FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

(PADAC)

Virtual Meeting

Tuesday, November 8, 2022

10:02 a.m. to 4:04 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

David H. Au, MD, MS

(Chairperson)

Professor of Medicine

University of Washington

Director

Center of Innovation for Veteran-Centered and

Value-Driven Care

VA Puget Sound Health Care System

Seattle, Washington

Scott E. Evans, MD, FCCP, ATSF

Professor & Chairman ad interim
Department of Pulmonary Medicine
Rebecca Meyer Brown and Joseph Mellinger Brown
Chair in Basic Science Research
University of Texas MD Anderson Cancer Center
Houston, Texas

Fernando Holguin, MD, MPH

James C. Campbell Professor in Pulmonary Medicine
Associate Vice Chair of Research
Department of Medicine
Director of the Asthma Program at the Center for
Lungs and Breathing
Director of the Pulmonary Translational Core
Division of Pulmonary Sciences and
Critical Care Medicine
University of Colorado
Aurora, Colorado

Edwin H. Kim, MD, MS

Associate Professor

Division of Pediatric Allergy and Immunology

University of North Carolina School of Medicine

Chapel Hill, North Carolina

Susanne May, PhD

Director

University of Washington Clinical Trials Center

Professor, Department of Biostatistics

University of Washington

Seattle, Washington

James M. Tracy, DO

Clinical Professor of Pediatrics

University of Nebraska College of Medicine

Allergy, Asthma and Immunology Associates, PC

Omaha, Nebraska

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Dawn M. Carlson, MD, MPH

(Industry Representative)

Vice President

Clinical Pharmacology

Abbvie, Inc

North Chicago, Illinois

TEMPORARY MEMBERS (Voting)

Michael D. Cabana, MD, MPH

Professor and Chair of Pediatrics

Physician-in-Chief

The Children's Hospital at Montefiore (CHAM)

Albert Einstein College of Medicine

Bronx, New York

Mary Cataletto, MD

Clinical Professor of Pediatrics

New York University (NYU) Grossman School of Medicine

Pediatric Pulmonologist

NYU Health

Mineola, New York

Michelle M. Cloutier, MD

Professor Emerita Pediatrics and Medicine

Departments of Pediatrics and Medicine

University of Connecticut School of Medicine

Farmington, Connecticut

Mark S. Dykewicz, MD

Raymond and Alberta Slavin Endowed Professor in Allergy and Immunology

Professor of Internal Medicine

Chief, Section of Allergy and Immunology

Saint Louis University School of Medicine

Saint Louis, Missouri

Paul A. Greenberger, MD

Professor of Medicine (Emeritus)

Division of Allergy and Immunology

Department of Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Sally Hunsberger, PhD

Biostatistician

Biostatics Research Branch

National Institute of Allergy and Infectious

Diseases

National Institutes of Health

Bethesda, Maryland

Bridgette L. Jones, MD, MSc, FAAAAI, FAAP
Professor of Pediatrics
Division of Allergy, Asthma, Immunology and Pediatric Clinical Pharmacology, Toxicology and Therapeutic Innovation
Children's Mercy Kansas City
Assistant Academic Dean, Student Affairs
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

Alex Kaizer, PhD
Assistant Professor
Department of Biostatistics and Informatics
University of Colorado-Anschutz Medical Campus
Aurora, Colorado

Randi Oster, MBA
(Acting Consumer Representative)
Co-Founder and President, Help Me Health
Fairfield, Connecticut

Jennifer A. Schwartzott, MS

(Patient Representative)

North Tonawanda, New York

James K. Stoller, MD, MS

Professor of Medicine

Chairman, Education Institute

Cleveland Clinic Foundation

Cleveland, Ohio

FDA PARTICIPANTS (Non-Voting)

Sally Seymour, MD

Director

Division of Pulmonology, Allergy, and Critical Care (DPACC)

Office of Immunology and Inflammation (OII)

Office of New Drugs (OND), CDER, FDA

Kelly Stone, MD, PhD

Associate Director for Therapeutic Review

DPACC, OII, OND, CDER, FDA

Elisabeth Boulos, MD

Clinical Reviewer

DPACC, OII, OND, CDER, FDA

Yongman Kim, PhD

Lead Mathematical Statistician

Division of Biometrics III (DB3)

Office of Biostatistics (OB)

Office of Translational Science (OTS)

CDER, FDA

Dong-Hyun Ahn, PhD

Statistical Reviewer

DB3, 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

(10:02 a.m.)

Call to Order

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

My name is David Au, and I will be chairing this meeting. I will now call the November 8, 2022 Pulmonary-Allergy Drug Advisory Committee meeting to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with the introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am the designated federal officer for this meeting. All voting members have confirmed via email that they have viewed the prerecorded presentations for today's meeting in their entirety. When I call your name, please

introduce yourself by stating your name and affiliation, and "I confirm."

Dr. Au?

DR. AU: Hi. I'm David Au. I am from the VA Puget Sound Health Care System and the University of Washington, and I confirm.

DR. STEVENSON: Dr. Carlson?

DR. CARLSON: Hi. I'm Dawn Carlson. I'm an industry representative, and I confirm.

DR. STEVENSON: Dr. Evans?

DR. EVANS: This is Scott Evans. I'm a pulmonologist at the University of Texas MD Anderson Cancer Center in Houston, and I confirm that I have watched the videos.

DR. STEVENSON: Dr. Holguin?

DR. HOLGUIN: Fernando Holguin, University of Colorado, and I confirm.

DR. STEVENSON: Dr. Kim?

DR. E. KIM: Edwin Kim, allergist/immunologist at the University of North Carolina. I confirm.

DR. STEVENSON: Dr. May?

DR. MAY: Susanne May, professor of biostatistics and director of the Clinical Trials Center at the University of Washington in Seattle, and I confirm.

DR. STEVENSON: Dr. Tracy?

DR. TRACY: Dr. James Tracy, clinical professor of pediatrics, University of Nebraska, in private practice, and I also confirm.

DR. STEVENSON: Dr. Cabana?

DR. CABANA: Good morning. This is Michael Cabana. I'm a general pediatrician. I'm physician-in-chief at the Children's Hospital at Montefiore and chair of pediatrics at the Albert Einstein College of Medicine in the Bronx. I confirm that I have read the documents and seen the video.

DR. STEVENSON: Dr. Cataletto?

DR. CATALETTO: Mary Cataletto. I'm a pediatric pulmonologist at NYU Long Island, and I confirm that I watched the videos.

DR. STEVENSON: Dr. Cloutier?

DR. CLOUTIER: I'm Michelle Cloutier. I'm a

pediatric pulmonologist at the UConn School of Medicine in Farmington, Connecticut, and I confirm.

DR. STEVENSON: Dr. Dykewicz?

DR. DYKEWICZ: Hi. Mark Dykewicz, allergy-immunology at Saint Louis University Saint Louis University School of Medicine, and I confirm that I have watched the presentations in their entirety.

DR. STEVENSON: Dr. Greenberger?

DR. GREENBERGER: Paul Greenberger, Department of Medicine, Division of Allergy and Immunology at Northwestern University Feinberg School of Medicine in Chicago, and I confirm.

DR. STEVENSON: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger, Biostatistics Research Branch and NIAID, and I confirm that I have viewed the presentations.

DR. STEVENSON: Dr. Jones?

DR. JONES: Dr. Bridgette Jones, professor of pediatrics at University of Missouri-Kansas City, and allergy-immunology and pediatric clinical

pharmacology at Children's Mercy Hospital in Kansas City, and I confirm.

DR. STEVENSON: Dr. Kaizer?

DR. KAIZER: Alex Kaizer, assistant professor of biostatistics and informatics at the University of Colorado, and I confirm that I have read the materials and seen the video.

DR. STEVENSON: Ms. Oster?

MS. OSTER: Yes. This is Randi Oster. I am the president of Help Me Health, and I confirm that I have read and viewed the videos in entirety.

DR. STEVENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: Hi. This is Jennifer Schwartzott. I am the patient representative, and I confirm.

DR. STEVENSON: Dr. Stoller?

DR. STOLLER: Yes. This is Jamie Stoller. I'm a pulmonary doctor at the Cleveland Clinic, and I confirm.

DR. STEVENSON: Thank you, panel members, for confirming. I will now continue introducing the FDA participants.

Dr. Seymour?

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

DR. STEVENSON: Dr. Stone?

DR. STONE: Good morning. This is Kelly Stone. I'm the associate director for therapeutic review, Division of Pulmonology, Allergy, and Critical Care, FDA.

DR. STEVENSON: Dr. Boulos?

DR. BOULOS: Good morning. This is Dr. Elisabeth Boulos. I'm a medical officer in the Division of Pulmonology, Allergy, and Critical Care, and the primary reviewer for this application.

DR. STEVENSON: Dr. Kim?

DR. Y. KIM: Good morning. This is Yongman Kim. I'm a statistical team leader for FDA.

DR. STEVENSON: Dr. Ahn?

DR. AHN: Hi. This is Dr. Dong-Hyun Ahn, primary statistical reviewer in the Office of

Biostatistics.

