneca and the FDA. To my panel member colleagues, please use the raise-hand icon to indicate that you have a question and to remember to lower your hand by clicking the raise-hand icon again after you've asked your question. If you have a follow-up question to an issue being discussed, please use the green checkbox that can allow me to identify your follow-on question building on a theme.

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 the end of your follow-up question with, "That is all for my question," so we can move on to the next panel member.

To my panel members, please start raising your hands so we can have clarifying questions to the applicant and the agency. In terms of management of time for everyone, we will go to 12:50 as noted in the schedule. We will then have the 40 minutes for lunch. We'll have the open public hearing session, and then we will resume clarifying questions for the applicant and agency.

Looking for questions from my panel members, Dr. Ofotokun, can you open the clarifying question period?

DR. OFOTOKUN: Thank you so much, Dr. Baden,

and I really thank the applicant and the FDA for a very clear presentation of this product.

My question has to do with additional data from surveillance, postmarketing surveillance, from Europe and Asian countries. This drug looks good. The efficacy and the safety data looks very promising. I was wondering if we have postmarketing data from Europe, Asia, and other countries where this drug has been approved and is now currently in use.

DR. VILLAFANA: Thank you. Tonya Villafana, global franchise head, AstraZeneca, just reintroducing myself.

Yes, we have approval in Europe, but nirsevimab has not been launched as of yet in Europe, and it hasn't been launched in Asia. We don't have approvals in Asia yet, just to clarify that point. The trial is currently under review in Japan and China.

I will call Dr. Manish Shroff to discuss our plans for surveillance.

DR. SHROFF: Manish Shroff, global safety

lead, AstraZeneca. Slide up. We do have a robust global pharmacovigilance plan. As indicated by Dr. Villafana, at this point in time, the product has not been launched yet; and therefore there is no postmarketing data available or additional data available. However, the global pharmacovigilance system does include that any adverse event reported in any of those countries, either in Europe or Asia, will be entered into a global adverse event database, we'll get the review, and the review would be on a periodic aggregate level. Thank you.

DR. BADEN: It is difficult for me to determine if the agency wanted to comment, but I will assume not, unless you start talking.

Dr. Green, you have a question?

DR. GREEN: Thank you. Michael Green, UPMC and University of Pittsburgh. The primary endpoint here is medically attended lower respiratory tract infection with RSV, but different locations may use their healthcare providers differently, and this was an international study involving multiple continents and multiple countries.

Given that that primary endpoint is seeing a healthcare provider and not necessarily requiring hospitalization, how do we balance how different locations use their healthcare providers to know that we're not missing cases in certain geographic areas. This is probably for the sponsor, but if the agency wanted to address it, I'd be happy to hear their answer as well. Thank you.

DR. VILLAFANA: So I'll go first from the sponsor. I'd like to call Dr. Amanda Leach to address the question, but just to start with the fact that this case definition that we had for medically attended RSV LRTI was developed in collaboration with global experts, and I'll Dr. Leach go through the rest.

DR. LEACH: The purpose of having a primary case definition that is clearly defined was to make sure that we had one single case definition as it was applied universally across the centers in the trial. We did some checking. We've looked at the frequency of the symptoms, the severity of the disease at different locations using this case

definition, and I can confirm they are the same. There are a couple of pieces of information which I think would be useful to share. The first is we looked at a more sensitive case definition of medically attended RSV LRTI, where we included those children who perhaps did not have a central test performed but had a local test performed, and there I can confirm that however we defined it in a more sensitive way, that we had a consistent estimate of effect.

The other thing that I think might be useful to remind ourselves of is the all-cause impact that we had, because what that actually tells us in terms of all cause is that it really means that we've had an overall benefit of the product that captures not only those cases that we know, but also those cases where perhaps RSV was just contributing to the disease. I have those numbers to show you, and I can just slide up to reinforce the all-cause numbers there.

Thank you. I hope I addressed your question.

DR. BADEN: Thank you.

Dr. Krug?

DR. KRUG: Hi. Can you guys hear me?

DR. BADEN: Yes.

DR. KRUG: So a disclaimer, this is really not a question, but I just thought that it would be important to speak to the larger public health impact here, if that's ok. It's not a specific question.

(No response.)

DR. KRUG: Well, I'm hearing nothing, so I'll just proceed.

DR. BADEN: Yes. Go ahead and please provide your comment.

DR. KRUG: Yes. And again, a great presentation today by both the sponsor and FDA; really quite interesting.

For as long as I can remember, and certainly pre-pandemic, RSV has been the culprit behind large surges in respiratory illness and large surges in the demand for health care at all levels, and this is true not just at the hospital level and in busy emergency departments, but also in ambulatory care

settings. Nearly every year, those surges result in a crisis in terms of the availability of inpatient beds; so where am I going to put this patient who's breathing really hard and they can't drink? And the critical point of the pyramid was really in critical care because the number of critical care beds is obviously smaller than the number of general inpatient beds.

Over time, the other thing that's been going on -- and we didn't become aware of this until the pandemic itself -- was that it has been a significant contraction in the number of available pediatric beds. Pediatric beds have been closing across the nation, in part, because institutions maybe used them for different purposes during the pandemic, in part, driven by economics, and in part, also recently driven by the fact that we don't have enough healthcare providers. So even at the largest children's hospitals, there's been a contraction of beds.

So again, this has impacted the care of children at all levels of care, and not just the

effect of children with RSV bronchiolitis, but for all other children that are seeking acute care and children seeking just day-to-day, well child care.

The recent triple-demic, as people were calling it this over the past few months ago, was a combination of COVID, influenza, and RSV. While we were seeing patients with all three illnesses, the primary driver of the surge was RSV; not the flu, and certainly not COVID. In fact, the primary driver for inpatient beds was, again, RSV. I think this put the awareness of the fact that we don't have enough inpatient care beds in the United States to care for our children, and that this mismatch is much greater than what's necessary in the adult population.

This resulted in children not being able to make their way to tertiary care because there were no beds at the end, and that created some very unsavory situations, where you had well-intended providers caring for a very sick child, who ordinarily don't do that because, ordinarily, they transfer the patient.

DR. BADEN: Dr. Krug?

DR. KRUG: Yes, sir?

DR. BADEN: We have limited time to clarify --

DR. KRUG: No, I was actually about to finish. The point is, putting aside, again, this excellent data that's been presented, RSV will continue to be a major threat to all children, not just the kids who get sick, because of its impact on our existing healthcare system. So thank you. Sorry if I took too much time.

DR. BADEN: No, no. Comments are appreciated, and we all agree, a very important issue. There will be more time for discussion from the committee members during our discussion session, our precious time to get clarifying information. I ask committee members to state their name before they ask their question, and be as targeted as possible so we can get as much facts from our colleagues as possible.

Dr. Kotloff?

DR. KOTLOFF: Hi. Karen Kotloff from

University of Maryland. Thank you so much for this beautiful presentation. I do have one clarifying question for both the sponsor and the agency, really.

We're asked to consider the BLA for infants, which was defined as through the first year of life, but we really have a paucity of data to assess the risk-benefit after 6 months, and I'm wondering if that has been considered and if there is anything we should know about, whether the decision has to be for 12 months or if it could be more nuanced to a specific age group.

DR. VILLAFANA: So maybe I will start from the sponsor. Would the FDA like to start?

DR. SINGER: Please go ahead.

DR. BADEN: Go ahead, Dr. Villafana.

DR. VILLAFANA: Yes.

As we've shown in the data from our studies, we do have representation of infants and children in our study across 12 months of age and the first year, albeit with fewer children represented above 8 months. I think the majority of infants who

would probably get nirsevimab in their first year of life will be 8 months or younger, but I think the FDA did a really nice job of laying out why we would want to have nirsevimab available for all infants up to 12 months of age, based on the fact that we could have changes in seasonality patterns, children may have missed dosing, or a child may relocate, and there's no real concern from our data package, as you can see. Looking across the spectrum from a safety perspective and from the exposures that we've shown as well, we would have no concern of dosing children for those first 12 months of life.

With that, I will turn it over to the agency to get their perspective.

DR. SINGER: Sure. This is Mary Singer, CDER, FDA. We've already presented the data on what data is available for children in the various age groups, and this is something we would like the committee to discuss a little bit further to help us decide whether there needs to be some type of limitation on the age for nirsevimab receipt.

Thank you.

DR. BADEN: Thank you,

Dr. Patel?

DR. PATEL: Hi. Nimish Patel, University of California, San Diego. My question is for the agency, and I was wondering if they would be able to pull up slide 60. It's the slide that has the proportion of individuals who are achieving the AUC target of 12.8 by the different subgroups of CHD/CLD, et cetera. It looked like there are three groups where the target attainment was 90-plus percent, but there's one group where the target attainment was 80 percent, and I wanted to get some clarification from the agency about that group.

Yes. So the CHD group, it looks like 1 out of 5 times, they don't hit that 12.8 target. In that group, are there any signals of why they're not hitting that target, and should the dose be increased so that there's a greater proportion who are hitting the 12.8 target?

DR. SINGER: Thank you for your question. I'll have Dr. Justin Earp answer that one for you.

DR. EARP: Hi. Thanks for the question. We definitely thought about this a little bit, too. We looked at this, and the primary explanation for this is that the CHD patients that were in this group for this trial had a higher body weight compared to the rest of the group. It was about 25 percent higher, and the body weight is definitely an important factor for clearance of this product, as well as the volume of distribution.

So it's definitely something that plays a role here. Is that true of all CHD patients? I think it's something we're evaluating a little bit further to see if a dose change would really be something to discuss.

I don't know if the applicant wants to comment if there are any other factors contributing to that, but body weight was about 25 percent higher for that.

DR. VILLAFANA: Yes. I'd like to ask Dr. Hamren to come up and address that.

DR. HAMREN: Ulrika Hamren, clinical

pharmacology, AstraZeneca. So while we've established efficacy through extrapolation based on comparable serum exposures, we've used different metrics to evaluate this. And what we were looking at just now was the AUC baseline clearance target, which, as noted, was barely met or just about 80 percent for one of the subgroups; noting that this is a small subgroup, so every infant in that range will be a big percentage. To ensure that we actually have comparable serum exposures in these groups, we've also looked at serum concentrations day 151, as shown in the cohort presentation. If I could have the slide up?

As noted, the AUC that was used for target attainment was derived using clearance derived at baseline, so based on baseline body weight. And these kids grow over time, and there is some difference in how they grow, so by looking at day 151 serum concentration, we account for that growth, and when we compare serum concentrations at day 151, we do see very comparable serum exposures in these children as well. Further to that point,

in our population PK analysis, we evaluate whether we do have any differences in CHD or CLD infants, and we see no significant differences in pharmacokinetics in these kids. Thank you.

DR. BADEN: I see that myself, Dr. McMorrow, and Dr. Lewis have follow-on questions. Thank you for modeling how to do this.

Dr. McMorrow, the follow-on?

DR. McMORROW: Yes. Thank you. I wondered if you could tell us whether there were differences in AUC by age in months, as well as by body weight overall, and what you considered as second season for your dosing of the trial, whether that was children under 24 months or children under 20 months; and if the former, how many children were dosed 20 months or older. Thank you.

DR. BADEN: Sounds like a question for the applicant.

DR. VILLAFANA: Yes.

Dr. Hamren?

DR. HAMREN: Ulrika Hamren, clinical pharmacology, AstraZeneca. We don't have any AUC

data to share versus age at dosing, but knowing that age and body weight is highly correlated, what we can share are nirsevimab AUCs across body weights at dosing for different gestational age groups. Slide up please.

This figure shows you the nirsevimab AUC throughout the whole year for the different gestational age groups, and on the X-axis you have the body weight at dosing, so you can see how the nirsevimab exposure varies with body weight. You also have the variability between subjects indicated, and you can see that the serum exposures are in a similar range in these age groups. They're also similar across gestational age groups. Thank you.

DR. BADEN: Dr. Lewis? And I will remind panel members to state your name prior to your question.

A follow-on, Dr. Lewis.

DR. LEWIS: Hi. I'm Tamorah Lewis, and I have a follow-on question about dosing. We saw slide CE-24 from the sponsor comparing different

AUC target attainment, so if you could pull that slide back up, it would be helpful.

My question is about the dose used in Season 2 and the fact that it's 200 milligrams, but the PK data that you guys have shown has much higher serum concentrations, and I think AUC exposures if I remember correctly. Since the sponsor plans to provide it in 50- and 100-milligram prefilled syringes, was a dose of 150 milligrams modeled in the children in Season 2, and do you think that that would achieve more comparable exposures?

DR. HAMREN: Correct. We have prefilled syringes of 50 and 100 milligrams, and the dose for Season 2 was selected to achieve comfortable serum concentrations across the expected weight range of Season 2. If we could have the slide showing exposures in Season 2?

As I said, the dose of 200 was selected to achieve serum exposures in that weight range across the expected body weight range. We do achieve slightly higher serum exposures with the

200-milligram dose in those infants or those children weighing less; however, we have no safety concerns with these exposures given that nirsevimab has no endogenous targets, and we also have large margins to the exposures that we've achieved in adults with no safety concerns. As you can see on this slide here, you see both AUC across the body weight range and predicted Cmax across the body weight range, so therefore, we believe that this dose achieves a positive benefit-risk in these infants or children. Thank you.

DR. BADEN: Dr. Havens, I see you have a follow-on question as well.

DR. HAVENS: Yes. Thank you. Peter Havens from Milwaukee. I appreciated the slide of AUC by body weight, but you've already pointed out that that's somewhat inexact because of the changes in body weight. Do you have the same slide of day 151 serum concentration by body weight that might be a better indicator of how many people actually got above the 6.8 microgram per mL target?

DR. HAMREN: Sure. Slide up. In this

figure, you see the day 151 serum concentrations versus body weight dosing for our three different gestational age groups. What's indicated in the gray shaded area there is the 95th percentile of exposures achieved in our Trial 04 in our efficacy trial, just for context. You can see that the range here is above 10 micrograms per mL versus that preclinical target of 6.8. Thank you.

DR. HAVENS: Great. Thank you. That's a great slide. Thank you.

DR. BADEN: One more follow-on, and it's a two-part; one to the agency. How comfortable are you with the 12.8 as a target of efficacy? And to the applicant, there may be different wasting states such as nephrotic syndrome or protein-losing enteropathies. Have you thought about differing clearance states that may impact dosing?

DR. SINGER: Thank you. I'll turn this over to Dr. Justin Earp.

DR. EARP: If we can pull up the slide 224, I believe. This is the applicant's exposure-response shown for the exposure metric

that was used here with the AUC baseline clearance, and we thought about that question, about 12.8, and where we end up.

The applicant also evaluated day 151 concentrations exposure-response, and they also evaluated AUC determined over the course of the 365-day period. Those relationships are not as clear with the lowest exposures, but what is apparent for all the relationships is that the exposures that are at the proposed dosing regimen fall into a plateau of maximal response, and consistently for those other metrics, they do appear to be significantly different than placebo when you look at it in this context. But 12.8 was something that I believe was determined early in their development as they were moving forward, and they noted the clinical experience from Trial 03 as rationale for increasing the exposures then, I believe. The exposure-response was conducted early with Trial 03 before they updated that analysis, including the results of Trial 04 as well.