DR. STEVENSON: Thank you, everyone. I will turn it back to the chair.

DR. AU: 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 committees take care that their conversations about the topic at hand take place in the open forum of this 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 topics during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration, FDA, is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, 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 the agency's need for a special government employee's services outweighs his or her 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 discussion 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 a discussion of new drug application, NDA, 214070, for a fixed-dose combination of budesonide and albuterol sulfate, BDA, metered dose inhaler, submitted by AstraZeneca and Bond Avillion 2 Development LP. The proposed indication is as-needed treatment or prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older.

This is a particular matters meeting during which specific matters related to AstraZeneca and Bond Avillion 2 Development's NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with the meeting. To ensure transparency, we encourage all standing committee

members and temporary voting members to disclose any public statements that they may have made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you, and I will hand it back to the

chair.

DR. AU: I need to do a sound check [audio feedback].

Is this better?

DR. STEVENSON: Hi, Dr. Au. This is Takyiah speaking. I'm not sure if your microphone maybe has some sort of obstruction.

(Discussion off the record.)

DR. AU: Why don't we proceed; if everyone can hear me ok?

We will proceed with the FDA introductory remarks from Dr. Kelly Stone.

FDA Introductory Remarks - Kelly Stone

DR. STONE: Good morning. On behalf of the Division of Pulmonology, Allergy, and Critical Care and the agency, I'd like to welcome you all to this meeting of the Pulmonary-Allergy Drugs Advisory Committee. We're convening the advisory committee today today to discuss new drug application for the fixed-dose combination budesonide albuterol MDI, developed for the as-needed treatment or prevention of bronchoconstriction, and for the prevention of

exacerbations in patients with asthma 4 years of age and older.

This is a novel combination product containing an inhaled corticosteroid in a short-acting beta-2 agonist and intended for use as a rescue or reliever treatment for asthma. This reliever product would be the first with an indication to prevent progression to severe exacerbations and the first product containing an inhaled corticosteroid for rescue rather than maintenance treatment.

We will discuss the overall development program for this novel combination product, however, a major focus of today's discussion will be on the benefit-risk assessment for pediatric patients. We look forward to a robust discussion to inform and advise the agency in its review of this new drug application. Although the feedback provided by the committee is advisory, we will consider all aspects of today's discussion in our review process. Once again, I would like to welcome and thank the members of the advisory

committee for your participation in today's meeting, as well as the applicant, members of the public, and my colleagues at FDA.

I will now turn it back over to you, Dr. Au. Thank you.

DR. AU: Both the Food and Drug Administration 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 applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, 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 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 the applicant's summary presentation.

Applicant Presentation - Ed Piper

DR. PIPER: Good morning to the chair, members of the advisory committee, and the FDA. My name is Dr. Ed Piper for AstraZeneca.

BDA MDI is a potential new asthma rescue treatment, and I'm pleased to summarize the Avillion and AstraZeneca position on the key topics that the committee will discuss today. Dr. Neil Skolnik will follow to provide his clinical perspective. I'm joined by a number of colleagues from AstraZeneca and Avillion, and collectively, we will address any questions, and Drs. Lugogo, Murphy, and Skolnik are on hand to offer their expert clinical perspectives.

Severe asthma exacerbations remain a major

issue across all ages, and there is a need for safe and effective new treatments to prevent them. But there's a paradox that the go-to asthma rescue treatment, albuterol, when used frequently without an inhaled corticosteroid is associated with an increased risk of severe exacerbation.

BDA is a fixed-dose combination of albuterol to provide rapid relief of symptoms and budesonide to treat airway inflammation. The clinical premise behind the development was that BDA MDI would reduce severe asthma exacerbation risk through the complementary action of these two well-known medicines.

The pivotal MANDALA study shows that when used as rescue, in addition to inhaled corticosteroid maintenance treatment, both doses of BDA studied reduced the risk of first severe asthma exacerbation compared to our albuterol. The efficacy profile of BDA 160/180, the higher dose tested, was compelling with a 27 percent reduction in severe exacerbation risk, together with clinically important reductions in systemic

corticosteroids use and increased odds of improved asthma control and asthma-related, quality-of-life scores.

These important clinical benefits were observed with modest use of BDA as rescue. The mean use of BDA 160/180 was 2.6 inhalations per day, which is equivalent to just over 200 micrograms of budesonide. On most days during the study, patients used 0, 1, or 2 doses of BDA. The numbers of inhalations are categorized on the graph here.

We assessed the overall benefit-risk for BDA MDI to be positive, taking into account the three positive phase 3 studies in over 4,000 patients; the reduction in severe exacerbation risk compared to albuterol, highest with BDA 160/180; and critically that the safety profile of BDA MDI was consistent with the known risks of both mono-components with no new safety findings identified.

We proposed an indication that reflects the clinical utility of BDA MDI. The principal

question for the advisory committee is whether a high degree of extrapolation of the BDA efficacy data in adults, to adolescents and children, is appropriate and supports the approval of BDA MDI from 4 years of age. This question is important, as the burden of asthma exacerbations in the U.S. presented here, as the annual rate of ED visits due to asthma remains stubbornly high for children, adolescents, and their families. The unmet need is clear, considering that half of children with mild to moderate asthma and two-thirds of those with severe asthma have at least one asthma exacerbation each year.

Given the potential for BDA MDI to address. severe exacerbation risk, we discussed the inclusion of children with the agency throughout development. We followed agency advice to include subjects from 4 years of age in our phase 3 studies and we enrolled 100 adolescents and 83 children into the MANDALA study. These cohorts were intended to be of sufficient size to collect safety data and for exploratory efficacy analysis. The

agency also recommended Bayesian analysis as an appropriate approach to support the assessment of efficacy in both pediatric populations.

The FDA guide sponsors that for conditions that exist across the age spectrum, evidence of clinical benefit from a drug in adults can support the prospect of direct benefit in children if there is confidence that the disease is similar and that the response to treatment will be similar.

We agree with FDA that a high degree of extrapolation of adult BDA data to the pediatric populations is necessary. Our rationale for extrapolation is based on important similarities in asthma across ages. These start with a general observation that the same principles are used for diagnosis, assessment, and treatment, while it's the same endpoint they used to assess efficacy in asthma.

We acknowledge that there are differences in immunological mechanisms at different ages, however, there are similarities that are especially relevant to BDA as a rescue treatment. All asthma

patients experience episodes of worsening symptoms and exacerbations in response to triggers, and these episodes are characterized by similar patterns of inflammation and bronchoconstriction; and the treatment approach is the same, using bronchodilators and systemic steroids for severe exacerbations.

These similarities support the conclusion that a rescue medicine that's effective in adults would also be effective in pediatrics, and this conclusion is further supported by studies of other ICS fast-acting bronchodilator rescue treatments, which show reductions in severe exacerbation risk across adults, adolescents, and children. We look forward to the committee's discussion on the appropriateness of extrapolation.

Turning to the efficacy data from the adolescent cohort in MANDALA, we acknowledge the small sample size, relatively few severe exacerbation events, and the wide confidence intervals that result. The primary endpoint estimate favored BDA 80/180, but was reversed for

the higher dose. Bayesian modeling with limited borrowing from the overall population resulted in favorable point estimates for both BDA MDI doses, but with credible intervals that cross unity.

We agree with the agency's analysis, which shows that in order to achieve statistical significance, higher degrees of borrowing are required. It's encouraging that all secondary endpoints tested numerically favored both BDA MDI doses compared with albuterol.

With regard to safety, the incidence of adverse events were low. Both BDA doses were similarly well tolerated and the safety profile in adolescents was similar to that in adults and consistent with the known risks of both mono-components.

The rationale for extrapolation of efficacy from adults to adolescents is supported by the literature. Here we see the results of a pooled meta-analysis from six studies of budesonide/formoterol rescue in over 1800 adolescents with asthma. Reduction in severe

exacerbation risk was 51 percent in the adolescent pool, and importantly, the results in adolescents were consistent with those in adults, supporting the rationale to extrapolate BDA MDI efficacy from adults to adolescents.

We wanted to prospectively address the rationale for the adolescent dose we proposed. Though the efficacy results appear to favor BDA MDI 80/180 over 160/180. We believe that this is likely due to chance as a result of the low numbers of adolescent patients. It seems implausible that the lower BDA dose would outperform in adolescents, given the very clear dose response in the overall MANDALA population across all endpoints. We also note that the patterns of use for both BDA doses was similar in adolescents. Therefore, as both BDA doses were well tolerated with no unexpected safety findings, we proposed BDA MDI 160/180.

Moving now to the data for the 80/180 BDA dose studied in children, there's uncertainty in BDA MDI benefit, with point estimates for both severe exacerbation endpoints approximately at

unity and with wide confidence intervals. The conclusions from the Bayesian analysis are the same as for adolescents, and secondary endpoints are inconclusive.

A similar pattern of use was observed for BDA MDI and albuterol in children. On over 40 percent of days, no BDA MDI or albuterol was used, and more than 8 inhalations were recorded on less than 1 percent of study days in both treatment groups, importantly indicating that rescue was not overused. The incidence of adverse events was low and the safety profile consistent with the known risks of the mono-components.

The potential risks associated with increased corticosteroid exposure in children are an important consideration, and we therefore simulated a worst-case scenario in which BDA MDI was inhaled every 20 minutes for a maximum of 12 inhalations either on a single day or on 6 repeated days, and this was in addition to maintenance budesonide at a range of approved doses.

The simulation shows here that the systemic budesonide exposure, measured as 24-hour AUC, is lower in the two age groups of children compared to adults and adolescents, and this concurs with the FDA analysis presented. And as I showed previously, it's very important to note that the pattern of BDA use in MANDALA reassures us that this type of worst-case scenario is both infrequent and would last only for a short period.

There is also literature that supports the effectiveness of the ICS/fast-acting bronchodilator rescue strategy in children. In the STAY study, in 4 to 11 year olds with poor asthma control despite maintenance inhaled steroids, the use of budesonide/formoterol rescue reduced the risk of exacerbation by 66 percent compared to the SABA rescue terbutaline, whilst on the right-hand side we see the TREXA study in which 6 to 18 year olds with well-controlled mild persistent asthma, rescue therapy with beclomethasone and albuterol showed benefits over albuterol taken on its own. This is shown here as a reduction in treatment failures

during the study.

So in summary, we believe that the positive benefit-risk of BDA extends to adolescents and children for the following reasons. Firstly, BDA MDI safety is consistent with the well-established safety profile of albuterol and budesonide, with no new safety findings identified in pediatric subgroups.

Secondly, there is a strong clinical and pharmacological rationale to extrapolate adult BDA efficacy to the pediatric population. And finally, there is strong plausibility that BDA MDI would reduce severe exacerbation risk, based on the strength of the overall population results in MANDALA, together with the published data of other ICS/fast-acting bronchodilator rescue combinations.

Given the important unmet need and considering the totality of data, AstraZeneca and Avillion believe that the potential benefits of BDA MDI outweigh the potential risks, and that it could be an important therapeutic option for pediatric patients, as well as for adults. So we

therefore propose the 160/180 microgram dose in subjects 12 years of age and older and the 80/180 microgram dose in those 4 to 11 years of age.

Thank you, and I'd now like to invite Dr. Neil Skolnik to provide his clinical perspective.

Dr. Skolnik?

Applicant Presentation - Neil Skolnik

DR. SKOLNIK: Thank you, Dr. Piper

I'm Dr. Neil Skolnik, professor of Family and Community Medicine at the Sidney Kimmel Medical College of Thomas Jefferson University. It is a privilege to be able to contribute my perspective to today's discussion. I am a paid consultant to the sponsor but have no financial interest in the outcome of this meeting.

I've been taking care of adults, adolescents, and children across the full spectrum of acute and chronic illness for the last 30 years, and most relevant to today's discussion, many, many patients with asthma. I am a family doctor. One

of my academic interests is in asthma, and I served on the NHLBI expert working group for contributing to the development of the most recent NIH asthma guidelines, so this is an area that I know well.

The rate of emergency room visits for asthma exacerbations has not changed since I started practice, over 30 years ago. This may be because our approach to rescue therapy is continued to be focused on acute relief of bronchoconstriction, leaving inflammation, which is a critical cause of bronchoconstriction, to go on unabated.

SABA when used alone only addresses bronchoconstriction, leaving patients transiently feeling better and vulnerable to severe exacerbations, as their inflammation continues to get worse, to the point where SABA is no longer effective at relieving symptoms, and the improvement in airflow requires administration of systemic corticosteroids.

BDA use as rescue therapy provides rapid bronchodilation while addressing inflammation acutely through non-genomic effects on the airways

that begin within minutes, as well as genomic effects that take their place over hours. The use of ICS as a part of rescue therapy is not a new concept, and as we've heard in my colleague's presentations, the idea is supported by evidence that quick-acting bronchodilator ICS rescue combinations reduce the risk of exacerbations versus SABA alone across severities of asthma in adults, adolescents, and children.

This is why both the international GINA recommendations and the United States NIH guidelines now recommend a strategy of using ICS when a quick-acting bronchodilator is used as rescue therapy across age groups. These guidelines are formulated with the intent of informing clinical decisions about treatment. In both the the GINA and the NIH recommendations, adults and adolescents are grouped together, and ICS quick-acting bronchodilator is recommended as rescue therapy.

For children, both GINA and NIH recommendations support the use of an ICS

quick-acting bronchodilator as rescue treatment; the difference between the two sets of recommendations only being at which step it is recommended Based on careful analysis of the data, some of which we've seen in the prerecorded discussions and some of which have been reviewed today, both GINA and NIH guidelines recommend that clinicians use an ICS quick-acting beta agonist for rescue therapy in children with moderate to severe asthma.

Let me now discuss why I as a prescribing physician would like to be able to use BDA MDI for my younger patients. In order to do so, let me discuss clinical decision making in primary care.

When I make clinical decisions for my patients, there are a number of factors I consider. First of all, as an academic family physician, I take the guidelines very seriously, and we've seen an approach that uses rescue therapy with BDA MDI is in line with the current guidelines. Then I look carefully at the data and peer-reviewed literature to assess whether that literature and

the guidelines are applicable to my patients.

Then I think about my clinical experience. With asthma, my approach to children, that is their assessment and their treatment, is essentially the same as it is for adolescents and adults. When I look at the MANDALA trial, I see results in adults that are consistent with what is known about the use of ICS quick-acting bronchodilator rescue therapy. I see no reason to believe that the efficacy in children and adolescents would be different than that in the population as a whole in the trial. The trial showed important decreases in severe exacerbations and decreases in systemic steroid use.

These results, along with the published data that Dr. Murphy shared in his recorded presentation and Dr. Piper reviewed just a short while ago, give me reason to believe in the efficacy of BDA MDI across age groups. Of critical importance, I believe that the risks associated with BDA MDI in children are well understood, based on extensive experience with both of its components over many

years, and I believe those risks are low and are manageable.

Let me re-emphasize this. Based on over 40 years of clinical trials and clinical experience with budesonide in adults, and over 20 years of worldwide experience with budesonide in children, as well as a similar level of experience with albuterol, we can feel comfortable that we understand any safety issues that there may be with BDA MDI. Favorable benefit-risk ratio with an emphasis on safety is what we seek and what our patients want in the medicines we use for treatment of any disease.

Finally, there are the approved indications for the medications I would like to use. As a primary care physician, I find myself in an uncomfortable and an unusual circumstance with asthma. While it is true that many specialists may feel comfortable prescribing outside of approved indications, most primary care clinicians try to prescribe medicines consistent with approved indications.

If I want to practice medicine consistent with the current guidelines, consistent with the peer-reviewed literature, and consistent with what I believe is best for my patients, I currently only have two options. One is to prescribe a budesonide/formoterol combination inhaler for maintenance and reliever therapy. If I do that, it is not consistent with the approved indications for prescribing that medication, and in fact it violates the statement in the label that it is not indicated for the relief of acute bronchospasm. Furthermore, if my patients are taking their maintenance inhaler, insurance often does not pay for the additional inhalers to be used for rescue therapy.

My second option is to recommend to my patients that they take their ICS every time they take albuterol. Use of an ICS in this way does not fit approved indications for ICS use. For my patients, this is burdensome, confusing, and impractical. That means they have to carry two inhalers with them at all times in case they need

rescue therapy, and we run up against the same insurance issues that I just mentioned if someone's also on a maintenance ICS. Insurance won't pay for additional ICS for rescue.

So I do what most of my colleagues do -- family doctors, pediatricians, nurse practitioners, and physician assistants across the country -- I don't practice according to what I think is best for my patients; instead, I prescribe an albuterol inhaler for rescue therapy.

From my perspective, BDA MDI provides us a much needed opportunity to align the approved indications with best clinical practices. Approval of BDA MDI would provide an option to address the paradox that Dr. Piper mentioned, that the go-to asthma rescue treatment albuterol, when used frequently without an ICS, is associated with an increased risk of severe exacerbation. Currently, in the United States, this happens far too often.

So we're left today with the principal questions. Is the disease similar enough in children and adults; is the process and underlying

physiology of exacerbations similar enough in children and adults; and is the response to treatment similar enough in children and adults to support extrapolation of the results of the MANDALA trial to children from adults? And is the totality of the evidence from clinical studies interpreted with clinical wisdom strong enough to support approval of BDA MDI for adults, adolescents, and children? For the reasons stated, I think it is.

The alternative, without BDA MDI, is primary care providers like me have no other options for rescue therapy but to prescribe albuterol for our patients. With BDA MDI, we could provide an important advance for the treatment of asthma in the United States, one that gives our patients anti-inflammatory therapy as a part of their rescue therapy, and by so doing decrease the rate of asthma exacerbations in adults, adolescents, and children, improving their quality of life and decreasing the burden of their disease.

Thank you, and I'll now turn the floor back to Dr. Piper.