So given the variability that we see in each

of these quartiles for the hazard ratio, the improvement relative to placebo, 12.8 in my mind is a little bit soft, but I do believe for all the exposure-response analysis, we're achieving concentrations in that plateau of response.

DR. BADEN: Thank you.

DR. HAMREN: Ulrika Hamren, clinical pharmacology. I'll respond to the question of protein wasting syndrome. In our efficacy trials, we don't have any children who have these conditions; however, in our ongoing study in immunocompromised infants and children, we do see a few subjects where that is the case with nephrotic syndrome. As can be expected in these children, there is a higher clearance in these, so some kind of consideration to dosing in these children will have to be made. Thank you.

DR. BADEN: Thank you.

I realize there are five more hands up. It is time for lunch. We will resume at 1:30 with the open public hearing session. At the conclusion of the OPH session, we'll resume the clarifying

questions in the order the hands have been raised, so please, colleagues, keep your questions ready. Thank you all. See you at 1:30 promptly.

(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. BADEN: It is now 1:30, and we shall resume. We'll 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, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship 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 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 in 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 that this open public hearing be conducted in a fair and open way, and where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please unmute, and you may

turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have five minutes.

MS. LEE: Good afternoon. My name is DeEtta Lee. I am mom to Paisley, my beautiful daughter who was born healthy and full term at 39 weeks gestation. When Paisley was 4 months old, my husband and I became concerned when she started to have difficulty breathing and eating. We immediately got her to a primary care physician who decided to admit her to the local hospital. She tested positive for RSV and was admitted for 2 days.

At the time, I knew very little about RSV. I recognized the name RSV because Paisley had been tested for it once before when she had a cold, but I didn't know much more than that, and Google definitely was not my friend during this difficult time. I certainly was not prepared to have our baby in the hospital so soon after birth. Watching Paisley struggle to breathe and eat, along with

numerous failed attempts at getting an IV in her was devastating to us as parents, and we constantly wondered what more we could have done for our sweet girl.

While our situation felt dire in the moment, we have since learned that there are many other families whose lives have been turned upside down because of this scary virus. The emotional and financial toll on families can be devastating. All we want to do as parents is protect our children. I wish there would have been an immunization available to Paisley when she was born that would have helped her fight back against RSV.

I hope that if the FDA determines that this new immunization that will help prevent RSV is safe and effective, they will move swiftly to approve it so other families will not have to watch their baby suffer as my husband and I did. Every family deserves the option to protect their child from RSV, its short-term and long-term effects. With swift approval, other relevant federal agencies can work together to make sure any necessary changes

are made to the vaccine infrastructure to ensure this new passive immunization can be equitably implemented, and implemented timely before the next RSV season begins in a few months.

Thank you for your hard work to bring safe and effective vaccines, immunizations, medicines, and devices to the market, which improve our lives. Thank you.

DR. BADEN: Thank you.

Speaker number 2, please unmute, and you may 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 five minutes.

DR. SONNEY: Thank you, and good afternoon. I'm Dr. Jennifer Sonney, president of the National Association of Pediatric Nurse Practitioners, or NAPNAP, speaking on behalf of our over 8,000 members. As to financial interests, NAPNAP did receive a small grant from Sanofi aimed at raising public awareness of RSV, but not specifically to promote nirsevimab.

Recognizing the sustained burden of respiratory syncytial virus that constrain our health systems, pediatric hospital beds, and the pediatric healthcare workforce, NAPNAP acknowledges the disproportionate threat to the health and well-being of infants and young children that RSV proposes. Immature immune systems and anatomically disadvantaged respiratory system place infants and young children at the highest risk for serious and life-threatening illness from RSV and other respiratory viral illnesses.

The CDC estimates 2.1 million outpatient visits among children under age 5 and up to 80,000 hospitalizations in that same population each year. During the most recent RSV season, children's hospitals across the country experienced overwhelming hospital admissions due to RSV that far exceeded a typical season.

NAPNAP supports the timely and complete immunization of all infants, children, adolescents, and adults to maximize population health and well-being. Our support for immunization extends

to innovative technologies that introduce antibodies to enhance the immune system and fight disease such as nirsevimab. Given the rise in severity of RSV cases across the country during the last few years that resulted in health systems vying for critical resources, including hospital beds, ventilators, and staff; the unseasonably early arrival and extraordinary spread of RSV in recent years further complicated by influenza and COVID-19, these all demonstrate the importance for the FDA and its colleagues at the CDC to use all possible means to review and approve safe and efficacious treatments to limit the incidence and severity of RSV in infants before the next RSV season.

NAPNAP believes the efficacy data for the RSV monoclonal antibody therapy make it a critical tool to combat RSV in newborns and young infants. While we have historically focused on the impacts of RSV on preterm infants and those with serious health conditions, a 2020 study in the Journal for Pediatric Infectious Diseases reported that

72 percent of infants hospitalized for RSV were full term and had no underlying health conditions, similar to the story of Paisley. In some children, severe RSV disease has even been associated with recurrent wheezing and asthma continuing into adulthood, and of course if symptoms worsen, RSV can go on to pneumonia, bronchiolitis, and other serious health conditions.

Because all infants and toddlers are at risk, it is imperative that safe and effective preventive therapies are approved and available to all young patients. In addition to the physical burden on infants and toddlers, acute RSV illness can cause long lasting psychological stress for patients' parents and siblings; lost wages impacting family stability; time away from other children; and reduce bonding with children.

A survey by the National Coalition for Infant Health and Alliance for Patient Access reported that more than two-thirds of parents caring for an infant with RSV experience financial burden or crisis for their families, and watching

their children suffer with RSV impacted their own mental health. From a workforce perspective, NAPNAP's frontline pediatric and family nurse practitioner members reported devastating staffing shortages in pediatric hospitals, some operating at 300 percent capacity this past RSV season. Our colleagues in primary care described overwhelmed community-based clinics, and compounding these concerns is that it is often the marginalized children that are most impacted, reflecting broad health inequities of RSV burden.

NAPNAP appreciates the FDA's timely attention to the review and approval of the RSV monoclonal antibody, nirsevimab, to improve health outcomes in newborns, infants, and toddlers. NAPNAP firmly believes and strenuously urges that all approved RSV immunization technologies, including monoclonal antibodies, be accessible to every infant and young child before the next RSV season; and looking ahead, we further advocate that these be accessible to all young children regardless of where they live or their ability to

pay, just as we do with other essential vaccines. Thank you.

DR. BADEN: Thank you.

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

MR. VACCA: Thank you. Good afternoon. My name is Bill Vacca, and I am the parent of Georgia Vacca, who's almost one year old in actually a week from today, and I am receiving no financial influence or support.

My wife Sarah and I know firsthand how serious RSV infection can be after our 4-month-old daughter, Georgia, contracted the virus late last year in October of 2022. We're very fortunate that Georgia was able to recover, and we hope that no other parent has to ever experience this like how we had to go through, and something that's still on our minds today.

Prior to our experience, we thought that RSV

was always a mild or serious matter if your baby was premature or was sickly, and with our daughter being fully healthy, full-term, RSV was not on our radar at the time, but I remember like it was yesterday. We were getting ready to drop Georgia off at daycare one morning when we noticed that she was breathing unusually. She obviously was not feeling very well, but we got the sense that it was much more concerning than just a common cold.

We have a 4-year-old daughter as well. We've been through colds, sinus infections, and all that stuff, but we were noticing that her nostrils were flaring and that she was retracting in her lungs and her stomach was retracting. Her chest was going up and down very fast, and it was scary to see her suffer, and hopefully it's something we never have to ever do again or no parent has to go through.

So we took a trip to the urgent care after going to our pediatrician who said you need to take her to urgent care immediately. We were advised to bring Georgia to the emergency room after urgent

care, where she was diagnosed with RSV. We spent four harrowing days in the hospital before we were allowed to bring our baby home, only to go back to the hospital just the next day -- just about a week later when Georgia's symptoms reappeared again. Her oxygen levels had been carefully monitored, and eventually after those 4 days returned to normal after having to wear an oxygen mask for those 3 days to make sure that she had the right levels.

Our pediatrician then put Georgia on a nebulizer, and she still actually uses that nebulizer to this day if she gets sick. We noticed that if she gets sick, her raspiness really increases, and she needs that nebulizer to regain that oxygen level to 94 to 98 percent. We are so grateful, though, to be on the other side of that all-encompassing terror and fear that we felt for those couple of weeks, and we're so thankful for the healthcare professionals who provided Georgia with exceptional care, and did everything that they could to make her feel comfortable. It was terrifying seeing her in this plastic box, but they

were doing everything they could.

During our time at the hospital, we observed the different typical interventions that doctors provided for babies that were battling RSV that had fluids administered intravenously to help with the hydrations; the IV; deep suction to clear out the nasal and throat passageways; and external oxygen to assist with the breathing.

Before this happened to Georgia, we didn't realize that there were tens of thousands of other families that had been impacted by RSV just like us. When we got to the hospital for that first time, there were parents of patients, of little kids that were basically 2 to 3 to a room because it had gotten so crazy during this past October. It's essential, though, and we're very fortunate that she was able to recover, but it's something that we don't take for granted, and we hope that no other parent has to experience this ever again.

We were encouraged to learn that there's a new solution expected to be available soon to help prevent RSV in infants who aren't eligible for

traditional vaccines. I believe that it's essential that all families have equal access to it, regardless of personal income, to protect our babies from RSV and keep more of them out of the hospital. Thank you again.

Clarifying Questions (continued)

DR. BADEN: Thank you.

The open public hearing portion of this meeting has now concluded. We appreciate the comments from families that have been so profoundly affected by RSV and we will no longer take comments from the audience. We will resume our clarifying questions.

To my colleagues, please use the raise-hand icon to indicate that you have a question and remember to put your hand down after you've asked your question. Please use the checkbox for the follow-on. 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.

As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up questions with, "This is all for my questions," so we can move on to the next panel member. Please unmute yourself and turn on your camera when speaking.

I will resume from the five speakers who had their hands up at the end of the pre-lunch session. We'll start with Dr. Wilfond, who was incredibly patient.

DR. WILFOND: Thank you. This is Ben Wilfond from the University of Washington. I really have several clarifying questions regarding Study 05, and particularly focusing on the population for which there's currently an approved preventive intervention for RSV already.

My first question, I think these are questions for the FDA. I'm curious to know why the FDA decided not to recommend a study that was powered for efficacy because, for me, that would be really important, given that there's already an approved medication. I love the design but not the

power.

The second question, to help me understand that better, is can you clarify, for the prior drug that was approved for this population, what was required then? I believe there was a much larger population that was necessary for FDA approval for that. And finally, my last question for clarification regards whether or not, in terms of our voting and activities, we have the opportunity to actually make a different decision for this population for which there's an effective therapy compared to, otherwise, children who would not be receiving a medication. So they're kind of interrelated, but they're three separate questions. Thank you.

DR. SINGER: This is Mary Singer, CDER, FDA.

Melisse Baylor, if you could take those questions --

DR. BAYLOR: Yes.

DR. SINGER: -- I think we'll start on slide --

DR. BAYLOR: 138.

DR. SINGER: I think it's 140 --

DR. BAYLOR: If we could start on 138 and then go to 145, I think that would help.

Sorry, Mary.

DR. SINGER: Slide 138, please?

DR. BAYLOR: As far as the endpoint that we chose for 03, 04, and 05, and how that was different from palivizumab, we used all three of the endpoints in all three main trials, and it did require one -- as you heard already, you had to have an RSV positive by the central lab, at least one finding on a physical exam related to the lower respiratory tract, and one measure of clinical severity; so respiratory rate, hypoxemia, or a clinical sign of severe respiratory disease that was hypoxic or a ventilatory failure; new onset apnea; nasal flaring; retractions, grunting, or need for IV fluids.

If you go to number 145 --

DR. SINGER: Slide 145, please?

DR. BAYLOR: -- the reason that we felt that the design was rationale for Trial 05 is we

couldn't do a placebo-controlled trial because Trial 05 enrolled infants with the highest risk of severe RSV disease and who were eligible for pali in the country or the site they were enrolled in. In addition, the noninferiority trial design wasn't considered feasible because it required a large sample size. So a trial of the size needed to determine noninferiority would take a considerable amount of time to fully enroll, and it was unlikely that such a large trial could be conducted within a reasonable amount of time.

Finally, the noninferiority margin couldn't be determined because there's no randomized placebo-controlled trial with the endpoint of medically attended RSV LRTI available to establish the treatment effect of palivizumab versus placebo in the high-risk population.

In addition, in a slide we presented already in the main part of the talk, we kind of discussed that while pali had used RSV hospitalization, we did present this to a panel of experts and discuss possible endpoints at an FDA-Duke meeting, and then

we did issue guidance and had expert opinion in response to the guidance about using an endpoint. Part of the reason that medically attended was picked for all patients was that the rate of hospitalization has decreased in the 24 years since pali's been approved, and more patients are being treated as outpatients. In addition, with enrolling patients that are term and healthy and not just the higher risk, you get to a rate of hospitalization that's very low, and it was thought to be hard to study such a low hospital rate.

Any other questions I can clarify?

DR. WILFOND: That was very helpful. Could you clarify my third question which has to do with in terms of our voting and discussion, whether or not there's a way of still distinguishing between these two groups, because --

DR. BAYLOR: Yes.

DR. WILFOND: -- I realize it would take more effort to do this, but for this population, I have no idea how to make a -- I'm concerned I don't know what to do.

DR. BAYLOR: Right. Yes.

I'm sorry. Go ahead.

DR. WILFOND: I'd love to hear from other people on the panel in the second-next question. I feel like I don't have the data to know whether or not this drug will be as good as what's currently available for those populations of children who are on oxygen. That's what I care about, and I don't feel like -- maybe I'm not stupid, or not stupid. Maybe I don't understand this well enough, but I just don't have the confidence that I know what should be done for those patients.

DR. BAYLOR: I think I would give that kind of a two-part answer, and the first part would be that it would be very difficult to have any kind of hospitalized -- especially with oxygen and ICU, and have a study performed just for that population because the numbers are just fairly small, and the noninferiority margins are unknown, so it would be difficult.

Then we've used at the FDA extrapolation to support pediatric efficacy. I think it was since

1994 that we've used extrapolation. The drug concentrations of nirsevimab that you do get in the higher risk population of Trial 05 are the same as it is in Trial 03 and Trial 04. In Trial 03 and Trial 04, there was evidence of efficacy. There's no rationale, that we know of, of why patients in Trial 05 would have different efficacy because the mechanism of action is the same, the disease process is the same, and we expect that the drug should act the same in that population, so we're using extrapolation to support that.

DR. WILFOND: Thank you.

DR. SINGER: And there will be a separate voting question on the extrapolation in that population.

DR. BADEN: Does the applicant have a comment?

DR. VILLAFANA: Yes, we do have a comment, and I think we'd like to show some data that we showed previously, the PK new data comparing nirsevimab to palivizumab just to help for further consideration for the question.