DR. PIPER: Thank you very much.

That concludes the sponsor's summary, and I'll pass it back to the chair. Thank you.

Clarifying Questions to the Applicant

DR. AU: Thank you very much.

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

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

(Pause.)

DR. AU: Why don't we start with Dr. Oster.

MS. OSTER: Yes. This is Randi Oster. I am not a medical doctor. I am the consumer representative, and what I'd like to do is ask Dr. Piper to talk a little bit about the 4,000 patients in the study, and explain to us when he talked about the triggers are the same, how this study looked at age and location of where they are for environmental triggers, so that if we decide to extrapolate data, it is clear that the study has looked at environmental factors that can be exasperation. Thank you.

DR. PIPER: Ed Piper, AstraZeneca.

Thank you. Indeed, 4,000 patients in the clinical development program, spread across three studies -- 3,000 of those patients in MANDALA, the study I referred to a lot -- this was a program run in a number of countries around the world, including the United States.

For example, in the MANDALA study, 27 percent of the overall sample was taken from the United States, so we can be confident that the patients recruited into the trial are relevant when

we come to consider U.S. practice, and indeed U.S. triggers that are present in patients in the U.S., and as we consider the application for U.S. approval.

We did capture data around environmental triggers in the study, so we have data that shows the sort of triggers that patients recorded, so we made an effort to collect that data. We haven't got an analysis to share with you at this moment about the breakdown of exactly what those triggers were, but I'll end my response there and see whether that satisfies your question around the 27 percent of patients being in the U.S. or not, or whether you have a follow-up question. Thank you.

MS. OSTER: Just as a follow-up, I just want to clarify for the record that we do not have the analysis for the triggers, and the environmental impact across the United States has not been defined at a level where there could be man-made issues. So we have to be careful that we do not extrapolate data from one part of the country to people in the other part. Thank you.

DR. PIPER: Ed Piper, AstraZeneca. Just to come back from that and give a tiny little bit more detail around U.S. sites, as I said, 27 percent of the patients. There were 125 different sites around the United States that enrolled patients into the MANDALA study, so I think we can have some confidence about the generalizability of the data from the U.S. population. Thank you.

DR. AU: Let's move on to Dr. Greenberger.

DR. GREENBERGER: Thank you; a couple questions. One would be inclusion criteria for MANDALA regarding bronchodilator responsiveness or not. My question is regarding the adolescents and children, if you have information on that.

The second is, could you just review for us those adolescents and children in step 2 who were receiving the investigational product versus the step 3 treated who received the investigational product? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. I'm going to start with your second question first, which is around looking at the background dose of

inhaled steroid.

One of the great strengths of the MANDALA study, I think, was that it recruited a broad population of patients, all of whom were taking inhaled steroids with or without a LABA and with the addition of one controller, additional controller, where required.

It was a broad study, but what we chose to do was to look at the different patients by background severity using different doses of steroid that they received using the GINA categorization. We can show you the breakdown of the data by background dose from the pediatric and adolescent sample, so we'll pull that data for you.

While we're pulling that data, your first question was around the inclusion criteria for reversibility in adolescents and children, and I'm going to pass you to Dr. Weinberg, our clinical expert, who will respond to that question.

DR. WEINBERG: Mark Weinberg, Avillion. The requirements from an inclusion criteria were that a pre-bronchodilator FEV1 of greater than 40 to less

than 90 predicted normal value for adults, and greater than 60 percent predicted normal for subjects age 4 to 17 after withholding medications, and then followed up for post-bronchodilator. With specific values, we can assess what we had for our adolescent patients. Thank you.

DR. PIPER: So to get back to the question of the background inhaled corticosteroids in the adolescent and pediatric patients, I'm going to pass to Dr. Church, our pediatric lead, to walk you through the split of background dose of ICS.

Dr. Church?

DR. CHURCH: Alison Church, AstraZeneca. What I'm going to share with you first is the proportion of adolescents in each category of ICS. For patients on low-dose ICS, about 32 percent of the adolescents -- slide up -- were on low-dose ICS; approximately 54 percent of patients were on medium-dose ICS; and 14 percent of patients were on high-dose ICS, so that's in the adolescents.

We also have that data in children. Slide up. In children, approximately 5 percent of

patients were on a background of low-dose ICS; 63 percent were on medium-dose ICS; and roughly 30 percent were on high-dose ICS.

I believe you also asked about reversibility. We did look at reversibility, and it was quite similar across the three treatment groups. In children, reversibility was 20 percent; in adolescents it was 29 percent; and in the overall population it was approximately 28 percent Thank you.

DR. AU: Any other follow-up questions, Dr. Greenberger?

DR. GREENBERGER: Yes --

DR. AU: Then I would move on to --

DR. GREENBERGER: Dr. Au, I do have a question.

My question on inclusion criteria is whether children or adolescents who did not have the 12 percent response to bronchodilator that were included.

DR. PIPER: Ed Piper, AstraZeneca. No, there were not. They were all reversible.

DR. GREENBERGER: Thank you.

DR. PIPER: Thank you.

DR. AU: Thank you so much.

Dr. Stoller?

DR. STOLLER: Yes. Good morning. This is Jamie Stoller. I have a question regarding figure 9 in the sponsor's briefing document, the strata of the subgroup analyses, and in some ways it's a possible follow-up to Ms. Oster's question. It regards the possibility of center effects.

Recognizing that MANDALA was conducted, I believe, in 11 countries, you stratified in the middle of figure 9 regional effects, particularly U.S. versus non-U.S. And I take note of the fact that the forest plot in non-U.S. is consistent with the overall impact, and yet the data from the U.S. groups sort of cross the line of unity. And I wonder, therefore, whether there is a center effect and whether you can comment on why that is, other than the possibility of inadequate power. So I'll stop there. Thanks.

DR. PIPER: Ed Piper, AstraZeneca. I think

you ended your question with a really important point, which is that we recognize the study isn't powered to draw statistically robust conclusions between any subgroup, and therefore we have to be very cautious about interpreting the data with respect to any difference in efficacy between the U.S. and the rest of the world.

As I mentioned in my first response, the U.S. cohort was 27 percent of the overall MANDALA sample, so what we see in terms of difference does not exceed what could be explained by chance alone. So I think in a summary, I think we believe strongly that this data doesn't suggest that there is a difference. Thank you.

DR. AU: If those are all the questions for Dr. Stoller, let's go to Dr. Holguin.

DR. HOLGUIN: Thank you. Good morning. This is Fernando Holguin, University of Colorado. My question is, I believe patients on biologicals were excluded. Would you mind telling us what was the rationale for that exclusion? And if so, is the BDA MDI application in the subgroup different

because they were excluded from the trial? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. We focused MANDALA on a population of moderate to severe patients with asthma in order to evaluate the additive impact to BDA's rescue on top of maintenance steroids. As I mentioned, it is a fairly broad trial already, with patients going from low-, medium-, and high-dose inhaled steroids plus or minus LABA; plus potentially one additional controller could be theophylline; it could be a leukotriene receptor antagonist; it could be a LAMA.

So we already had a trial that was very broad and heterogeneous, and I think one of the strengths is showing a 27 percent reduction in a population that's as broad as that is, is clinically compelling. We did take a decision not to include patients with biologics because I think we acknowledge those are a very severe patient population that would, unfortunately, represent a relatively small proportion of the overall

population, and we thought that was just too far in terms of opening a really broad trial to be too broad. So we did make that decision. Your observation is correct, and the reason behind it from our perspective. Thank you.

DR. AU: Any follow-up questions from Dr. Holguin? If not, would you --

DR. HOLGUIN: Thank you, Dr. Au.

So you're not concerned that the BDA MDI would be used in this population?

DR. PIPER: As I said, we didn't run the study including those patients. I think there's every reason to believe that the product would still be effective in those patients, but they are a special population, as you identified, and I don't have data to be able to offer you to address your question. I think it's a good point to make. Thank you.

DR. AU: Great.

If there are no other follow-up questions, let's move on to Dr. Evans, please.

(No response.)

DR. AU: Dr. Evans, I don't hear you.

DR. EVANS: I apologize. I seemed to have been double-muted. This is Scott Evans. Can you hear me now?

DR. AU: Yes, quite well. Thank you.

DR. EVANS: I apologize for that. This is Scott Evans from MD Anderson. I have a pharmacokinetics question. I recall from the videos a comparison between exposures to the BDA MDI and the approved Pulmicort Respules in children. I think some of those data are in table 2 of the sponsor document now.

My question is -- please refresh me from what I thought I learned in the video -- what is the systemic exposure achieved in children following the use of the BDA MDI at the expected usage versus the approved usage of Pulmicort Respules? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. I think what I can show you is the systemic exposure to budesonide that we've estimated through population PK modeling, in addition to maintenance treatment

in adults, adolescents, and children. I think that might be a useful place to start trying to answer your question. Let's show you that data and see whether it will address what underpins your question. I'm going to ask Dr. Asimus, our clinical pharmacology expert, to share that data.