DR. HAMREN: Ulrika Hamren, clinical pharmacology, AstraZeneca. In addition to the serum nirsevimab exposures that we've shown and compared across these populations, we have also looked at RSV neutralizing antibody levels and compared them to palivizumab, as shown in the core presentation.

This figure is very similar to the one that was shared in the core presentation, where you see the mean RSV neutralizing antibodies over time for nirsevimab in purple and palivizumab in gray for Season 1 to the left and Season 2 to the right. We've also overlaid the predicted palivizumab levels following five monthly doses, so you also see the peak levels of palivizumab here.

You can then see here that the nirsevimab neutralizing antibody levels are approximately 10-fold higher and more across the full time course over 360 days. We do know that palivizumab works in this population, and therefore, we believe that nirsevimab should be as efficacious as palivizumab, and therefore have a positive benefit-risk in these

children, with the addition of being delivered as a single dose instead of five monthly doses. Thank you.

DR. BADEN: Thank you.

I'm looking for green checkboxes and don't see them.

Dr. Siberry?

DR. SIBERRY: Thanks very much, Chair, and thanks for the great presentations. This question is for the applicant, Dr. Leach, and I may be pulling up the efficacy slide number 15.

I share your interest in having us consider the trial for safety cohort data as additional evidence of efficacy, but to do that I'd like to make sure that we are aligned with it being very similar to the primary cohort that was prespecified for efficacy. You mentioned that South Africa did not participate, I think you said, in the safety cohort, and it looks to me that as a result -- go back one --

DR. VILLAFANA: Dr. Leach?

DR. SIBERRY: -- there were only about

1 percent in the safety cohort of black participants even though there was more than 25 percent in the primary cohort. So I interpreted that to mean that about a quarter of your primary cohort came from South Africa.

I wanted to ask did you look at the primary cohort for South African participants alone and without South African participants to do some additional reassurance about the comparability of what we might be comparing here between the primary and safety cohorts? I assume, but would like you to confirm, that women with HIV were allowed to have their uninfected infants participate, and if so, how common that was. Thanks.

DR. LEACH: Yes, certainly.

Actually, it was such an unusual circumstance in South Africa that I'd like to show you the data from South Africa itself because as we were -- perhaps if you could draw the slide for me? Thank you, and let's show that slide now. What actually was happening -- slide up, please -- in that primary cohort, actually, the cases were

driven by what was happening in the Northern Hemisphere. By the time we enrolled in South Africa, it was already affected by the COVID pandemic and the restrictions that are applied. So what you're looking at here is just the cases in South Africa, there on the left, where there was no transmission during the primary endpoint period but it began after day 150, completely atypically and a-seasonally [ph]. And there you see that we have 6 cases in both groups, remembering the 2 to 1 randomization, and there seemed to be a trend to efficacy that was after the 5-month period.

So your question really was relating back to whether we can compare the data from the safety cohort and the primary cohort. What I believe that I can assure you -- if we could get that data back up again -- is that actually -- please, if you could put it up; slide up -- this is the data that you've seen that, actually, when we look at the estimates of effect, they both fall within the overall estimate, and we believe they are similar. So I don't believe any difference in populations

has altered that result. Thank you.

DR. SIBERRY: Okay, and the question about the HIV-infected women being able to enroll their uninfected infants?

DR. LEACH: Indeed, we had no restriction on that part, but I couldn't tell you how many of the mothers were HIV positive, but there was no restriction. Thank you.

DR. SIBERRY: Great. Then finally, you also just showed that slide that showed efficacy beyond 5 months. A lot of the efficacy has been premised on an injection that gets protection through a typical RSV season, but did you consider the potential need to re-dose within a first season infants who live in places that had an atypical seasonality or, say, tropical places that had ongoing seasonality?

DR. LEACH: Clearly, what we have is a product that gives 5 months consistent efficacy with perhaps an indication that efficacy can extend beyond that. We haven't investigated multiple dosing at this point in time. Thank you.

DR. SIBERRY: Great. Thanks so much.

Back to you, Chair.

DR. BADEN: Dr. Ofotokun has a follow-on question.

DR. OFOTOKUN: Yes. This may be really interesting in terms of differences in the duration across the geographical location that may be affected by climate. I recall when Dr. Baylor was presenting, one of the points that was made was that in the temperate part of the world, say the United States where you have cold weather and warm weather, RSV is usually during the more colder part of the year, if this product is approved, you probably give it before the RSV season begins. But in the warmer part of the country, like Florida and Hawaii, we do have -- so it's not seasonal; RSV is not seasonal, and you see RSV infection across different seasons of the year.

The question I have is really the efficacy or the way this product will be used in temperate versus the non-temperate region. Do we imagine that in places like Hawaii or Florida this is

something that will be given throughout the year, then elsewhere with weather, you have seasonal duration in RSV, that it will be given before and during the RSV season. I just wanted some clarity on that.

DR. VILLAFANA: Yes. I think we discussed the indication statement previously, which is that we anticipate that nirsevimab will be given prior to or during the RSV season, depending on when the infant is born relative to the season. I fully understand your question on places where the seasonality may not be as predictable, and we don't have efficacy broken down into those specific jurisdictions, as you said, but I think this is something that we expect to work on with the CDC and others to get some guidance in terms of how they will recommend nirsevimab use in those situations, very similar to how maybe palivizumab has been used.

As we've shown, we know that nirsevimab in the context of the studies we've done can cover for a typical at least a minimum of 5 months, and

potentially more than 5 months, as you've seen with the data from South Africa, and that will be something for future study and discussion. Thank you.

DR. BADEN: Panel members, please remember to state your name prior to your question.

Dr. Ofotokun, you actually were up for the next line of questioning if you still have a question.

DR. OFOTOKUN: Okay. Igho Ofotokun. I think I will yield to others. Thanks.

DR. BADEN: Thank you.

Dr. McMorrow?

DR. McMORROW: Thank you very much to the Chair. Meredith McMorrow, CDC. I just want to reiterate some of the points that Dr. Krug made earlier about the impact of RSV disease in children. This is a really exciting point to be at, where we have potential products to address this in a broader portion of the infant population.

Positive immunization is really essential for younger children who have immature immune

systems and may not be able to mount an active immune response to other types of vaccines. It's particularly important as a mechanism to protect the youngest infants, and those are also the infants that we know are at highest risk of RSV-associated severe disease.

By 8 to 11 months of age, the risk of RSV-associated hospitalization is typically in the U.S. under 1 percent. It's about a quarter the risk of that in infants 0 to 2 months of age, and this is predominantly for two reasons, one that the infant is larger and the airways are larger, so they're less susceptible to bronchiolitis, but also that they've had some degree of prior exposure often. Because of those larger airways and/or some degree of prior exposure, they are at lower risk of lower respiratory tract infection when they are infected with RSV disease.

Again, I really appreciate that the FDA pointed out that the majority of infants in the primary trial looking at the first season indication was under 8 months of age, and the

second season indication is a much smaller population that's been studied, and I wondered if you had had a chance, because it was a relatively small study, to look at whether any of those infants had prior RSV exposure and if you have any data on RSV antibody concentrations in those infants prior to their Season 2 dosing, and how many of the 220 children were under 20 months of age at the time of dosing, and whether there were differences in response by dosing weight and age in that second season.

I know you responded to the earlier question with trial data from Trial 03 and 04, where you had first season data, but I wondered if you had any second season data as well. Thank you. That's all my questions.

DR. VILLAFANA: Thanks. And just to clarify, this is with regard to the second season in Trial 05 --

DR. McMORROW: Yes.

DR. VILLAFANA: -- that you're asking.

Thanks. I'd like to ask Dr. Kelly to come

up and go through the neutralizing antibody data from that study.

DR. KELLY: Good afternoon. My name is Beth Kelly. I'm a clinical virologist and immunologist at AstraZeneca. I'll have a slide up, please. You saw this data previously from my colleague, Dr. Leach, in her core presentation.

On the left-hand side, you see the neutralizing antibody responses throughout Season 1, and on the right-hand side, in those infants who had CLD and CHD and were re-randomized to a second dose of nirsevimab or another dose of palivizumab, you see the neutralizing antibody responses on the right-hand side.

Now, you can see that the baseline levels of those infants on the right-hand side of Season 2 who received nirsevimab, in the plum color, are very high and, actually, these are the residual neutralizing antibody responses afforded by nirsevimab in the first season. So those are still around 7-fold above the first time that they got the first dose of nirsevimab, and those are much

higher levels than natural immune responses.

So it's really hard to see natural immune responses in the presence of even levels of neutralizing antibodies of nirsevimab that have been there for a year, but you can see in the group that had palivizumab, that these infants have pretty similar levels to those infants at the beginning of Season 1.

What we know about those infants after one season is that around two-thirds or three-quarters of infants will have had a natural exposure to RSV and, importantly, as Bill showed in his core presentation, nirsevimab does not inhibit a natural immune response to infection. So we get neutralizing antibodies that are afforded by both nirsevimab, as well as those neutralizing antibody responses that are afforded by natural infection. Thank you.

DR. BADEN: Dr. Jackson?

DR. VILLAFANA: Just --

DR. BADEN: There are some follow-ons, but --

DR. VILLAFANA: Oh, sorry. Because I know we haven't fully answered Dr. McMorrow's question, we're going to do that analysis that you requested for the less than 20 months and come back to you.

DR. BADEN: Thank you.

Dr. Jackson has a follow-on question.

DR. JACKSON: Yes. Mary Anne Jackson, pediatric ID from Children's Mercy and the University of Missouri-Kansas City School of Medicine. This relates a bit to Dr. McMorrow's question about age and risk of infection. If you'll pull up slide 74, the FDA's presentation, this relates to the implications of the maternal RSV vaccine and the potential that will shift the age at risk for children with their first RSV episode. The question is, have you thought through what that shift might look like?

Then the second part, epidemiologically, I assume that there's no data in an additional at-risk group of children for severe disease, and those are children with neuromuscular diseases, particularly with swallowing dysfunction, and they

usually have some of the longest hospitalizations that we see for children with RSV, so thank you for answering my question.

DR. BAYLOR: For your question regarding neuromuscular diseases, we did show the CDC list for increased risk. We did not include neuromuscular disease and a couple of other diseases on that list because there were no patients enrolled with any of those diseases. We had one Down syndrome, and I think we had two CF patients, which is a little bit controversial as far as the need for pali. So we have real knowledge gaps in the subpopulations you talk about.

We also feel that with the proposed indication being patients that are vulnerable to severe RSV disease, that those types of patients would fit under that category, and it wouldn't restrict it or limited it to any patients that might need it but that weren't in the studies or there weren't good data for.

DR. JACKSON: Then the potential in shifting

the age at first infection if maternal RSV vaccines are widely implemented, understanding that you can't predict uptake, but it's obviously not going to be as high as what you'd hope.

DR. BAYLOR: Right. I think the two things, in my opinion -- kind of off record for this question -- is there's a potential for shifting it, because I think we've seen the data for the maternal vaccines, and it could end up with a shift. I think that would be something that we might learn from epidemiologic data, and the question would be whether or not we as an organization postmarketing would discuss with AstraZeneca another study that could be done if that's what we see what was happening.

I also am very hopeful that other organizations may be able to do some studies comparing the maternal vaccine and nirsevimab and help with advising how they should be used together and what works.

DR. JACKSON: Thank you very much for that.

DR. BADEN: Further follow-on to the

applicant about the potency of the product, how does the potency of palivizumab versus nirsevimab compare? You've showed different titers, but potency also is important there. And a corollary to that, to the maternal immunization question, do you have any insights into the immune responses of vaccination versus your neutralizing monoclonal and how one will think about potency as we try to measure success or vulnerability by levels?

DR. VILLAFANA: And to clarify, with regard to the vaccination question, maternal vaccination versus the potency of nirsevimab over time; yes?

DR. BADEN: Both, but hopefully the palivizumab, it's a little more straightforward, and nirsevimab is quite complicated.

DR. VILLAFANA: Yes. I'd like to ask Beth Kelly to come up and address the question.

DR. KELLY: Beth Kelly, clinical virology, AstraZeneca. Can I have the slide up, please?

Here, I'm showing you the data from Trial 03 in preterm infants on the left and Trial 04 in term and late preterm infants on the right. What these

are, are RSV neutralizing antibody levels afforded by nirsevimab in the plum color or those maternal antibody responses in the placebo group, which decay over the course of the clinical trials.

Now, what we've done is to map on a palivizumab reference line, and what this is, is the peak levels of palivizumab, the neutralizing antibody levels after a first dose of palivizumab. And what you see here is that nirsevimab is significantly more potent than palivizumab, where nirsevimab, in both the preterm infants as well as the term and the late term infants, really only crosses the neutralizing antibody line around 360 days after dose. This is very similar to the data that we see in nonclinical models, both in vitro, as well as in preclinical models in vivo, where, in vitro, nirsevimab is over 100-fold more potent than palivizumab.

I think you asked about the levels of neutralizing antibodies for nirsevimab as compared to maternal vaccines, and as Dr. Villafana mentioned, it's very difficult for us to directly

compare, given that both products were investigational when we were developing nirsevimab, but, again, that palivizumab reference line may become useful there because we did see some data at a recent VRBPAC where those were presented, and you'll see our line crossing around 360 days post-dose and the maternal vaccines tend to cross around 180 days or 6 months post-dose. Thank you.

DR. BADEN: Thank you.

Dr. Stokes?

DR. STOKES: Thank you. Stacy Stokes from George Washington University in Washington, DC. My question is for the applicant, and I think it is in regards to slide CS-11. This goes back to the long-term follow-up in Trial 04.

My question is in regards to the data around hospitalizations, and I believe, if that slide can be pulled up, there was implication that the hospitalization rate was improved on that follow-up year, but based on efficacy data from Trial 04, I'm not quite sure you can extrapolate that improvement in data. So I wanted to ask sort of a two-fold

question. One, am I missing something in that interpretation; and two, is there a plan to have forthcoming data from the safety cohort combined with the primary cohort to really look at that risk of hospitalization or number of hospitalizations one-year plus out? Thank you.

DR. VILLAFANA: Yes. Thank you. I believe we do have that data to share. I'd like to ask Dr. Vaishali Mankad to come up and share that data.

DR. MANKAD: Good afternoon. I'm Vaishali Mankad, and I'm a medical director with Global Clinical Development at AstraZeneca. I'm a pediatrician and an allergist-immunologist.

Thank you for your question. I believe this was two-fold. Let's first have slide up. This is the data that was shared by my colleague, Dr. Shroff, on the Trial 04 primary cohort data for the first RSV season shown on the left and the second RSV season on the right. I believe Dr. Stokes' question first related to the second season data, where we see no cases of medically attended RSV LRTI with hospitalization and no

severe disease, consequently.

We see a lower incidence of medically attended RSV LRTI in the second season compared to the first season. One thing that that data tells us is that we don't have a shift in the burden of disease by giving nirsevimab prior to the first season into the second season. The children are also older. But we do have data that was recently available from all subjects in Trial 04, so now the safety cohort has also been followed through the second RSV season. This data was recently submitted to the FDA in response to an information request, and I'd like to share that now.

Can I have the slide up, please?