DR. ASIMUS: Sara Asimus, AstraZeneca. Slide up. This slide shows the simulations that we have performed to evaluate the exposure of BDA MDI on top of the use of Pulmicort Respules. This slide shows the AUC over 24 hours with and without maintenance treatment. The maintenance treatments are given by different symbols, and the different dosing scenarios with BDA MDI are given in different colors.

As you can see, systemic exposure to budesonide is scaling linearly with increase in total dose of budesonide, and the maximum increase in exposure compared to maintenance is about twofold in the MANDALA maximum scenario. And if the children are taking 2 or 3 extra inhalations, the increase in exposure is about 18 percent and

28 percent, respectively. Thank you.

DR. PIPER: That was an analysis we had. Does that help to answer your question, or would you --

DR. EVANS: No, it actually does. You covered the two elements in one slide that I was asking, so thank you.

DR. PIPER: Thank you.

DR. AU: I believe the next person is Dr. Tracy.

DR. TRACY: Yes. This is Dr. Tracy. This question is for Dr. Piper.

As I looked at all of the stuff and had a chance to review, obviously, it would have been nice to have larger sample sizes to improve the power for both the pediatric and adolescent groups. But recognizing that, really, the central question here is, is there enough disease similarity between adults and kids, I was wondering if either as a sponsor -- and I'll ask this of the agency also.

Obviously, as a sponsor, you think that things look pretty good, but were there any

specific areas that maybe just gave you pause and made you want to think that maybe there isn't sufficient similarities in these two populations? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. As I described in my presentation, we believe that the context of a rescue treatment with similarities in asthma are sufficient to warrant the extrapolation of efficacy that we are proposing. It's probably no surprise that I come back to you to say, no, I don't think we had concern. We've thought about this very carefully, but we do believe that extrapolation is a justifiable thing to do for BDA for the reasons described.

I think the other thing that I'm sure you picked up from my presentation is some of the data from other fast-acting bronchodilator inhaled steroid combinations is also reassuring because we see, certainly for budesonide/formoterol, similar benefit in terms of reduction in severe exacerbation risk across this span of ages, and we also see that product is safe in all those age

groups.

So for those two reasons, I think we feel confident that the extrapolation is appropriate here, but understand that's going to be a major topic for for this meeting. That's our perspective. Thank you.

DR. STEVENSON: Dr. Tracy, any follow-up?

DR. TRACY: No. I was expecting that answer, but I just wanted to hear what he had to say.

DR. AU: Right. Thank you so much.

The next is actually me. I'm David Au. I guess I have a question that really kind of speaks to the rationale for including children and adolescents to be analyzed [indiscernible], which is I think the thrust of the argument here presented by the applicant is really focused on the preponderance of evidence outside the clinical trial that are being presented here.

I guess the question I'm asking is, why include adolescents and [indiscernible] if we're being asked to consider indications that are not

directly derived from the trial data that you're presenting here today? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. It's a little difficult to hear the question, but let me repeat it as what I understood you asked.

DR. STEVENSON: Hello, everyone. This is Takyiah speaking, the DFO.

Dr. Au, I do believe you may be on speaker phone. It may help if you do have headphones or microphones, to maybe use that instead because, yes, it is difficult to hear your question and when you speak.

DR. AU: I apologize. Is this better?

DR. STEVENSON: Yes, that is a little bit better, yes.

DR. AU: [Indiscernible - audio feedback].

DR. STEVENSON: I'm so sorry, Dr. Au. Your signal is probably still going in and out.

DR. AU: I don't have a solution for me.

Why don't I do this? Let's move on to Dr. Cloutier, and I will try a different telephone. How about that?

DR. STEVENSON: That's fine. Thank you, Dr. Au. Sorry for the interruption.

DR. AU: No, not at all.

DR. PIPER: Ed Piper, AstraZeneca. I think I caught the gist of the question, so let me try and help, which I think the question was, what is it that you learned, having included a small sample of pediatric and adolescent patients, given the challenges around exploratory efficacy analysis?

I think I'd just like to point out two really important things that we did learn from including the pediatric and adolescents. One was the safety because this was an opportunity to explore BDA MDI being used as needed in response to symptoms, and the safety profile that we observed was reassuring.

I think the second thing that I showed in my presentation was also the pattern of use, particularly in pediatrics, where one of our issues was to make sure that the product wasn't being overused, and I think comprehensively we saw that the product was not being overused, with no BDA

being used on 40 percent of days and the profile being skewed very far to the left in terms of the pattern.

So that's what I thought the question was, so I hope that's helpful in addressing what we did see from the pediatric and adolescent populations. Thank you.

DR. AU: Thank you very much. I don't have a follow-up at this point.

Why don't we go ahead and move on to Dr. Cloutier.

DR. CLOUTIER: Thank you. This is Michelle Cloutier. The MANDALA study was conducted in patients who had uncontrolled, moderate to severe, persistent asthma. That's your primary efficacy study.

Are you recommending that the BDA MDI be used in individuals with asthma at all ages 4 and up, in asthma of all severities?

DR. PIPER: Ed Piper, AstraZeneca.

Your observation, Dr. Cloutier, is absolutely right. MANDALA was conducted in

uncontrolled, moderate to severe patients, but we included mild asthma patients, defined as those either taking SABA on their own or low-dose inhaled corticosteroids plus SABA in the program, particularly in DENALI.

I'm going to ask Dr. Weinberg to just walk you through what we learned from DENALI in mild patients, particularly with emphasis on some exploratory data and exacerbations. So I'll pass the microphone to Dr. Weinberg.

DR. WEINBERG: Mark Weinberg, Avillion. Our exploration in mild asthma was the DENALI study, where we looked at a thousand patients receiving the drug qid, which would support the combination rule and also administer the drug as these drugs are currently labeled. Given that this was qid administration and that it was a 12-week study, we did not specify severe exacerbations as a prespecified endpoint to look at, but certainly did look at it in an exploratory manner.

Slide up. Interestingly, what we saw was with placebo patients, there were 14 severe

exacerbations during the 12-weeks; albuterol administered qid had 20 severe exacerbations with fully 10 percent of those patients requiring treatment with systemic corticosteroids; and then for the BDA arms, 4 and 5 patients. So his is some supportive data in mild asthma that we have, as well as the very good safety data that comes out of the DENALI study. Thank you.

DR. CLOUTIER: Thank you.

If I could follow up with that, how are you recommending that this therapy be used in children 5 to 12 years of age who have mild asthma? And the reason for that is, first of all, the NAEPP guidelines do not recommend this therapy in children 4 to 11 years of age because of the low-quality data, a low certainty involved with these data.

TREXA did not support intermittent ICS albuterol rescue for the primary outcome, and also, the goal of that study had been to demonstrate the added value of ICS albuterol to prevent exacerbations, and they did not do that either.

Turpeinen's study, which is the other study that you quote support that, really had a very different study design with 6 months of continuous ICS therapy before randomization, and that study demonstrated a superiority of daily ICS over intermittent therapy.

So do you have additional data or other data to support use of the BDA MDI in mild persistent asthma in children 5 to 12 years of age? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. There isn't additional data. I think you've highlighted the data well. I showed in my presentation, I did reference TREXA, and the data that I showed -- slide up -- was this data, which was in a patient population with mild persistent asthma.

I cited, on the right-hand side of this graph, the comparison between the patients that received beclomethasone and albuterol as needed on its own as rescue, compared to the patients who received albuterol on its own as rescue. The reason for doing that was to show that, clearly,

the addition of beclomethasone in this case, in the rescue, prevented treatment failures in the TREXA study. But that was the data that I presented and the reason why I presented it. I think the remainder of your observations are sound. I don't have other data to present. Thank you.

DR. CLOUTIER: Thank you.

DR. AU: Great. Hopefully, this is better; I've switched phones.

DR. STEVENSON: Yes, we can hear you much better. Thank you.

DR. AU: That's great. I'm happy to hear that. Thank you.

Dr. Kim?

DR. E. KIM: Edwin Kim, University of North Carolina. I don't have any conflicts in this.

My question is focused on the children ages 4 to 12 and the efficacy data that appears to be inconclusive. In thinking about BDA as a rescue therapy, I guess my question is around your slide 11, where there is a lot of justification for extrapolating from adults, to adolescents, to

children, and makes the point of treatment and diagnosis all being identical. But the dose selected for that younger group was the lower dose, and the high dose was not studied.

I wonder could you speak to whether you would anticipate that the higher dose could be more effective in prevention of severe exacerbation. Thank you.

DR. PIPER: Ed Piper, AstraZeneca. I'm going to pass to Dr. Church to take you through our rationale for selecting the 80/180 dose for the 4 to 12 age group, and that will explain why we're not thinking about the higher dose.

Dr. Church?

DR. CHURCH: Alison Church, AstraZeneca. When we considered what doses we would take into the MANDALA study, we made that determination based on what we knew about the drugs and also what had been shown previously with budesonide/formoterol's rescue, as well as based on a dose ranging study that we conducted. Generally speaking, the ICS dose for children is usually one-half that for

adults, and considering safety, that's the dose that we chose to take into the MANDALA study.