So now we are looking at the data for all subjects in Trial 04 in both the first season on the left to day 151, and in the second season to the right, from day 362 to 511. In this larger data set, there are 8 additional cases of medically attended RSV LRTI in the placebo group and 12 additional cases in the nirsevimab group in the second RSV season that are contributed by the

safety cohort. You can see that we now have three participants in each treatment group that have had a medically attended RSV LRTI with hospitalization, and those same participants met the very severe endpoint.

You can see from this larger data set that the incidence of medically attended RSV LRTI and hospitalization remains similar in the placebo and nirsevimab groups, so this suggests that we see no evidence of antibody-dependent enhancement, in that there's similar incidence between the treatment groups and no indication that there is an increased severity of disease in nirsevimab recipients as compared to placebo recipients. Thank you.

DR. BADEN: A follow-on, if I may, and very much appreciate the hard work that the applicant is doing to try and prove the negative of ADE; however, the numbers are small. Will there be continued vigilance to monitor for evidence of ADE a year later, or some period of time after dosing, to grow the data set of absence of ADE?

DR. VILLAFANA: So there's no continued

follow-up of the study, Trial 04, that Dr. Mankad just showed, but I'd like to ask Dr. Shroff to come up and address pharmacovigilance.

DR. SHROFF: Manish Shroff, global safety lead, AstraZeneca. At this point of time, there are no studies planned with regard to long-term follow-up. Any study like that would be a little impractical because there could be multiple mechanisms with regard to enhanced disease. However, utilizing the routine pharmacovigilance, if there are any cases of reduced efficacy, or lack of efficacy, that will be processed as per signal management, and any early signs, once again, would be evaluated. Thank you.

DR. BADEN: Thank you.

Dr. Havens?

DR. HAVENS: Thank you very much. This is for the sponsor. I was interested in slide CE-18, which seemed to suggest that there was very little RSV after about day 130 or day 90. The placebo curves flatten out in Trial 04 after about day 90. Does that change our ability to understand the

protective efficacy?

One way to get to that question would be to look -- we saw the day 151 quartile analysis of the AUC data, efficacy by AUC, but I wondered if you had the day 151 concentration data by AUC in the same quartile analysis, that might be reassuring. I appreciate the South Africa data, which gets to this point nicely.

So does the RSV season drop off here in Trial 04 after about day 90; so it's hard for us to interpret that?

DR. VILLAFANA: First, to address your question, the first part of your question, I think I'd like to ask Mr. Currie to come up and talk about the consistency of efficacy over time and what we've done from a statistical perspective to analyze that, and then come back and address your second question.

DR. HAVENS: Thank you very much.

MR. CURRIE: Alex Currie, biostatistics, AstraZeneca. We have with that the efficacy over the 150 days, so I've got two slides to show you.

Can we have slide up, please? So presented here, you'll see Trial 03 and Trial 04 presented, broken down by 0 to 90, 0 to 120, and 0 to 150 days with the efficacy estimate, and as you can see, we do have consistent efficacy through the 150 days for both studies.

We do have an additional analysis -- slide up, please -- where we've broken that down by 30-day increments. So again, you'll see Study 03 and Trial 04, and we have the hazard ratios presented, which in terms of calculating efficacy, it's 1 minus the hazard ratio. So as you can see, for Trial 03, for 0 to 30 days, we've got 68 percent efficacy, and as you can see over the 30-day intervals, we've got consistent efficacy.

When we look at Trial 04, we see that we've got consistent efficacy through to 120 days; however, due to the atypical RSV season, we do see the attack rates dropping down, where we had only one case in the last 30 days; therefore, the efficacy estimate is very challenging to be made and should be interpreted with caution, and you can

see that in terms of the wide confidence intervals. But overall, we can see that we've got consistent benefit through the 150 days. Thank you.

DR. BADEN: Dr. Green?

DR. GREEN: Thank you. Michael Green, University of Pittsburgh.

DR. HAVENS: Could you finish up with the question about the efficacy by the day 151 concentration; not the AUC, but the --

DR. VILLAFANA: Yes.

DR. HAVENS: -- plasma concentration quartile, which you showed us earlier?

DR. VILLAFANA: Yes.

DR. HAVENS: This is the second part of the question, and then the --

DR. VILLAFANA: Absolutely.

DR. HAVENS: -- third part of the question is going to be, the people with the low concentrations at day 151, could you show us that by ADA? Because you mentioned that ADA drops the concentration, but we never really saw the data for that.

DR. VILLAFANA: Thanks. I'd like to ask Dr. Hamren to come and address those questions.

DR. HAMREN: Ulrika Hamren, clinical pharmacology, AstraZeneca. We'll first address the question about the exposure-response analysis based on serum concentrations day 151. Slide up, please. This forest plot shows you this analysis. At the top, you have the efficacy estimate for the overall in this pool. This is a subset of the full primary cohort and the proposed dose pool with those infants in who we have serum concentrations available. So therefore, the efficacy estimate is slightly different compared to the primary analyses in these studies.

The overall is at the top, and then you have the efficacy estimates by exposure quartile with Q1 being the lowest exposure and then increasing in serum concentrations, and you see that these estimates are consistent with the overall estimate, and there is no clear ordering of these, proving that we have consistent efficacy across this serum concentration range.

Moving to your second question, which was about ADA and effects on serum concentrations, we see no clear effects on serum concentrations day 151. Slide up, please. This figure shows you the day 151 serum concentrations by ADA status, so those who are ADA negative at all time points versus those who are ADA positive at any time point. As you can see, the serum concentrations in the ADA positives subjects are within the range of those who are ADA negative; so no clear evidence of effects on serum concentrations through day 151. Thank you.

DR. HAVENS: Thank you. That's very helpful. That's the end of my questions. Thank you.

DR. BADEN: Thank you. I did not mean to cut you off, Dr. Havens.

DR. HAVENS: Oh, no, no; no problem.

DR. BADEN: Thank you for the follow through.

Dr. Green?

DR. GREEN: Yes. Hi. Michael Green,

University of Pittsburgh. This is really a procedural clarifying question for the agency. All the other committee meetings that I've participated in, the decision making has been by the agency on both approval and I guess sort of a recommendation. But I'm trying to understand, for this product, what is the role of CDC, and how will they use any recommendations we provide, or that they will do it completely independently and give recommendations on how to use, and we're really giving advice on whether or not to approve this product. Thank you very much.

DR. SINGER: Mary Singer, CDER, FDA. The FDA will take the advisory committee's votes and discussion into account when making our decision about approval, and then the CDC will make their separate recommendations, if nirsevimab is approved, about how it should be used.

Does that clarify your question?

DR. GREEN: Yes. So it's parallel to what happens with vaccine as opposed to what happens with an antibiotic. Thank you very much.

DR. BADEN: So I'll recognize myself for a new line of questioning. Dr. Baden.

I have two questions, hopefully relatively straightforward. One has to do with safety and just making sure I understand the safety data to the applicant. You presented rashes and some other findings. The half-life is months, so these safety events, or adverse events, were observed, were managed, and resolved all within weeks, presumably; yet, the drug levels, as you've presented, were relatively high for months.

Is that a correct interpretation of the data being presented, for the most part, in large part?

DR. VILLAFANA: In large part, yes.

DR. BADEN: So that the rashes were not progressive despite the drug level being substantive.

DR. VILLAFANA: Correct.

DR. BADEN: Thank you. I assumed that was the case, but I didn't want to assume

On the flip side, in terms of efficacy, I'm trying to understand viral escape and viral

resistance, and you presented some of that in the briefing and today. In those individuals who had high titer antibody and had viral breakthrough infection, any insight as to why that occurred? Were the levels not high enough? Was there viral escape? Any insight or is it unknown?

DR. VILLAFANA: Great question, and I'll ask Dr. Kelly to come up and go over everything we did to look through the breakthroughs with great depth.

DR. KELLY: Beth Kelly, clinical virology, AstraZeneca. I think the mechanism of breakthrough is something that's really interesting to us as well, and while we don't have a firm conclusion as to why breakthrough occurs yet, we have evaluated a number of potential mechanisms, and I'd really like to walk you through that. So starting out, you mentioned nirsevimab serum concentrations, and as you mentioned, and as you've seen from my colleague, Dr. Hamren, from some of the data already, the serum concentrations of those infants who had breakthrough infections were within the range of those who did not have a medically

attended RSV lower respiratory tract infection; so it wasn't that they didn't get enough drug.

You heard a little bit about ADA as well, and you heard that ADA is rare in our trials overall, and I can say that they're rare in those infants who had medically attended RSV lower respiratory tract infections as well, and we never saw an ADA event prior to the RSV event; so it wasn't ADA.

You heard a little bit about monoclonal antibody escape variants from my colleague Dr. Leach, so 99 percent of those infections that we saw within our clinical trials were very susceptible to nirsevimab, and no shift in susceptibility. Only 2 infants in the entire study had variants that had reduced susceptibility to nirsevimab; so it wasn't escape.

We also looked at co-infections. We thought that co-infections might be a reason why we would see breakthrough. Maybe the RSV event wasn't actually causing the lower respiratory tract infection; it was just hanging around with

something else that was triggering the lower respiratory tract infection and, again, there we kind of came up negative. We saw in the placebo and nirsevimab groups, the rates of co-infections were balanced.

And lastly, we looked at viral load. We had this hypothesis that those infants who had a breakthrough might have had higher inoculating dose; so maybe they were just exposed to a higher amount of inoculum and there wasn't enough antibody to really mop all that up before the viral infection could really get kicked off, and we didn't see that either; so there was no evidence of higher viral load when those infants presented for care.

So overall, I've told you a lot of things that aren't the cause of the breakthrough infections, but this is something that's pretty consistent with other prophylactic monoclonal antibodies, including against other viruses. So where we see a threshold of efficacy achieved, in higher drug concentrations, even in the context of

things like challenge studies, where you have a measured viral inoculum, doesn't increase that viral dose. Those are the things that we've interrogated already, and we will continue to do further investigations. Thank you.

DR. BADEN: Thank you. And it looks like viral escape is not a predominant mechanism, so the likelihood of losing efficacy, as we've seen for monoclonals against some other viruses, seems less likely.

DR. VILLAFANA: Correct, yes.

DR. BADEN: Dr. Green has a follow-on.

DR. GREEN: Thanks. Michael Green, Pittsburgh. You looked at viral load, but do you have any epidemiologic data on your event case reports in terms of intensity of exposure? For instance, those that break through, were they in day care and differentially exposed compared to those that did not? Did they have other individuals in the household that were symptomatic at that time, although maybe it was mild, so that there was an ongoing continuous exposure that maybe

challenged the protective benefit as opposed to just looking at a quantitative viral load? Thanks very much.

DR. VILLAFANA: Yes. Unfortunately, we don't have that data, that level of epidemiological data in this setting.

DR. BADEN: Thank you.

Dr. Kotloff?

DR. KOTLOFF: Thank you. Karen Kotloff from University of Maryland. I have two sort of related questions. One is to understand what happens when somebody gets infected. Have you examined whether this is sterilizing immunity for the most part and there is no boosting? So this antibody, when the levels become unprotective, is the child without any natural boosting? So that's one question.

Then the second sort of related question is we know that recurrent RSV infections are very common, and natural infection is not really immunizing, and I'm wondering whether your hypothesis is that this is so broadly protective and a shared epitope so that this does much better

than natural infection in terms of protecting.

DR. VILLAFANA: I'd like to ask Dr. Kelly to address what happens to the natural immune response in infants given nirsevimab. Hold on.

DR. KELLY: Beth Kelly, clinical virology, AstraZeneca, and I'll have a slide up. Here I'm going to show you a little bit of data from our Trial 04 primary cohort, showing us that nirsevimab does not inhibit a natural immune response to RSV in RSV-exposed infants. We've done some analyses on post-fusion F, which we have recently published, but we know that folks are most interested in RSV neutralizing antibody responses given that we're giving them an RSV neutralizing antibody response.

So what we've done here in this analysis is to look at infants who are exposed to RSV and look at what their levels of neutralizing antibody responses are after that exposure. So in this case we're looking at day 361 in infants who have had an RSV exposure, and on the the left in green, you'll see placebo subjects, and on the right in plum, you'll see the nirsevimab subjects.

Now, we've had to do a subgroup analysis here because, of course, we've given these infants a neutralizing antibody. So what we had to do was only look at those infants who had cleared their nirsevimab levels and had undetectable serum concentrations of nirsevimab at day 361. So in this case, all the neutralizing antibodies that you see in this case are those that are afforded by natural infection.

So what you can see in this figure here is that in those infants who had an RSV exposure, whether it was the infants with a medically attended RSV lower respiratory tract event or those infants who had an RSV exposure that was not brought for medical attention, you had very similar levels of neutralizing antibody response. So again, nirsevimab is not inhibiting that ability to generate a natural immune response, which again helps in the second season as well and may get to some of those questions of ADE we've been talking about.

I think the second part of your question was

how did those levels of nirsevimab induce neutralizing antibody responses compared to natural infection, and I'd like to have a slide up to show you some of those data here.

On the left-hand side of the slide, you'll see Trial 03, so preterm infants, and on the right-hand side, we've got Trial 04, so term and late preterm infants again. And here we're looking at neutralizing antibody responses in infants who've received nirsevimab in plum or infants who've received placebo in green, and what we've done is stratified that by whether or not those infants had an RSV exposure, and it's clearest if we look at the placebo group in both trials in green.

So those infants who have not had an RSV exposure, you see their antibodies decay over time until the point where they're below the lower limit of quantification versus those infants in the placebo group who had an RSV infection, and those levels are boosted. But in both cases, you can see that the levels that are afforded by nirsevimab, either with an infection or without an infection,

are substantially above those that are provided by natural infection. Thank you.

DR. BADEN: Dr. Ofotokun has a follow-on.

DR. OFOTOKUN: Yes. Thank you so much. I just want to press on this case of infants that had breakthrough infection after immunization, especially those that were severe enough to be hospitalized. One good thing about some of the studies that you've done is you've really recruited from a broad range of demographics. You have 29 percent of participants in 04 and 20 percent in 03, which is just really impressive. Often, a lot of poorer outcomes happen in people from underrepresented minority, low socioeconomic status, and I wanted to see those individuals that had breakthrough infection after your product. I wanted to know more about this population, the demographics of this population.

DR. VILLAFANA: Yes. Thanks for the question. I'd like to ask Dr. Leach to come up and address the question of breakthrough infections and what we see across different populations.

Dr Leach?

DR. LEACH: Just calling a slide, I believe the question relates to when we start thinking about those more serious breakthroughs that end up in hospital, whether we see anything different across the subgroups.

Now, slide up, please. This is efficacy against hospitalization taken from all subjects in Trial 04, and you'll see the overall estimate, which we've mentioned before, is 76.4 percent. And when we look at this by subgroup, you'll see that the estimate of effect is always favoring nirsevimab and falls within the confidence interval of the overall effect. So I hope that's reassuring. Thank you.

DR. OFOTOKUN: Just a quick follow-up here. If I look at race and look at the black, African American, confidence interval, you can see that line crosses your predefined -- I don't know if you want to elaborate a little bit more on that.

DR. LEACH: I think what might be helpful to show is the actual by race data actually from the

U.S., which we have, so slide up. This is looking at Trial 03 all subjects and Trial 04 all subjects. This is medically attended RSV LRTI itself, rather than with hospitalization, to have enough numbers to be able to see some patterns there. You'll see that in both studies, both Trial 03 and Trial 04, we have efficacy demonstrated in the black, African American, population. It doesn't reach statistical significance in the Trial 04 all subjects, but you have a confidence interval that is separated from zero in the Trial 03. So it's when you take all the data together that I think you have confidence there is efficacy across subgroups, and actually this is supported by PK analysis, looking at our PK levels by race and ethnicity. Thank you.

DR. OFOTOKUN: So if I look at this data, would you say this is some issue of the number; that you don't have enough numbers to achieve the precision you're looking for? Can we interpret this as saying the trend here is that it seems that people, black, African American, are likely at a disadvantage when it comes to severe disease, at

least hospitalization. I just want some clarity on that.

DR. LEACH: Oh, I'm sorry if I haven't been clear. No, I believe the data is pointing in the other direction; that actually African Americans have similar to the overall protection both against medically attended RSV LRTI, as well as with hospitalization. And if you would like, I can just show you -- slide up now -- the PK data that is by racial group, which I believe is reassuring that in the black, African American, population, the levels of nirsevimab are similar.

DR. OFOTOKUN: Thank you.

DR. LEACH: Thank you.

DR. BADEN: Thank you.

I have one last question while I make sure none of my compatriots have any more questions, and this is to the agency.

The second dose was given in about 220 participants. I just want some guidance from the agency on how to think about the extrapolation to year 2 framing when the empiric data are limited

but the biologic rationale is so strong, a precedent for extrapolation in this setting.

DR. SINGER: Mary Singer, FDA, CDER.

DR. BADEN: Any agency/colleague comment?

DR. SINGER: Hold on a minute here.

Justin Earp will try to answer that question. We do extrapolation a lot with pediatric populations.

Justin, please add.

DR. EARP: Yes. So as you said, the key points that we've defined around the extrapolation have been really around the nature of the disease etiology. The fact that the target remains the same across populations and across seasons -- I guess now we're talking from Season 1 and Season 2 -- the biggest thing that jumps out in my mind with Season 2 is you're going to 200 milligrams, so your exposures are going to be that much higher at this point.

I've outlined these assumptions that we make when we extrapolate but, really, I don't know that we're going to find, from the data set that we

currently have, that evidence for comparison I think you're looking for on top of this. But given the precedent that I've seen in this area, the extrapolation -- just my personal take, for me specifically -- has been that this is a reasonable starting point, but we'd certainly welcome any input that you or the committee members have today on thoughts about those considerations that we're taking here.

DR. BADEN: Thank you.

Dr. Green may get the last question.

DR. GREEN: Thanks. Mike Green, Pittsburgh. This is to the applicant. We're not going to consider the answer to this question, really, in our decision making, I don't think, but can you share with us what is the age and type of immunosuppressed children you have in your ongoing study looking at that population? Thanks very much.

DR. VILLAFANA: Yes. I'd like to ask Dr. Mankad to come up and go through the populations in the MUSIC study.

DR. MANKAD: Vaishali Mankad, clinical development, AstraZeneca. Can I get the slide up? The populations in Trial 08 are infants up to 24 months of age who are entering their first or their second RSV season and are followed through 360 days post-dose. You can see here these are the percentage of subjects that meet inclusion criteria, qualifying them for enrollment, and these are children who have either a primary immune deficiency or a secondary immunodeficiency due to HIV virus infection, organ, or bone marrow transplant, or receiving immunosuppressive chemotherapy or other immunosuppressive therapy, including high-dose systemic corticosteroids or immunosuppressive therapy.

As you can see, these infants and children can meet more than one of these criteria to qualify for enrollment. On the right-hand side of the slide, you can see the demographic characteristics of the 100 children that have been enrolled in this trial. Thank you.

DR. GREEN: Thanks very much. The

performance of this study is very appreciated by those of us that care for these children.

DR. MANKAD: Thank you.

DR. BADEN: Thank you.

I thank everyone in the clarification session, especially the applicant and the agency for being so versatile in responding.

We will now proceed with the charge to the committee from Dr. Belew.

DR. VILLAFANA: Dr. Baden, just one request for a minute? We're generating an answer to the response for Dr. McMorrow. Should we just send that when we're done? I'm not sure it's quite ready yet, but we will have a response to her question.

DR. BADEN: I mean, I guess the agency's happy to receive it. I think we're going to move to the formal part.

DR. VILLAFANA: Okay. We can follow up later then. Thank you.

DR. BADEN: Please. I think that would be reasonable because I think it's important that

we're able to get to the voting and discussion matters for the agency. But, Dr. Villafana, we really appreciate the vigor of the responses and the completeness to respond to all the questions. Thank you.

DR. VILLAFANA: You're welcome

DR. BADEN: So we will now proceed with charge to the committee from Dr. Belew.

Charge to the Committee - Yodit Belew

DR. BELEW: Thank you, Dr. Baden.

Good afternoon. Again, Yodit Belew. I am the associate director for therapeutic review in the Division of Antivirals, Office of Infectious Diseases, CDER, FDA, and I will be providing the charge to the committee.

This morning, we heard from both the FDA and the applicant about the data contained in this BLA to support use of nirsevimab for the prevention of RSV disease. To briefly remind you, the proposed indication is prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season; children up to

24 months of age who remain vulnerable to severe RSV disease through their second RSV season, and the proposed dosing is as follows: for the first season, a single 50-milligram IM injection for infants weighing less than 5 kiolgrams and a single 100-milligram IM injection for infants weighing at least 5 kilograms; for the second season, a single 200-milligram IM injection for children less than 24 months of age who remain vulnerable to severe RSV disease through their second RSV season as proposed.

We also heard this morning that RSV disease can be severe or serious. To date, palivizumab is the only FDA-approved product for the prevention of RSV disease in certain pediatric patients, and summarized here are the specific populations for whom palivizumab is approved.

For this biological application, three clinical trials provided the safety and efficacy data. Trial 03 was conducted in neonates and infants born at least 29 weeks of gestation up to 35 weeks of gestation and entering their first RSV

season. Trial 04 was conducted in neonates and infants born at least 35 weeks of gestation and entering their first RSV season.

In Trial 05, the trial was conducted in two seasons. Season 1 enrolled neonates and infants born at 35 weeks of gestation, less than 35 weeks of gestation, including those less than 29 weeks of gestation. Season 1 also included infants with chronic lung disease of prematurity or hemodynamically significant congenital heart disease. Season 2 enrolled children up to 24 months of age who remain vulnerable to severe RSV disease.

Key efficacy and safety considerations for this application included efficacy of nirsevimab in neonates and infants born during or entering their first RSV season as assessed by chronological or gestational age; the efficacy of nirsevimab in children less than 24 months of age who remain vulnerable to severe RSV disease during their second RSV season. With respect to safety, the key considerations included hypersensitivity reactions,

including anaphylaxis and other serious adverse events, including death.

The first voting question is as follows. Is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory disease in neonates and infants born during or entering their first RSV season? Second, we ask the committee to discuss the following. Please comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Discuss the population or subpopulation for whom nirsevimab administration in the first RSV season would be most appropriate.

The second voting question is, is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season?

The last question, which is a discussion question asks, in the context of potential future availability of maternal RSV vaccine to protect

infants from RSV disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who receive RSV vaccination?

We thank the committee for their time today, and we look forward to your deliberations. Thank you.

Questions to the Committee and Discussion

DR. BADEN: Thank you, Dr. Belew.

The committee will now 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'd like to remind public observers that while this meeting is open for public observations, public attendees may not participate, except at the specific request of the panel. Dr. Jankowski will provide the instructions for the voting.

DR. JANKOWSKI: Thank you, Dr. Baden.

This is She-Chia Jankowski, the DFO. Our first question is a voting question. Voting members will use the Zoom platform to submit their vote for the 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 voting 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 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, there will be a momentary pause as we tally the 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 the list, and each voting member will state their name and their vote into the record.

Are there any questions about the voting process before we begin?

(No response.)

DR. JANKOWSKI: Hearing none, I just want to note, question number 3 is also a voting question and will follow the same procedure.

Since there are no further questions, I will hand it back to Dr. Baden, and we can begin. Thank you.

DR. BADEN: There are no questions about the process, so question 1 -- Oh, Dr. Kotloff has a question.

DR. KOTLOFF: Sorry. I was slow on that.

How does the discussion filter in? I had asked before, for example, if there's a nuance, if we feel that the data support a certain chronological or gestational age but not another,

how does that factor into our voting?

DR. BADEN: May I ask the agency to respond?

(Pause.)

DR. BADEN: Thank you, Dr. Farley.

DR. FARLEY: Hi, Dr. Baden, and sorry for the delay.

Thank you, Dr. Kotloff, for the question. I think there are two opportunities to opine on the issue that you bring up. The first is, I would imagine, as the chair usually does, that the committee will have an opportunity to explain their vote after their vote, and that the panel will be polled. And secondly, of course we've crafted a discussion question, which is question number 2, which I think also addresses that issue.

I think what we were imagining is that the committee, if there was a group of infants that they felt that the benefit-risk was favorable for within the phrasing of question 1, that you might consider an affirmative vote and then explain your position in either the discussion or question number 2, but I ultimately defer to the

chair on that issue.

DR. BADEN: Thank you, Dr. Farley. I was going to have a similar answer, but I want the agency to lead in how this is framed.

The voting question is whether or not we think, as individuals given all the data, there is efficacy in any circumstance. Then after the vote, we each will formally state our vote in the record and explain our rationale. Then, Dr. Farley, as the agency has provided provocative discussion questions, that opens up a lot more discussion about the nuance of where efficacy may be known or not known, and there needs to be more thought as we go forward as a community to understand the risk-benefit in different vulnerable communities. I think I'm understanding the guidance from the agency as we've done in other meetings.

Does that seem reasonable, Dr. Kotloff?

DR. KOTLOFF: Yes, very much. Thank you.

DR. BADEN: If no other questions about the process, and as highlighted, we'll vote, and then we will have plenty of time to discuss and explain

the nuances of our thinking, we should probably move to the first voting question, and I think I need to formally read this into the record.

Question 1, a voting question, is the overall benefit-risk assessment favorable for the use of nirsevimab for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season. A) If yes, please discuss your rationale; B) If no, please comment on what additional clinical data are needed to support this indication.

Are there any questions about the question?

DR. OFOTOKUN: This is Igho Ofotokun from Emory. I think the way the question is phrased, it assumes this distinct RSV infection and the distinct RSV season in all parts of the country at all times. But from the data presented, the presentation, that is not necessarily the case. So it's a little confusing. What if I live in Georgia where the weather is warm and maybe no seasonal pattern to RSV, then that question becomes --

DR. BADEN: Dr. Ofotokun -- and, of course,

I always appreciate the agency chiming in -- my interpretation of this is might there be benefit of this monoclonal in infants who have yet to be exposed to RSV, and where it's seasonal, it becomes easier to think about the seasonal deployment as discussed, and where it's not seasonal, then the deployment will require more nuance from oversight agencies.

Is that it, Dr. Farley?

DR. FARLEY: Yes, I agree with your response, Dr. Baden. And again, while voting is very important, the agency really values the discussion period that follows the vote so that you can share your recommendations and any nuances to your vote. That's very important to us. Thank you.

DR. BADEN: Thank you.

Dr. Krug?

DR. KRUG: Hi. This is Steve Krug. I'm from Lurie Children's Hospital, Chicago. I'm a pediatric emergency physician. There's a lot of excellent networking that goes on amongst those of

us who practice various specialty medicine, and while the RSV season looks different in Georgia, at least based upon feedback from colleagues who work at the children's hospitals there, in Florida and Texas -- I can't really comment on Hawaii -- there are still surges. There is still a surge. The surge may occur in various bursts through the year at odd times.

And again, getting back to the comments I made much earlier, part of this is a public health intervention.

DR. BADEN: I just want to say one thing. We have to be very careful about process. We need to vote before we explain how we're going to vote, so it's very important not to express how you might vote prior to the vote, and then afterwards, we'll have discussion as to the rationale each of us has given how we voted.

DR. JANKOWSKI: This is She-Chia Jankowski. Thank you, Dr. Baden, for mentioning that.

To the panel members, please vote as it is, and the wording itself, please go ahead and let's

get ready to vote as what's been written. We really welcome your rationale after the vote. Thank you so much.

DR. BADEN: And to Dr. Krug, we are going to be very interested in your thoughts, so the thoughts that you're sharing, we want to hear. Let's do that after we vote. Thank you.

Let me turn it back to Dr. Jankowski for the next step in the process.

DR. JANKOWSKI: Thank you, Dr. Baden, Dr. Krug, and everyone else.

We will now move non-voting participants to the breakout room.

(Voting.)

DR. JANKOWSKI: Thank you for your patience. Again, this is She-Chia Jankowski. Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. JANKOWSKI: Thank you for your patience. Again, this is She-Chia Jankowski, the DFO. The voting has closed and is now complete. The voting

results will be displayed, and it is displayed right now, and there are a total of 21 yeses, zero noes, and zero abstentions.

Back to you, Dr. Baden. Thank you.

DR. BADEN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. Please also answer the subparts A or B based on your vote, obviously 21 to 0, yes. Please unmute yourself and turn on your camera when speaking. We'll start with the first person on the list.

Where is the list?

DR. JANKOWSKI: Sorry about that, Dr. Baden. We'll pull it up momentarily. Thank you.

DR. BADEN: Thank you; that way it will be an orderly discussion. And to the panel members, here is an opportunity to share your thoughts as to why you voted yes, and other important considerations for the agency as they consider whether or not to move this therapy forward.

Dr. Jackson?

DR. JACKSON: Thank you. Mary Anne Jackson, pediatric ID, Children's Mercy, UMKC. My vote is yes, and it relates to four different factors. First off, this is one of the most important infectious diseases, resulting in significant illness in the pediatric population, so there's a need. Two, I think the presentations we saw assured me that there is good immune-based data, there's good safety data, and there's good efficacy data that shows that the product will prevent a significant number of cases of RSV lower respiratory tract disease.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Michael Green, University of Pittsburgh, pediatric infectious disease. I voted yes. Like Dr. Jackson, I thoroughly agree that this is a very important problem. I've been taking care of kids with RSV for more than 40 years, and I'm excited about this. I think the data that we saw showed primary efficacy against medically attended RSV lower respiratory tract infection in

both studies, and the secondary endpoint of hospital was shown in the first study, and perhaps was shown in the second study if you combined the primary data set and the safety data set.

There was no real significant safety signal to worry about, there was no real viral breakthrough, and I think that by expanding the availability of this RSV protective strategy to all children less than 12 months of age, we're going to have great benefit. The value of giving it as a single dose I think is going to make its operational implementation much easier and assure, hopefully, a more equitable availability of the product to all children who could all benefit. Thanks very much.

DR. BADEN: Thank you.

Dr. McMorrow?