Slide up. One of the reasons that we thought the 80-microgram dose would be the correct dose comes from the STAY study, in which budesonide/formoterol at the dose of 80 was studied as a rescue on top of budesonide/formoterol, and what we observe here is a 66 percent reduction in the risk of severe exacerbations. So that is the reason why we chose to take the 80-microgram dose into children. And we did see improvements -- or reductions in risk of severe exacerbations and rates with the 80/180 dose of budesonide/albuterol within the MANDALA study. Thank you.

DR. E. KIM: I don't have any follow-ups. . Thank you very much.

DR. AU: Thank you.

Ms. Oster?

MS. OSTER: Yes. This is Randi Oster, the consumer representative. I would just like some clarifying statements around the understanding that this is a rescue treatment and it is effective.

However, when we look at children and growth, I would like to understand -- there were some indications that growth is affected by some of these products, and yet I don't know if children just take this for the 24-week period or we're looking at children that take this over their childhood; what is the effect of growth rates on them, as well as there were charts that talked about the cumulative lifetime dose of corticosteroids with depression and anxiety.

Dr. Church's information that she shared did indicate there were some mood swings, vomiting, and behavioral issues that I'd like to understand that because we want to extrapolate from adults, specifically the effect that this could have on children, and adults are no longer growing, but children are. Thank you.

DR. PIPER: Ed Piper, AstraZeneca. Your observations around growth are spot-on. I would say that we didn't undertake a formal growth study in our development program, given that there is a large body of data with budesonide and other

inhaled steroids in examining the effect on growth in children. We know that as a backdrop to the use of BDA -- and I think it's very important to state, from a patient perspective -- that we'll be including information about those well-known effects on growth of inhaled steroids in the patient package insert to make sure the patients, the children and their carers, are aware of what is known around this topic. The language that we'll use will be consistent with the approved class labeling of inhaled steroids that's familiar with us today.

So that issue is not lost on us, and it's very important that people are informed about it. But as you've seen from the pattern of use data that I showed you, in pediatrics, our belief is that the additional exposure BDA MDI to children is relatively low, and we're not expecting any incremental impact on slowing of growth velocity as a result of use of BDA MDI's rescue. Thank you.

DR. AU: We are a little bit behind time now.

Dr. Cabana, let's take your question, and we'll call that the last question before moving on.

DR. CABANA: Thank you. This is Michael Cabana.

Dr. Piper, my question was about slide 15 in your presentation. It was about the BDA MDI dose proposed for adolescents. It seems that there's an odd result here, where the 80 over 180 outperforms the 160 over 180, but you're endorsing the 160 over 180 dose because it's likely due to chance that the result was due to low numbers.

But it looks like they're about 30 patients in each group; I think 34 and 32. Why do you think the odd result happened with the higher dose, the 160 over 180? Isn't it equally possible that the 80 over 180 had an unlikely result due to chance and could have favored albuterol sulfate instead? Why do you think it's the 160 over 180 that performed in an unlikely manner?

DR. PIPER: Ed Piper, AstraZeneca. We thought about this question very carefully as we reviewed the data and determined the dose that we

would apply for adolescents, and as I described, it doesn't seem plausible to us that the 80-microgram dose of budesonide would outperform the 160-microgram dose. And that's based particularly on the effect in the overall study, which showed such a clear dose response for the higher dose, not only for the primary endpoint, but also for the secondary endpoints, and indeed the exploratory endpoints. So given that, typically we see the adult and the adolescent dose being the same; and in the absence of finding a plausible explanation, we went with the 160/180 dose.

I don't have the data at my fingertips. I think you mentioned that sample sizes were in the 30s. I think what we have to recognize here also is the the actual number of exacerbation events in the adolescents were very small. They were a fraction of that. I don't have the data with me, but it's something like 8 or 9 events. So the probability of skewing what you observe as a result of one or two events falling in a particular pattern I think is very high, so that really, on

top of the reasons I previously gave you, explains why we proposed the higher dose. Thank you.

DR. CABANA: This is Michael Cabana to follow up. If it's possible that the 160/180 could have been skewed to small numbers, couldn't the 80/180 been skewed due to small numbers? And isn't it a possible hypothesis as well that both doses don't work for kids less than 18? It seems like they both had equal sample sizes, and there's equal chance that the 80/180 could have been just by chance as well.

DR. PIPER: Thanks. Ed Piper, AstraZeneca. There are a couple of points to raise, I think, in response to that. I think it's really important that we appreciate that the MANDALA data that we do have with the small sample actually don't rebut the assumptions that underpin our belief in extrapolation. The BDA MDI data that we observe in adolescents and children are within the range of the variability that we could expect, given the small sample sizes in the pediatric subgroups, the adolescent group in this case, and the overall

treatment group, so what we observed is not out with that difference in sample size.

The second reason for our confidence in the higher dose and the effectiveness of that dose is the data I showed you coming from the pooled analysis of the budesonide/formoterol data in adolescents and comparing that to adults. And what you saw from that data was clear consistency in reduction of risk of severe exacerbation in adolescents and in adults. And in that study, the budesonide/formoterol dose, budesonide was studied as 160 micrograms. So that was an additional reason why we feel confident that we are proposing the correct dose here for adolescents. Thank you.

DR. CABANA: Thank you.

DR. AU: Thank you.

If there are no more clarifying questions for the applicant, we'll now proceed with the FDA summary presentation.

FDA Presentation - Kelly Stone

DR. STONE: Good morning again. This is Kelly Stone, and I'm a pediatrician and

allergist/immunologist, as well as the associate director for therapeutic review in the Division of Pulmonology, Allergy, and Critical Care here at FDA. It's my pleasure to provide this overview to you this morning, and the purpose of this overview is really to highlight critical elements of our review of the BDA program to supplement details that were provided in our briefing document and prerecorded presentations and to focus today's discussion.

Again, we've gone through this, that BDA is an oral inhalational aerosol that delivers a combination of either 40 or 80 micrograms of budesonide and 90 micrograms of albuterol per inhalation.

The proposed dosing regimen was patients 12 years of age and older and 2 inhalations of the 80/90 BDA, which gives you a total dose of 160 micrograms of budesonide or 180 of albuterol per dose; and for children 4 to less than 12, 2 inhalations of the 40-microgram budesonide and 90 microgram albuterol. For both doses, it's not

to exceed 6 doses or 12 inhalations over a 24-hour period.

The proposed indication is for the as-needed treatment or prevention of bronchoconstriction, which is consistent with the current wording for SABAs. In addition, it adds for the prevention of exacerbation in patients with asthma 4 years of age and older. Just to highlight terminology, I may refer to high-dose BDA, which is the 160/180, and low dose, which is the 80/180 dose.

To briefly provide an overview of asthma, asthma is a chronic respiratory disease characterized by bronchoconstriction and airway hyper-responsiveness, as well as airway inflammation. Although inhaled corticosteroids to address airway inflammation have been approved for the maintenance treatment of asthma, inhaled corticosteroids have not been approved for reliever treatment of asthma exacerbations.

Asthma is a common disease with an estimated U.S. prevalence of approximately 8 percent in both adults and children. It represents one of the most

common chronic childhood illnesses. Asthma is heterogeneous with a spectrum of phenotypes and endotypes and a range of severities and symptoms. All patients with asthma, however, regardless of baseline severity or age, are vulnerable to episodic bronchoconstriction and increases in airway inflammation in response to triggers or acute exacerbations. Exacerbations can be managed with as-needed short-acting beta agonists, or for severe exacerbations, with systemic corticosteroids, which may themselves be associated with significant morbidity.

Severe exacerbations may also require hospitalization, higher prolonged systemic corticosteroids, and may result in death. The goals of asthma treatment are to control symptoms and prevent exacerbations, and the foundation of treatment is traditionally comprised of controller inhalers such as budesonide and reliever treatments to alleviate symptoms such as albuterol.

Since BDA was developed for use as a reliever inhaler, I'll provide additional

background of the current landscape for reliever medications. Presently, there's only one class of drug, short-acting beta agonists, that are approved in the U.S. as reliever treatment for asthma, and albuterol accounts for the majority of clinical use.

No reliever therapy carries the indication to prevent severe exacerbations. In recent years, however, there has been a paradigm shift in the approach to reliever treatment informed by the literature on asthma and subsequently reflected in recent guideline revisions.

The first concept is as-needed use of an ICS and quick-onset LABA as both maintenance and reliever therapy often known as SMART, which is now recommended by both GINA and NIH guidelines for some steps in asthma management. We note that no ICS LABA, fixed-dose combination inhaler is currently FDA approved for this indication.

Similarly, there's literature regarding concomitant as-needed use of an ICS with SABA in response to the symptoms, which is recommended by

both set of guidelines as an alternative treatment for patients with mild asthma. BDA would represent the first FDA-approved ICS-SABA, fixed-dose combination.

As highlighted in the briefing document and the prerecorded presentations, although the mono-components of BDA, budesonide and albuterol, had both been FDA approved for many years, BDA would represent a novel product in several ways. First, the proposed indication to prevent exacerbations would be new for a reliever treatment for asthma.

Second, this would be the first approved product with an inhaled corticosteroid for reliever treatment rather than only for maintenance treatment, representing a new intended use for an inhaled corticosteroid in the treatment of asthma. And third, this would be the first fixed-dose combination product combining an inhaled corticosteroid and beta agonist, either short-acting or long-acting.

The meeting goals are to discuss the data to

support the efficacy of BDA for the proposed indication, and particularly to discuss if extrapolation of adult data to pediatric subjects is appropriate and if additional data is needed. We also ask the committee to discuss the safety data for BDA for the proposed indication, with a particular focus on pediatric safety concerns, and then we'll have questions about benefit-risk assessment that we break down into three age groups: greater than or equal to 18 years of age; 12 years of age to less than 18; and 4 to less than 12. We break them down because we believe that the benefit-risk assessment may be different for the different populations.

The two trials most relevant to the BDA application are MANDALA and DENALI. MANDALA was designed to demonstrate the contribution of an inhaled corticosteroid to the combined ICS-SABA combination when used as needed to prevent severe acute asthma exacerbations, and the agency views this trial as the primary source of efficacy data because of the size of the trial, the exacerbation

endpoint, and the administration of the investigator product as intended in real-world practice.

DENALI was designed to assess the contribution of each mono-component to the effect on lung function and satisfies the combination rule. Although MANDALA and DENALI are both discussed in our briefing document, MANDALA will be the focus of this morning's presentation to focus advisory committee discussions.

This is the design of MANDALA. It was an event-driven variable duration with a minimum of 24 weeks, randomized, double-blind, active-comparator controlled trial in subjects with moderate to severe asthma. Starting on the left side, there was a 2 to 4 week screening and run-in period, where patients were provided SABA, and then subjects greater than or equal to 12 years of age were randomized 1 to 1 to 1 to either high-dose or low-dose BDA or albuterol sulfate, and there are approximately 3,000 patients in this age cohort.

Subjects 4 to less than 12 were randomized

1 to 1 to either low-dose BDA or to albuterol sulfate, and following randomization, subjects were instructed to use BDA/PRN in response to triggers and to alleviate symptoms just as they would with their usual reliever medication or SABA. The key efficacy analyses were performed at the primary completion when 570 severe acute exacerbations had occurred and the last enrolled adult reached 24 weeks of treatment.

As noted at the bottom, all patients came in on background asthma maintenance treatment that consisted of medium- to high-dose ICS with or without an additional controller, or low- to high-dose ICS plus LABA, plus or minus additional controller treatment. For all subjects who met the primary completion date or discontinued treatment, there was a 2-week follow-up period.

MANDALA was powered based on adult and adolescent subjects greater than 12 years of age, with a total planned sample size of 3,000, or 1,000 per treatment arm, which was calculated to provide 87 percent power to observe a 25 percent reduction

in the risk of severe exacerbation. In addition, up to 100 patients in the 4 to 11 year age group was planned to be equally randomized to either albuterol sulfate or the low-dose BDA.

In MANDALA, among 3,132 patients who were randomized, 3,123 were qualified for the full analysis, defined as all subjects who were randomly assigned and took any amount of BDA, and these subjects were composed of adults, adolescents, and children. As noted in the figure, the majority of patients were adults, so for high-dose BDA, both adults and adolescents were enrolled, with adults composing about 97 percent of the patients, and there were 83 children enrolled to receive low-dose BDA or albuterol.

This is the result of the primary efficacy endpoint, which is time to first exacerbation. Looking at the high-dose BDA group, the hazard ratio was 0.73 in comparing high-dose BDA versus albuterol sulfate, favoring BDA, and the risk reduction was statistically significant, indicating a significant delay in time to first severe

exacerbation.

Descriptively, looking at the number of subjects with severe exacerbations, the proportion of subjects with the severe exacerbation was 6 percent lower for a high-dose BDA group compared to the albuterol group. Looking at low-dose BDA, the hazard ratio was 0.83 in comparing low-dose BDA to albuterol, favoring BDA.

However, the reduction was marginal with a p-value of 0.041 and with a 3 percent difference in the proportion of subjects with a severe exacerbation. Of note, the low-dose BDA efficacy comparison included children 4 to 11 years of age, increasing the sample size for the low-dose group in albuterol. The type 1 error for these comparisons was controlled under Hochberg's step-up method, which I'll discuss in a second.

This is a Kaplan-Meier curve for the full analysis stats, looking at the cumulative probability of severe exacerbation on the Y-axis over time from randomization on the X-axis. The red curve represents the high-dose BDA group, the

purple curve represents the low-dose BDA group, and the blue curve represents the albuterol group. As you can see, there is separation of the red curve from the albuterol blue curve from the beginning, and demonstrating consistently lower cumulative probability of a severe exacerbation throughout the study duration.

Looking at secondary endpoints, there were several clinically meaningful secondary efficacy endpoints that were included in the primary analysis. The endpoints listed in the table are under the order defined by a prespecified hierarchical testing procedure to control type 1 error rate.

For each secondary endpoint, it was evaluated looking at high dose, followed by low dose. For annualized severe exacerbation rate, the rate ratio was 0.76 for high-dose BDA compared to albuterol, favoring BDA, and the reduction was statistically significant. For low-dose BDA, the rate ratio was 0.8, which also was statistically significant.

Moving on to total annualized dose of systemic corticosteroid use, the results showed that the mean use of systemic corticosteroids was 33.4 percent lower for the high-dose BDA group compared with the albuterol group, and the difference was statistically significant. However, for the low-dose BDA group, although the main use of systemic corticosteroid was 25 percent lower in the BDA arm, the result was not statistically significant; and according to the type 1 error rate control plan, the valuation for the rest of the endpoints was considered exploratory.

Finally, this forest plot summarizes the results of the primary endpoint by age-based subgroups. The blue dots here represent high-dose BDA, the red dots, low-dose BDA. While the hazard ratio for time to first exacerbation favors BDA in the overall population and in the subgroup greater than 18 for both low- and high-dose BDA, point estimates for the proposed doses for 12 to less than 18 and 4 to less than 12 subgroups demonstrate point estimates that favor albuterol sulfate over

BDA. However, since the confidence intervals were wide due to small sample size and included the null value of 1, these results are not statistically reliable.

One of the major points for discussion today will be extrapolation. In order to support efficacy in pediatric subjects, Bayesian analyses were used to understand the amount of adult information needed in the pediatric analyses to demonstrate efficacy. One possible decision rule for concluding a statistically significant treatment effect of BDA in the pediatric subgroups is evaluating whether the 95 percent credible interval excludes the null value of hazard ratio equal to 1.

I will show you the results of the Bayesian borrowing approach conducted by the agency using a robust mixture prior approach. Note that the applicant used a different approach, but we note that the findings from these methods overall were consistent. Shown in this figure is the Bayesian analysis borrowing data for high-dose BDA in

adolescents 12 to 17 years of age. This table shows that in order to obtain a hazard ratio less than 1, as shown here, the number of borrowed adult events would be 95, and that correlates with the percentage of total events from adults in 84.8 percent.

To derive a statistically significant effect of high-dose BDA in this age group with an upper 95 percent credible limit less than 1, approximately 96 percent of the total events in the analysis would need to be borrowed from adults. So what this demonstrates is that in the adolescent age range, a high degree of Bayesian borrowing greater than 95 percent would be required to achieve meaningful results.

Similarly, here's the Bayesian analysis borrowing adult data for low-dose BDA in children 4 to 11, again using a robust mixer prior approach conducted by the agency. This table shows that to obtain a mean hazard ratio less than 1, approximately 89 percent of the total events in the analysis would need to be borrowed from adults and

adolescents. To derive a statistically significant effect of low-dose BDA in the 4 to 11 age range with an upper 95 percent credible limit less than 1, approximately 96 percent of total events in the analysis would need to be borrowed from adults and adolescents, again demonstrating that a high degree of Bayesian borrowing is required to achieve meaningful results.

As a result, the concept of pediatric extrapolation will be central to today's discussion. Pediatric extrapolation can extend what we understand about a drug in the adult population to pediatric subjects based upon careful clinical and pharmacologic considerations. Thus, that can help reduce the burden of pediatric data requirements for drug development programs.

The framework shown on the left is from recent FDA guidance on pediatric extrapolation that shows the framework with these arrows. On the red end, it looks at similarity in disease and response to treatment between reference and target pediatric population. On the left, it refers to the disease

as being different in response to treatment being different. On the right, as you get to the green area, there's sufficient evidence that it's the same disease and response to treatment.

Similarly, we look at the evidence of support. On the left in the red area, no data or large gaps in knowledge, and on the right, we have high-quality data with high confidence to extrapolate a significant amount of data. So in this case, where a high degree of extrapolation is needed, it's appropriate, based on this model, if the disease was the same in adult and pediatric patients.

If the response to treatment is the same in adult and pediatric patients, there's high confidence in evidence and there are no significant knowledge gaps, and we are asking the advisory committee to discuss these aspects of the available data to help assess whether extrapolation is appropriate, and the degree of extrapolation that is appropriate.