DR. McMORROW: Yes. Meredith McMorrow, CDC. Likewise, I supported the efficacy assessment, the benefit-risk assessment. RSV is the leading cause of hospitalization in infants in the United States, and the high efficacy shown against medically

attended RSV-associated LRTI and hospitalizations that was reproducible across multiple settings was reassuring to me. I also found the safety data reassuring with few SAEs and no deaths related to the investigational product, and look forward to further discussion.

DR. BADEN: Thank you.

Dr. Patel?

DR. PATEL: Nimish Patel, University of California San Diego. I voted yes for a number of reasons. The drug performed extraordinarily well in a variety of cohorts, including those that were preterm and those that were at term, and those who were at high risk for RSV. I think the once seasonal dosing is a huge advance, and this is probably the closest thing to an RSV vaccine that we have, and it really moves the field forward, especially considering all the comments about how severe RSV is and the tolls taken on their health systems.

DR. BADEN: Thank you.

Dr. Kotloff?

DR. KOTLOFF: Hi. This is Karen Kotloff. I voted yes because I think that there is a very well-characterized burden of severe disease that needs to be prevented. I think that a single dose that's long-acting improves compliance. I think that the data were robust and they addressed a diversity of relevant risk groups and demographic groups, and were very well conducted. I think that the safety data were also compelling.

I think there are a couple of nuances that will need to be addressed. I think in terms of gestational age, the group less than 29 weeks gestation, I think the burden in that group is generally demonstrated, and I think data on PK could be extrapolated to make convincing recommendations in that group. The nuances that I think, though, will need to be addressed when it comes to policy recommendations are, one, that I don't know that we have enough data to assess benefit-risk in the kids who are older than 6 to 8 months of age because they had so few events that it's really a matter of is the disease burden

sufficient to warrant a recommendation in that age group.

I also think that implementation, especially with a lot of variance these days in seasonality, will be challenging and will have to be considered very carefully. I think that effectiveness studies that address some of these issues will also be really important post-licensure.

DR. BADEN: Thank you.

Dr. Cataletto?

DR. CATALETTO: Mary Cataletto, pediatric pulmonary, recently retired from NYU School of Medicine. I voted yes because I thought that the presentations were very comprehensive. I thought that the data was very robust both in terms of the efficacy and the safety. This is a tremendous problem, particularly in the postneonatal and young infants that we see in our daily clinical practice. I'd like to see more information, however, looking at the seasonality areas of seasonality, and also the different types of immunodeficiencies that are tremendously affected by this disease. Thank you.

DR. BADEN: Thank you.

Dr. Krug?

DR. KRUG: Hi there. Steve Krug. Again, I'm from Lurie Children's Hospital in Chicago and the Feinberg School of Medicine. I'm a pediatric emergency physician, and I have literally taken care of thousands of children with RSV. I voted yes, and I voted yes for many of those same excellent reasons that were already offered. This is a pathogen that has a substantial impact on the lives of young children, again, causing significant morbidity and mortality. It has a profound impact on healthcare providers, and it has a substantial impact on other children who just happened to be sick and need to be admitted to the hospital, and particularly children with special healthcare needs.

I think the point raised by, I think, Dr. Kotloff, I think we need to look at the gestational group less than 29 weeks because they appear to have that same risk profile as well, and it was probably a difficult group to study, so

that's more work to be done. I do agree that the seasonality differential that might occur in a certain part of the nation might require modified practice patterns but, again, thank you.

DR. BADEN: Thank you.

Dr. Hazra?

DR. HAZRA: Yes. Hi. Rohan Hazra from NICHD, NIH, and I voted yes. I do not disagree with anything that the other committee members have stated so far. I think what I'd like to just add is really to praise the sponsor on two really very, very well designed and well executed trials, so that really gave me a lot of confidence for my yes vote.

I also want to acknowledge how much input they took -- they mentioned it both in the slide set and in comments -- from experts throughout the field, as well as the regulatory agencies; not just at the beginning and through their planning, but then through the complications of the pandemic and whatnot, too. So it really resulted in some very, very clean, very convincing data, so I really

wholeheartedly voted yes. Thank you.

DR. BADEN: Thank you.

Dr. Stokes?

DR. STOKES: Hi. Thank you. Stacey Stokes from George Washington University and Children's National in Washington, DC. I voted yes as well. I would, again, just echo what a lot of people have said about the efficacy and safety data just being quite robust across demographics and gestational ages.

I also thought about this entire presentation in the context of practice and public health, and was thinking about morbidity and my patients who have RSV, and the correlation potentially down the road of development of asthma and the profound morbidity that's associated with that; resource utilization from primary care offices to ICUs and the impact that a medication like this may have; opportunity and costs with the lens of equity for families that have to keep children at home, even if they're not hospitalized with RSV; and the potential for improved health

equity overall relating to the simplicity of dosing and frequency, which I very much appreciate.

The only other thing that I'll mention is I did hesitate a little bit in the greater than 8-month old demographic just because I felt like the robustness of that data was not as strong but overall encapsulated that in my yes vote.

DR. BADEN: Thank you.

Dr. Lewis?

DR. LEWIS: Hi. Tamorah Lewis, neonatologist from Sick Kids in Toronto. I voted yes. I agree with everything that the other panelists have already said, and the only thing I would add is that as a neonatologist, I see a lot of late preterm and term children in the first 2 months of life who end up hospitalized in the ICU with RSV, and because the currently approved preventive medication is very restrictive in the population, there are a lot of children that fall outside of that, that suffer, and their family suffers, in the ICU, so that was a big driver of my decision.

DR. BADEN: Thank you.

Dr. Diekema?

DR. DIEKEMA: Hi. Doug Diekema. I practice pediatric emergency medicine and bioethics. I voted yes for many of the same reasons that have already been spoken. The incredible importance of a disease that affects almost every child before the age of 2, the impact of that disease on their families, on the children themselves and the healthcare system, all make a product like this very important. I was convinced by the efficacy data. I was reassured by the safety data, and this particular product offers the advantage of a single dose, which will not only increase compliance and real-world efficacy but also, I think, improve equity.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Hi. George Siberry, USAID. I voted yes. I thought that the studies as presented showed clear evidence of efficacy and reassuring evidence of safety across all the subgroups

presented, and I think that this could be a real game-changer, so that yes is an enthusiastic yes. Thanks.

DR. BADEN: Thank you.

Dr. Wilfond?

DR. WILFOND: I voted yes, and certainly for the population of people for whom there is no currently available medication, I think this is absolutely fantastic, and I'm really, really excited about the possibility of this being approved, and available, and used.

I still have ambivalence about the population of kids with chronic lung disease and prematurity, who I care for. I think the benefit of the one-time dose is less significant because often those are kids who need to be seen on a regular basis by their local pediatricians. More importantly, that's part of why they come in is because they need to get their their monthly immunization.

I appreciate that parents ought to have a choice about which one to do, but I worry that we

have limited data. With the extrapolated data only, there will be some parents who I believe might make a reasonable decision to prefer another medication, and I worry that that won't be available. Because the larger population of healthy children is so great that formularies and insurance companies are likely to say, indeed, this will cover everybody. I appreciate the comments about the extrapolated data suggesting efficacy, but I'm still not sure about efficacy compared to a drug for which we have a 25-year experience with, and that just makes me uncertain. There was such confidence among the presenters that, of course, this is better. I will acknowledge and may be a little skeptical that that's really the story.

DR. BADEN: Thank you.

Dr. Havens?

DR. HAVENS: Thank you. Peter Havens, recently retired from the Medical College of Wisconsin and Children's of Wisconsin. I voted yes. I feel like the efficacy data clearly are shown up to age 6 months. I think that after age

6 months, the data are sparse, so this might be considered approval by extrapolation for those over age 6 months. I worry about the strength of proven benefit after 3 to 4 months given the data that we saw on fall off in benefit at that time.

While the estimate of the relative risk reduction is really quite robust across all study groups, the absolute risk reduction really differs by different groups. For example, the absolute risk reduction will be quite small in older term infants, whereas it's likely to be much larger in premature infants, especially those with chronic lung disease; however, I think that that's not the job of this group to decide that. I note that the labeled FDA indication for palivizumab is really quite different than the AAP guideline on when to use palivizumab, so I think we need to keep that in mind, that guideline groups -- CDC, the AAP -- are going to come up with when they think it's appropriate to use. It's our decision to say whether it's safe and effective. So that's why I voted yes.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger, biostatistician. I voted yes. The efficacy endpoint as defined in the protocol was clearly met, and it was met across the different subgroups. I thought this was a very well-designed study and implemented, especially in this difficult situation that rates are very low and especially going into COVID, so I thought that was a very strong study.

I was impressed by the primary endpoint being very clearly defined, especially because it was an international study, and I think that's a strength of the study that that primary endpoint had a clear definition, and I thought the safety was reassuring. Then also, I was struck by the FDA's analysis, where they imputed for missing data, and the benefit held up across when they imputed different things for the missing data, so I do think the efficacy is a strong endpoint. That's all. Thank you.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Hi. This is Dr. David Hardy from Los Angeles. I am an adult infectious disease practitioner, so I haven't seen a lot of RSV in my practice, except for in older people. But I can certainly attest to the fact, having heard and read about this and better understood what this disease process causes in terms of not only morbidity for children but difficulty in the family situations, and away from work, and all those sorts of things.

This product really does, I think, advance what is out there already on the market because it makes it easier to use because of a very keen molecular change in the molecule. It pushes, and advances, and broadens the patient populations that can benefit, and we'll talk about the other one in a few minutes I know. But I think efficacy and safety have been shown very clearly by the two clinical trials that we reviewed in detail, and that there's really no reason that this product should not be made available for marketing in the U.S.

DR. BADEN: Thank you.

Dr. Baden, infectious diseases, Brigham and Women's in Boston. I also voted yes. As already stated, RSV is a really bad disease. In addition to the safety, efficacy, immunology mechanism, very clearly shown and very demonstrated, the considerations include -- in addition to it working, as the efficacy has shown -- there still are many more questions that have to be thought about. Safety in 3,000 is not safety in 3 million. Safety for a year is not safety for a longer time, although that should be much less of a risk in this setting.

Understanding efficacy targets such as the 12.8 viral escapes, I think there are many more questions that the community will have to be vigilant on to optimize efficacy, but the investigators, the company, and the sponsor conducted a very well-done study under very trying conditions. And as Dr. Hazra said, with COVID and the world shutting down, they were still able to conduct a high-quality study with an event rate to

demonstrate efficacy, and some of the event rate issues I'm sure were impacted by COVID that the sponsor was very diligent at addressing in a very transparent fashion. So overall, the efficacy is clear, more work to be done, but they've demonstrated important benefits.

Dr. Perez?

DR. PEREZ: Thank you. Federico Perez from the Cleveland VA Medical Center. I voted yes because I was convinced by the consistent and robust finding across a large body of data that nirsevimab for RSV protected infants from RSV illness. This indicates the possibility to protect all infants across the entire season with a single dose, which I find a very powerful intervention. This is also with a drug that appeared to be well tolerated with no safety concerns in term and preterm infants. Thank you.

DR. BADEN: Thank you.

Dr. Ofotokun?

DR. OFOTOKUN: Thank you. Igho Ofotokun. I am an adult infectious disease specialist at Emory

University here in Atlanta. I also share the same sentiment as my colleagues. I am very impressed with the efficacy, as well as the safety data, and I really want to commend the applicant, as well as the agency, in addition to the community members who came to speak about this product.

I am particularly impressed with the details of the study, the fact that they collected data on special populations, including at-risk minority populations and the immunocompromised population enough to give us a level of certainty that this drug is going to work across the board. So I was very impressed, and that was why I voted yes.

The only intents of the policy going forward, the number, the sample size for the special populations, the immunocompromised patients, the underrepresented minority, is small, of course, as should be expected. I think going forward, should this drug be approved as we design the postmarketing surveillance study, post-approval study, these are the populations that I really would encourage the agency to pay attention to the

design such that more robust data can be collected from the immunocompromised population, as well as the population underrepresented minorities and other at-risk groups.

Again, a statement about the seasonality of RSV, when this drug should be in different geographical locations based on the seasonality of RSV should be something that the applicant should think about as we make a final decision should this product move forward; otherwise, I think it's a great product. Thank you.

DR. BADEN: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Walker. I voted yes. I share the same sentiments that have been shared by my colleagues. Furthermore, as the consumer representative, I voted yes because I firmly believe that the children are our future, and I believe that this product will ensure not only a sustainable but a healthy future for them; so huge kudos to the applicant, the agency, as well as the testimonials that were shared by the family members

who were previously affected by this. Thank you.

DR. BADEN: Thank you.

Ms. Shackleford?

MS. SHACKLEFORD THOMAS: Hi. Jasmine Shackleford Thomas here, representing the Lupus and Allied Diseases Association. I voted yes. I'm coming from a parent/caregiver perspective. I have four children who battled RSV simultaneously, ranging from the ages of 2 to 9 in October of 2022. As a result of RSV, I have a child who is now officially diagnosed with asthma. He was already at risk before, but I do believe that RSV definitely played a factor in his official diagnosis. So based on seeing how the virus can affect children of various ages is a major factor and why I voted yes, as well as the safety and efficacy information presented today.

DR. BADEN: Thank you.

For question 1, the vote was was 21 to 0 that efficacy and safety has been established. The panel was impressed with many features of the study design, study conduct, study implementation, study

engagement, with the agency's experts, community, and broad communities, including underrepresented communities in research. The biology of the intervention is clean and straightforward. Safety did not show any concerns, consistent with how these products behave. The immunology was very supportive, and the efficacy with a clean definition was robust across a variety of analyses. The single-dose use is incredibly attractive.

Given all of that, certain caveats were raised to just take under advisement. The issue of comparison with palivizumab, particularly for those children who already benefit from its use, needs to be looked at with care before practices change without high-quality comparative data. The absolute versus relative risk needs to be looked at carefully, as not all populations or subpopulations may have the same amount of benefit, and that should be thought about. Important populations like immunocompromised patients need to be better thought about to understand how this behaves and considerations for deployment as one understands

seasonality in different regions and how that might impact how this is deployed.

So overall, all committee members were impressed with the conduct of the study and the clean results that were presented, but as all good research points out, there's still more work to be done, but the committee believes this is an important advance.

We should now move to the discussion question. Before we go to the discussion question, for the panel members, did I misrepresent anything in the summation to the agency for question 1?

(No response.)

DR. BADEN: Not hearing a groundswell of misrepresentation, thank you. I would like to move to slide 4 and to question 2, which is a discussion question.

Question 2 reads as follows. Please comment on the benefits and risks for nirsevimab when assessed by chronological and gestational age groups. Discuss the population or subpopulation for whom nirsevimab administration in the first RSV

season would be most appropriate.

Any questions about the wording of the discussion question?

(No response.)

DR. BADEN: If there are no questions about the wording, I will open the floor to discussion about the issues raised here. As Dr. Farley mentioned earlier, the agency is incredibly interested in our thoughts and reflections, so please speak up as to how you think about the issues here for them to carefully consider as we move forward.

Dr. McMorrow?

DR. McMORROW: Thank you, Dr. Baden. Meredith McMorrow, CDC. I just wanted to respond to a question raised by Dr. Ofotokun. We are planning to look and to speak with jurisdictions where seasonality of RSV is less well defined and/or places that have year-round seasonality, so that should nirsevimab receive FDA approval and consideration by the ACIP, that we would be able to come up with implementation strategies that would

address places that don't have clear seasonality. Some of those discussions have centered around either a longer duration of months of the year where one might administer it and/or kind of continuous year-round administration for newborns.

So there are some alternatives that we're exploring, and just say that we are starting to think about those things in terms of places that have less well-defined seasonality. Thanks.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Thanks. George Siberry, USAID. I think that the information we have about risks is reassuring across all chronologic and gestational age groups. I think the question about benefits is a little bit different. It was remarkably consistent in Study 03 and Study 04 across the different groups there, so I don't think we need to parse too much. But I'll just say that for the older infants and for children with high-risk conditions, that's come up as an area of discussion.

I think that the role here is to say, in my opinion, there's no safety concern in those older infants, just too limited participation to be able to document the potential reduction in the risk of RSV. But I think that a lot of that conversation is for our CDC and professional society guidelines colleagues, and not about enough evidence to license the drug for all infants.

Then second -- and, Chair, I'll ask your opinion on this -- for the children with high-risk conditions, do you want us to defer discussing those until after the next question, which refers to the study of other children with high-risk conditions, or do you want us to address that here for newborn infants with high risks, say, pulmonary or cardiac conditions?

DR. BADEN: I think that voting question 2, question number 3, gets at that directly, so we should probably discuss that after voting question 3. I accept your comment that the issue of extrapolation underlies this whole discussion, so many of the thoughts will extend both to

discussion question 2 and voting 3, but I would prefer that we vote on the second voting question before we discuss the second voting question.

DR. SIBERRY: Very good, then I'll end there. Thank you so much.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Mike Green, University of Pittsburgh. I strongly agree with Dr. Siberry. I think that answering the question about whether we should use it in 7 month olds or 9 months olds, really, we don't have the data yet, but this is unique in that it's more like a vaccine. And as Dr. Siberry said, the ACIP and CDC, as well as specialty groups and organizations like the American Academy of Pediatrics and others, will likely weigh in to provide guidance.

If and once this is approved, I do think, though, that it would be wonderful if the applicant, and the agency, and the CDC, and the other societies strongly encourage postmarketing and real-world data acquisition and systematic ways

to try to formalize and fill in the gaps and knowledge that we currently have, but I don't think that should limit making this available on a broad basis to anyone that's less than a year.

I will just add the point that the epidemiologic basis of thinking that the older infant may be at less risk was probably really called into question for those of us that took care of kids in the last year, where it wasn't just the 11-month olds that were having more important illness, but toddlers as well. So this was a really important eye-opening experience, where the behavior of this virus changed, whether that was because of lack of exposure during the years of COVID when we wore masks and we didn't go out and about, or other things. But I think we can get at this through the work of postmarketing, real-world data acquisition. Thank you very much.

DR. BADEN: Thank you.

Dr. Krug?

DR. KRUG: Hi. Thanks. This is Steve Krug, pediatric emergency physician at the Lurie

Children's Hospital and Feinberg School of Medicine. Again, I really want to applaud the solid work by the applicant/sponsor and, again, the outstanding work done by the FDA today.

Based upon the data that I've seen, I think that there's a real benefit exceeding risk here, although, again, while these were well-powered studies, we'll learn a lot more from studies done on even larger numbers of children. While I have an opinion on this, I would absolutely defer to groups like the AAP, CDC, ACIP, and many others who will likely collaborate guidance for all of us to follow as we see how this works. I will point out, though, that not just during the pandemic but, again, the world pre-pandemic, plenty of otherwise incredibly well, healthy, beautiful children who are more than 6 months of age, including toddlers, are desperately ill with RSV, and particularly large numbers of these children, in addition to the children who appear to be at great risk during RSV season. So I think we'll learn a lot more about this as we hopefully get to start to use it. Thank

you.

DR. BADEN: Thank you.

Dr. Kotloff?

DR. KOTLOFF: I apologize because I actually did address this in the first statement. But I think that this study was not designed with the primary endpoint being subgroup analysis, so we are recommending approval based on the study design. But I do think, as people have said, that it's the CDC advisory groups that will incorporate epidemiology into making these recommendations, and that will be critical.

For example, there wasn't sufficient data after 6 months. If you look at the subgroup in these particular studies, I think to say there's benefit, but that wasn't the design. But the CDC can look at that, and look at the burden of disease, and look at whether there are subgroups of older kids who should have a recommendation. So I think we've done our job, and that taking it from here will be up to the CDC.

DR. BADEN: Thank you.

Dr. Havens?

DR. HAVENS: Peter Havens from Medical College of Wisconsin. So we all agree that other groups are going to make the epidemiologic determination. The question for this group is, is there enough data in the over 6-month or over 8-month for the FDA to approve the drug, and are we doing it based on data or are we doing it based on extrapolation from what we know in the younger kids? That's, I guess, my question for the group that I'm really interested in.

DR. BADEN: I have a comment for Dr. Havens, but let me let Dr. Ofotokun talk first, and then I'd like to share my thoughts, as Dr. Havens has provocatively raised a key question.

DR. OFOTOKUN: Yes. Igho Ofotokun from Emory, Atlanta. I think when we think about this question, if you look at the data broadly, regardless of the subgroup that was looked at, whether the younger or the older age group, even the at-risk population, the signal is there that there was benefit. I think that was clear across.

I think the agency data, the scatter plots that they showed at the beginning of their presentation really clearly represented that no matter what group you look at, there was that trend towards benefit.

I think the issue here is they were not designed to address those questions, but I think, overall, if you say do no harm, there's no reason to think that this would not benefit even the older group of patients who are at risk, who will need this. Like others have said, that is a question for other agencies to address, but there's no red flag to want to say this is going to be harmful for individuals that are 6 months or older. And when you look at the data, even though it's sparse and it's not sufficient, there is evidence that there is a trend towards benefit, and the risk across board has been just minimal.

DR. HAVENS: Well, for sure. I agree that there is no evidence of risk, but a 10- or 12-month-old child is much bigger, so they're going to be 10 or even 12 kilos if they've tripled their

birth weight by 10 or 12 months. So thinking about the appropriate dose in somebody who we haven't really studied is different. In the second year group, they doubled the dose; it was safe, so I'm not worried about safety, but I do wonder about efficacy in terms of potentially dosing and making this jump based on extrapolation.

DR. BADEN: Dr. Havens, I share your concern, but as the agency commented, they routinely extrapolate, and part of the issue of extrapolation is what's the strength of the logic behind it given the needs of the untreated, and from my perspective, the biology of this agent is so clean, so that the risks of the unknown seems smaller.

I do have concerns about safety in that a drug that hangs around for a year for a rare safety event, that could be trouble because you can't unring the bell. But there was no evidence of that, and it's something that will have to be monitored for carefully. But the question of the likelihood of activity of this agent against its

target remains high whether it's child A or child B. I do think -- and we harped on this in some of the discussion, what is a protective titer -- the 12.8, as magic as that is, I'm not convinced is as clean as it needs to be. But that's the kind of measurement that can be iterated on and improved on, which ultimately, is it really the dose or is it really the level, which are inextricably linked given the size of child. But the biology is straightforward and compelling, and the agency wants some guidance as to does that make sense to extrapolate, and there's a rationale there.

DR. HAVENS: Sure. But in Study 03, they already changed the dose from 50 to 100 because at 5 kilos, it didn't seem to be enough. So if we're looking at this in a milligram per kilogram dose, it would be interesting to see the day 151 concentration by milligram per kilogram dose administered.

DR. BADEN: To take your comment to the next step, which doesn't need to happen, but I will,

what you're proposing is that, if approved and if used, and if used through extrapolation, that systematic measurements are done to really work out dosimetry, as kids have different metabolism or sizes, so that they can get the dosing optimized.

DR. HAVENS: The further you get away from 5 kilos, the lower the per kilo dose is, extrapolation works with milligrams per kilogram, not necessarily with a straight milligram dose in somebody who's rapidly gaining weight, and kids triple their birth weight by 10 months.

DR. BADEN: Point well made.

Seeing no other hands, and the hour is late, my temptation is to skip the break and go right to question 3, the second voting question.

Is there any objection to that?

(No response.)

DR. BADEN: If not, then I think we'll move on to the next question, question 3, which is a voting question.

Is the overall benefit-risk assessment favorable for the use of nirsevimab for the

prevention of RSV lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. If yes, please discuss your rationale. If no, please comment on what additional clinical data are needed to support this indication.

First, are there any questions about the wording of the question?

(No response.)

DR. BADEN: If there are no questions or comments concerning the wording of the question, we can begin the voting. Dr. Jankowski will guide us through the process.

DR. JANKOWSKI: Thank you, Dr. Baden. This is She-Chia Jankowski, the DFO. Please bear with me for a moment before getting ready to vote.

(Pause.)

DR. JANKOWSKI: We will now move non-voting participants to the breakout room.

(Voting.)

DR. JANKOWSKI: Voting has closed and is now

complete. The voting result is displayed. There are a total of 19 yeses, 2 noes, and zero abstentions. Thank you.

Back to you, Dr. Baden.

DR. BADEN: Thank you.

We'll now go down the list and have everyone who voted state their name and vote into the record. Please also answer subparts A or B, based on your vote and thoughts. Please unmute yourself and turn on your camera when speaking. We'll start with the first person on the list, Dr. Cataletto.

DR. CATALETTO: Mary Cataletto. I voted yes because I thought the data regarding efficacy was good. I share some of the concerns that people have about over the 8-month old, but this is a high-risk population, and that swayed my decision.

The other thing has to do with the question itself, talking about first or second season. I think we need to clarify the recommendation, and CDC and the other organizations will probably do that in terms of how we handle areas of the country where there's no seasonality to the RSV

epidemiology, so I voted yes. Thank you.

Dr. Wilfond?

DR. WILFOND: Yes. I also also voted yes. And as someone who had already expressed concerns about some of the subpopulations, I very much appreciated all the comments of other members pointing out, again, the distinction between our role and of other entities who will be looking at this in the future. So I feel much more comfortable with supporting the FDA decision, but also really hope, and really want to trust in my other colleagues, and other agencies, and entities, to look more carefully at both the quality of the data now, as well as what further research is needed to make evolving guidelines over time.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: George Siberry, USAID. I voted yes. I think that there is adequate safety information, good results that look aligned with expectations across other groups, good PK information, and this is a critical population to

potentially benefit from this, so I voted yes.

DR. BADEN: Dr. Patel?

DR. PATEL: Hi. Nimish Patel, University of California San Diego. I voted yes. [Indiscernible].

DR. BADEN: Can you come closer to your microphone?

DR. PATEL: Sure. I voted yes.

DR. BADEN: That's better.

DR. PATEL: The Season 1 efficacy data was quite compelling, and extrapolating that into year 2, or Season 2, knowing that the exposure was doubled just made the argument a little bit more solidified, and the safety data was quite strong, so that was why I voted yes.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Michael Green, University of Pittsburgh. I voted yes. I acknowledge the limitations of the data relating to efficacy, but I believe the PK data supports extrapolation, which has been the practice of FDA. Further, I think the

PK data -- taken along with the fact that we have long experience with using palivizumab -- really, in this age group, that is 12 to 24 months for at-risk patients, to my understanding, the mechanism or the biology of how the biologic works is quite similar, so I would anticipate that it should work. We clearly need to get postmarketing and real-world data to help inform this should it be approved by the agency. And again, I think that this is something that can be looked at and modified in terms of how it should be recommended by the other agencies and organizations that will have that responsibility. Thank you very much.

DR. BADEN: Thank you.

Dr. Krug?

DR. KRUG: Hi. Steve Krug from Lurie Children's Hospital and the Feinberg School of Medicine. I very much agree with what's been said so far. The data supports the concept of extrapolation to this older age group, and I think there's, again, still very good safety data. The question at hand here -- and again, we will rely

upon other groups to provide specific guidance -- is on the highest risk subpopulation amongst children from ages 12 to 24 months, so that's why I voted yes.

DR. BADEN: Thank you.

Dr. Kotloff?

DR. KOTLOFF: I voted yes. This is the established group with the highest disease burden most in need of being prevented. There's biologic plausibility. There is a strong precedent that this would work with the existing approved monoclonal antibodies. There were no safety signals. There was a suggestion that incidence was the same as a preparation with proven efficacy, and it met criteria for extrapolation, so that's why I did it. Thank you.

DR. BADEN: Thank you.

Dr. Diekema?

DR. DIEKEMA: Doug Diekema, University of Washington and Seattle Children's. I agree with everything people have said before me. This is a particularly important problem for the group in

question here. I was convinced by the efficacy data and reassured by the safety data.

DR. BADEN: Thank you.

Dr. Havens?

DR. HAVENS: Peter Havens, from the Medical College of Wisconsin. I voted yes. I'm quite comfortable with extrapolation in the context of the robust PK data, noting that they doubled the dose. The difference with this extrapolation data versus the other is for the older kids under a year, there's inadequate PK data. This has adequate PK data, so I voted yes.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Hi. This is Dr. David Hardy from Los Angeles, LA County USC, infectious disease, adults. I voted yes because I think, again, although the data was not as strong for this group simply because it was not powered in the clinical trial that was done, unfortunately, this group of high-risk children remain I think some of the most vulnerable, and therefore in need of a

preventative intervention that would prevent them from getting a higher risk for mortality from this disease, so that's why I voted yes.

DR. BADEN: Thank you.

Dr. Baden, Boston. I voted yes as well. As already stated, the biology PK is pretty straightforward. I think the key issue going forward is to make sure that the PK in the relevant populations like this one is understood, and the viral susceptibility is also maintained because the underpinning of the biology here is that interaction, and I think target tissue attainment shouldn't change. So as long as the community maintains an eye on the underpinnings of extrapolation, and they stay solid, then the extrapolation I think is likely to be successful. Thank you.

Dr. Stokes?

DR. STOKES: Thank you. Again, Stacey Stokes from GW and Children's National in DC. I voted yes. I don't have too much to add. In addition to what everyone said, I will just say

that the conversations around feasibility of Trial 05 options was very helpful to me, as well as the understanding of extrapolation in this context; so definitely thank you to the group and to the sponsor for going through that multiple times. I also really appreciated, and what helped in my vote, the RSV neutralizing antibody level data, and helped to solidify my vote as well. Thanks.

DR. BADEN: Thank you.

Dr. Lewis?

DR. LEWIS: Hi. Tamorah Lewis from Sick Kids in Toronto. I voted yes. I think the key to extrapolating in this group is that the sponsor showed really strong exposure matching data, and it was helpful to see the PK data over the wide range of weights that can be seen in these older children going into their second season. I found that reassuring. So in addition to what everyone else has said, that's why I voted yes.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Thank you. Federico Perez,

adult infectious diseases, Cleveland VA Medical Center. I voted yes because it appears to me that for children of the highest risk facing their second RSV season, nirsevimab offers advantages. And even though this decision is based on extrapolation, the PK data regarding the high level and long duration of sufficient antibody levels is strong, and this extrapolation is therefore reasonable. As pointed out by the verbatim molecular surveillance of variants is also an important consideration, and numerous discussions of parents and expert pediatric care providers following guidance by public health and professional organizations will be necessary to ensure proper use of this product vis a vis the alternatives. Thank you.

DR. BADEN: Thank you.

Ms. Thomas?

MS. SHACKLEFORD THOMAS: Yes. My previous answer to the first question kind of plays into this. I think, again, coming from the caregiver perspective and the safety data presented, that

played a major role in me voting yes. Thank you.

DR. BADEN: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker. I voted yes, and I can concur with everything that has already been expressed. Thank you.

DR. BADEN: Thank you.

Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun from Emory University, adult infectious diseases. I voted yes for the reasons many others have articulated. I think for children at risk of RSV up to the age of 24 [sic - months], I see that there could be benefit, and I do agree with all of the caveats that better PK/PD data needs to be collected in this population, but the information that was presented was strong enough for me to think that there is definitely going to be a benefit in this population, so thank you.

DR. BADEN: Thank you.

I need to remind panel members to state their name for the record.

Can Ms. Thomas state her name for the record, please, in association with her vote?

MS. SHACKLEFORD THOMAS: Sure. My apologies. Jasmine Shackleford Thomas. I voted yes.

DR. BADEN: Thank you.

Dr. Hazra?

DR. HAZRA: Yes. Hi. Rohan Hazra from NICHD, NIH. I voted yes. The agency clearly has laid out a plan for extrapolation for these populations, and the company, again, did a really nice job with a trial through some difficult circumstances. As other folks have raised, I think there are still a few issues that will need to be addressed in postmarketing and other studies. One is that group with congenital heart disease had a slightly larger proportion that was below that AUC target after the first dose, and then certainly both groups had higher than the comparison after that second dose, but still certainly well below the exposures seen in the adult studies.

I'll also just add, for these populations,

it may be a little bit harder to do routine surveillance, but likely many of these populations are in other long-term natural history type studies for their conditions, so there may be opportunities to work with NIH and other research organizations to be able to get some of the surveillance and data collected for these populations. But once again, I was very comfortable voting yes.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger, biostatistician. I thought about this a long time and ended up voting no. I think I just was uncomfortable with extrapolating quite that far, and I worried that if I voted yes, then maybe there wouldn't be quite as much studying done. So it's a bit of a weak no, but hopefully that will just emphasize that I feel like we do need more data on this. I think we need to do more studies to totally understand this. So it's a weak no, but I just wanted to make sure people realize that I feel like we need a little bit more data. Thank you.

DR. BADEN: Thank you.

Dr. Jackson?

DR. JACKSON: Mary Anne Jackson, pediatric ID, Children's Mercy, UMKC School of Medicine. This is a very nuanced no, and I'll tell you the reason why. There's no question that there's a very significant burden of disease in both morbidity and mortality in this patient population. What worried me was within the congenital heart disease population, it was a smaller population that was studied, and it wasn't very well nuanced because many of these patients are undergoing multiple different surgeries during that second year, where they may have a complete exchange of their blood volume and may require re-dosing.

So we don't have the data in that group, but I feel very comfortable about the safety information. I understand the PK information, but in that congenital heart population, this may need to be very nuanced, and if it can be in post-licensure studies, then I'm very comfortable with that.

DR. BADEN: Thank you.

Dr. McMorrow?

DR. McMORROW: Yes. Thank you. I apologize for dragging my feet on this one, but my debate was between yes and abstain, and that's because I thought we were asked to extrapolate on both efficacy and safety. There was very little data presented. Only 220 infants received this in the second year of life; however, I do believe that there is little risk of a safety signal from this product.

I also thought about abstaining because I recognize the lower risk in the second year of life; however, the comparator product, palivizumab, I did feel like the peak concentrations were higher from nirsevimab in terms of geometric mean antibody concentration. And if I recall correctly -- and others from the FDA or the manufacturer are welcome to correct me -- I believe you don't achieve palivizumab levels until you've received your second or third dose. So for infants in whom follow-up can be challenging, having to come in for

monthly injections may be a hurdle to equity and feasibility, so I think the single-dose option made me vote in favor of this. Thank you.

DR. BADEN: Thank you.

Dr. McMorrow, we need you to state your name and vote for the record.

DR. McMORROW: My apologies. Meredith McMorrow, CDC.

DR. BADEN: And you voted yes.

DR. McMORROW: I voted yes.

DR. BADEN: Thank you. I am tasked with making sure we follow procedure, so I appreciate the committee's sense of humor as I try to fulfill my obligations.

So in terms of question 3 as a summary of the committee's comments, to some degree question 3 and question 2, as Dr. Siberry already alluded to, are based upon the same way of thinking. So in trying to share the summation of the committee's discussion for the discussion question and the voting question, the vote was 19 to 2, yes, and the fundamental concepts about extrapolation, the

committee is largely comfortable with given that the biology of this particular product is understood. PK can be measured and target susceptibility is known, but these are things that will have to be monitored and assessed.

The role of other bodies, such as the ACIP, the Academy of Pediatrics, will allow more contours to how this can be used clinically, so there's more opportunity as more data emerges and as guidance bodies weigh the emerging information to help provide guidance to the community on how to use these agents.

Some of the members noted that the challenges with the noninferiority design and the event rate, which is low when both agents are active and when there is a shutdown, that it is difficult to do an efficacy trial, but many members noted that the efficacy signals were all in the same direction even if underpowered for certain groups. So there wasn't a concern of a flipping of efficacy as much as a power to detect signal, depending on which community we were looking at.

The PK in different groups needs to be looked at carefully, as noted in the congenital heart disease group, where the PK looked a little different, and as Dr. Havens, one of our members, mentioned, that dosing may be different based on weight and rapid change in weight, and that needs appropriate attention.

The two no votes, our colleagues raised very important issues to pay attention to, both from an agency standpoint, and an applicant standpoint, and a community standpoint. We have to be careful when something is approved, to then stop learning, and that we do not have efficacy data. We have extrapolated data that many of the committee think make sense, but we should not take that as a signal to not continue to do rigorous study, and that is a concern when there isn't pressure to do those studies, even though it's clearly potentially a benefit to the community to better define how these agents work. And I think the sentiment was to encourage the agency, and more importantly, the applicant, to generate the relevant data so that we

can be data driven.

Then the other important comment from our committee members who voted no is that there's nuance in these high-risk populations, and the PK -- how drugs are used, how blood volume is changed -- really is very nuanced in these populations. So to understand how to use these agents in those populations requires high granular detail to best apply it in those specific circumstances as opposed to more general circumstances. Overall, the vote 19-2, but the committee largely thought the extrapolation approach had a solid foundation in this setting.

I once again open the floor if any committee members think I misrepresented any of the important concepts.

(No response.)

DR. BADEN: If not, we can move to the last question, which is slide 9.

Question 4, a discussion question. In the context of potential, future availability of maternal RSV vaccine to protect infants from RSV

disease during their first RSV season, what additional data may be helpful to inform future recommendations regarding the use of nirsevimab in infants born to mothers who receive RSV vaccination?

Are there any questions about the wording of the question?

(No response.)

DR. BADEN: If there are any questions about the wording of the question, please speak up. My impression from colleagues whose hands are up is they're ready to discuss.

(No response.)

DR. BADEN: And seeing nobody speaking up about the question, then what I'd like to do is to open the floor and start with Dr. Patel in opening this discussion.

DR. PATEL: Yes. When I read this question, I think of two potential data gaps. They are likely to be women who are unable to take these investigational products and receive a maternal RSV vaccine -- so if there's a certain selection bias

of those women and the children that are born to them -- if nirsevimab still confers the same benefit, but also if there's an additive benefit in individuals who've received an RSV vaccine and their infants received nirsevimab, is there additivity that's experienced.

DR. BADEN: Thank you.

Dr. Cataletto?

DR. CATALETTO: I have no additional comments. Thank you.

DR. BADEN: Oh, I'm sorry. I apologize. I was misreading my screen.

Dr. Jackson? My mistake.

DR. JACKSON: Thanks very much. Additional data that might be helpful with the future availability of maternal RSV vaccine and regarding the use of monoclonal antibody really relates to how the epidemiology of this disease might change and, as was discussed just briefly earlier, whether or not the average age of disease may be pushed out to an older older age for first infection, and whether or not we have all the data we want for

those older infants in terms of dosing. And I'm talking about 8 months and older, specifically.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Mike Green, Pittsburgh. I think one of the things -- at least I don't have a knowledge of the data and I don't know how well the data were collected in the vaccine trials -- is that women will pass transplacental antibody to their unborn babies differentially, based upon gestational age. So the amount of antibody that a 33-week gestational age baby will have in a mother that was vaccinated is likely very different than a 39-week gestational age baby.

So one would love to have those data available to you and perhaps stratified by age groups, just being sort of off the top of my head, 32 to 34, 35 to 37, 38 to 40, something like that, to see if there's a differential benefit based on the gestational age that the baby is born at.

Then also as was mentioned just a moment ago, the potential additive benefit that happens if

you give the monoclonal, long-acting antibody on top of antibody that comes across the placenta, do you enhance the level of protection? Because while we had efficacy, we did not have a hundred percent efficacy, and there could be differential efficacy. So if the applicant could be so motivated, and if they could cooperate either with the vaccine makers to do a trial, or if they used as an inclusion criteria women that were vaccinated as an inclusion criteria for who they enrolled for babies to really try to look at this study, stratified by gestational age, and looking at both PK differences and also efficacy differences in those that got both versus those that got only one; and then, of course, double checking the safety signal to make sure that nothing untoward happens by doing this. Thanks very much.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Thanks very much. George Siberry, USAID, and I want to endorse first what Dr. Green has suggested, especially the

stratification of the different gestational ages. I'd also add to consider as lab specialists, if it's feasible, to do in vitro or animal studies that can confirm that the immune sera following the maternal RSV vaccination -- so obtained from those pregnant women -- does not interfere with the neutralizing activity of the monoclonal antibody in this product. It's unlikely, but I think it's important to document that the serologic response in the mother that would then be passively transferred to the infant wouldn't interfere, at least in vitro, with the neutralizing activity.

Beyond that, I think the rest could all happen post-licensure, and I would hate to see any restriction on using this product in infants if it is going to be used routinely in infants based on whether Mom got the RSV vaccine, but I would love to see a study that can tease apart especially infant getting this or not, in addition to the mother vaccine; is there an added benefit or is it simply just as good? That would be useful to know where to put resources and what to emphasize.

Thanks.

DR. BADEN: Thank you.

Dr. Kotloff?

DR. KOTLOFF: Yes. I think that public policy will require a trial that looks at these interventions alone and separately, comparatively. Financially, I don't think that our healthcare system could tolerate universal recommendations for both, and I imagine that there will be niches for each, kind of in the way that varicella vaccine and VZIG worked its way out. So I think there will need to be studies that are done to figure out when one is more useful than the other. I don't think that would interfere with licensure, but I think it would interfere with policy guidelines.

DR. BADEN: Thank you.

Dr. Ofotokun?

DR. OFOTOKUN: Igho Ofotokun from Emory. I think I'm making the same points here, that it would actually depend on the vaccine and the durability of the passive immunity from the mother to the baby. And I think until we have those data,

it's going to be really difficult on how to position this product. My sense is how much of this passive immunity is passed on to the baby and how durable is that passive immunity? So we will need additional data to look at the durability of the passive immunity to the baby, and whether we need to continue to study the efficacy comes to the point of getting more data in the older children who are at risk of developing RSV. So in terms of additional studies, it would really depend on the characteristics of the vaccine that is being produced.

DR. BADEN: Thank you.

Dr. Baden. I'll make some comments. Similar to what Dr. Kotloff and Dr. Ofotokun has said, I think with tetanus and pertussis, there are examples of where maternal vaccination prevents neonatal disease. So I think there is a strong logic here, and there are some data emerging in the vaccine field, as suggested. What gets tricky, as raised, is what's the correlate of protection? Do we understand what that is? Is it antibody,

neutralizing antibody? Are they measuring the same thing in a passive antibody versus a vaccine and placental transferred antibody?

So it may not be the same moiety of protection, so that has to be understood, and the durability of that placental transfer, whether it's a month, 6 months, and then the burden of infection in the neonate to know at what point passive immunity would add to maternal derived immunity. So that has to be worked out scientifically.

The additional issue that I think we have to think about is equity. I worry about certain communities getting multiple layers of protection and other communities not getting any. We have to think about, as we deploy our resources, that we understand what the benefits are and we make sure that those benefits can reach as broadly as possible given the scientific basis of those benefits and the deployability in the relevant communities. So I think there's a lot more science that's needed to really answer this question, but it will be very real, perhaps soon.

Other comments from panel members?

(No response.)Beyfortus HARMONIE

DR. BADEN: Not seeing other comments, then to summarize the discussion for question 4, several panel members thought that there is opportunity to increase the efficacy through multimodality protection, and with the monoclonal, there was clear benefit, but the benefit was not perfect.

So therefore, additional modalities such as maternal vaccination can help approach the asymptote of even higher protection levels. However, raised by several of the panel members is there's a lot of biology that's unknown here, so the biology has to be understood in relation to the specific products that come forward.

So this is obviously a theoretical question, but understanding how the specific products may lead to immune protection that can be transferred to baby and how that can be optimized scientifically will depend on the specifics, but conceptually an important area to think about to see how best to augment protection in neonates,

whether it's through a maternal transfer or through this product as we better understand how it works and can be deployed.

Any other additional comments for this question?

Dr. Hazra?

DR. HAZRA: Yes. I just want to reiterate I think something Dr. Jackson raised about also this issue of potentially pushing out first disease to that older age group greater than 6 months, which is the one that Dr. Havens was very concerned about that we may not be dosing correctly. So I would add that issue to this, too.

DR. BADEN: Thank you.

If there are no more comments, then before we adjourn, let me just say that I would like to thank the committee for really a marathon session; to the applicant and the agency for incredible data presentations and discussion; and to the community participants, particularly the OPH speakers, for really making palpable the reality of this condition and how important it is for, as a

community, therapies to emerge that can be deployed to prevent this severe illness.

Let me, before we adjourn, give the last comments to the agency.

DR. HAZRA: I just raised my hand. Lindsey, I also just want to thank you. You did a fantastic job as chair, so thank you for leading us.

DR. BADEN: Thank you.

Dr. Farley, the floor is yours.

DR. FARLEY: On behalf of the review team at the FDA, we want to thank the panel for just an outstanding discussion today. You've given us very valuable feedback to consider as we conclude the review of this application, and to thank the applicant for working with us to facilitate an efficient discussion today, and a thorough one. I want to thank the open public hearings speakers, as well as those who submitted comments to the docket, which we've also reviewed. So thank you very much, and back to you, Dr. Baden, to adjourn us.

Adjournment

DR. BADEN: We will now adjourn the meeting.

Thank you all.

(Whereupon, at 4:43 p.m., the meeting was adjourned.)