The safety database, this summarizes the

size of the safety database, which is primarily from MANDALA with over 3,000 patients and a thousand patients from DENALI. Just to point out in red, the number of patients in the 4 to less than 12 age range is small at 93, and 12 to less than 18, 125 patients.

Since MANDALA use was an event-driven, variable duration trial in which the investigative product was used as needed, it's important to understand drug use patterns. On average, as shown in the second column, adults who are enrolled in the treatment period or longer than adolescents or children, a function of late randomization of pediatric objects is relative to the primary completion date.

This means the smaller a proportion of the pediatric sample size -- and accrues up 24 weeks of data, -- is demonstrated in the third column, where 88 percent of the overall analysis set received greater than or equal to 24 weeks of treatment compared to 70 percent and 66 percent in the 4 to 11 age range.

In the last column, we see that the mean and median number of daily inhalations was not only relatively balanced between randomized treatment arms, but also across age groups. Of note, children 4 to 11 reported a greater proportion of days without any investigator product at 45 percent compared to 25 percent in the total population. Regarding overuse of investigational product, this was a rare event with less than 1 percent of study subjects, including 1 adolescent and 2 children, using greater than 12 inhalations on more than 2 consecutive days.

In conclusion, these data suggest that BDA overuse was not a frequent event during the MANDALA study period and that use patterns across randomized treatment arms, as well as across age cohorts, were similar.

We focused on ICS-related adverse events. We analyzed both local and systemic ICS-related adverse events. For local, the incidence was low and balanced across treatment arms. Oral candidiasis occurred more in the BDA arm than the

albuterol arm, as would be expected. Looking at systemic adverse events, the incidence was low and balanced across treatment arms. For the pediatric population, we note that there is a small sample size in duration of exposure. Overall, the incidence of both local and systemic adverse events was low, and there was no significant pattern by age group.

Just to summarize the efficacy results, in the MANDALA study, the primary efficacy endpoint was met and supported by secondary endpoints. Results in adults greater than 18 are statistically significant, but the results in the two pediatric age groups, 4 to less than 12 and 12 to less than 18, are uncertain. There are wide confidence intervals due to the small sample size, with the upper bound exceeding 1. A high degree of Bayesian borrowing would be required to achieve meaningful results. DENALI met the dual primary efficacy endpoint, and this satisfied the combination rule.

In terms of safety, the strengths of safety results, the safety database was adequate for

review. Use of greater than or equal to 12 inhalations of BDA was not a significant issue during the study period. No new signals were identified, and the adverse event pattern was consistent with the well-characterized risk of ICS in SABA. Background ICS was also associated with risk of ICS-related adverse events.

Areas of uncertainty in the safety data includes a scope of the pediatric data, which is limited in size and duration of exposure, the data does not account for potential overuse in the real world, and long-term effects are unknown, for example, growth, bone, density and others.

For the discussions of the advisory committee, the forest plot demonstrated here identifies the areas of uncertainty. Of central importance for the committee discussion, we note that the efficacy results for the adolescent population, both high and low dose, are inconclusive, and for the 4 to 12 year age range with low-dose BDA, it's inconclusive.

Regulatory considerations specific for

pediatric development for BDA, the applicant proposed enrollment of subjects down to 6 years of age and older, and we recommended expansion down to 4 years of age and older, based on experience with budesonide and albuterol in this age group. The agency recommended a Bayesian borrowing approach, but no agreement on the degree of borrowing or statistical plan was made.

In terms of precedent, inhaled products are locally acting. Extrapolation of efficacy based on pharmacokinetic data is not appropriate. Typically, adolescents are enrolled in adult efficacy trials with subsequent dedicated trials in younger children. The division has led to some degree of extrapolation in the past, however, the unique things here is the BDA program is a novel combination, it's a novel indication for prevention of severe exacerbations, and it's a novel intended use. In terms of precedent, generally, areas of extrapolation have been with established indications for either the drug or drug class, so this would be unique.

Again, I show you the criteria that should be considered in determining whether extrapolation is appropriate and the level of extrapolation. Then finally, I'll close with an initial table looking at benefit-risk summary by age group. For the greater than or equal to 18 years of age subgroup, both pivotal trials met the FDA agreed-upon primary endpoints. BDA high dose demonstrated benefit in reducing severe exacerbations and reducing systemic corticosteroid use.

In terms of risk, there are no new signals identified, and labeling and routine pharmacovigilance should be able to manage any risk from the product. In areas of uncertainty, it's a novel indication and intended use; the effects on asthma control and quality of life were not significant; and then ICS-related adverse events may be different with real-world use.

In the 12 to 18 year age range, the efficacy data for the high-dose BDA is inconclusive. Again, in terms of risk, there are no new signals

identified, but based on the inconclusive results, extrapolation of data from the adult population would be needed. An area of uncertainty that we're asking the advisory committee to help provide feedback on is what degree of extrapolation from adult data would be appropriate. The scope of the safety database is small and long-term risks are not captured.

Finally, in the 4 to less than 12 year age range, the efficacy was inconclusive for low-dose BDA; again, there were no new signals identified for adverse events; and the appropriate degree of extrapolation for this age group may differ from that for the 12 to 18 year age range. And again, we would like the advisory committee to provide feedback on that. The scope of the safety database was small and long-term risks were not captured.

We're going to ask this afternoon for the advisory committee to discuss the data to support the efficacy of fixed-dose combination of budesonide and albuterol, or BDA, for the as-needed treatment of bronchoconstriction and for prevention

of exacerbations in patients 4 years of age and older. And we're going to ask specifically, for children 4 to less than 12 and 12 to less than 18, if extrapolation of adult data to pediatric subjects is appropriate; and if so, discuss the appropriate degrees of extrapolation.

We're going to ask the committee to discuss any potential safety concerns, particularly for children, and there will be voting questions on benefit-risk assessment for use of BDA for the proposed indication in patients greater than or equal to 18 years of age, 12 to less than 18 years of age, and 4 to less than 12 years of age.

Well, this concludes the agency's presentation with this, and I turn it over to Dr. Au. Thank you very much for your attention.

Clarifying Questions to the FDA

DR. AU: Thank you very much.

I know we are pretty close to our noontime break for lunch. I was going to ask the committee if they'd be willing to have discussions for about 15 minutes into our lunch break, and then if there

are additional questions, we can re-engage after the open public hearing session, if that's ok with everyone.

If there's any dissent, please let me know, but in the absence of that, can I ask for any clarifying questions for the FDA?

Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific person, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That's all for my questions," so that we can move on to the next panel member.

So let me go ahead and open it up for discussion.

Ms. Oster, you have the floor.

MS. OSTER: Yes. Thank you. This is Randi Oster, and my question is for Kelly Stone. I would like to know, is there precedent with the FDA? When we need to go and use data of up to 478 people, do we look at that from a perspective of race or location to tie back?

The reason for this question is the data that was given to us is that 75 percent death rate is higher for black than white, yet the data that we were given in the studies only showed 13 percent of the people were black. And therefore, I just want to make sure that if we were to choose to extrapolate data, there is a correlation between location. Thank you.

DR. STONE: I'm sorry. This is Kelly Stone, FDA. Thank you for that question.

I just want to make sure I understand your question. You're asking about whether the adult population from which the data will be extrapolated is representative of the general population? Is that your question?

MS. OSTER: Right. The concern is, I just want to identify as part of the process is that we correlate where we're extrapolating the data from so that we're not mixing from one population to the other when the data has shown that it is not necessarily equal, based on what has been presented and what was given to us.

DR. STONE: In our analysis, as we're reviewing the data from these studies, we do look carefully at that. I can't give you any specifics right now, but we do consider those factors in our analysis.

MS. OSTER: Thank you.

DR. AU: Great.

Dr. Stoller?

DR. STOLLER: Yes. This is Jamie Stoller, a question for Dr. Stone. It regards precedent with regard to Bayesian extrapolation.

I understand that this is a unique indication, and you've made that very clear. My question is, in instances when you have actually used pediatric extrapolation, has there ever been

an instance in which the magnitude of the extrapolation has been as big as your analysis suggests, more than 85-90 percent of the data? What's been the magnitude of extrapolation that's been acceptable to the agency as evidence of pediatric extrapolation? I'll stop there.

DR. STONE: Hi. This is Kelly Stone, the FDA again. If I understand your question, is there precedence for full extrapolation of efficacy data from adults to children, the answer to that would be yes.

For products where PK matching is available and we think that the disease is the same between the age groups, full extrapolation can be used in those cases. Certainly, there are examples of full extrapolation of data. This is a little bit more challenging in that it's a locally acting product, and you can't use PK for matching.

So the answer to your question is, yes, there are examples, but for inhaled products, the considerations are a little bit different and a little bit more challenging.

DR. STOLLER: Thank you. That completes my question.

DR. AU: Thank you.

Dr. Greenberger?

DR. GREENBERGER: Thank you. This is a point of clarification for slide 9. This has to do with the fact that -- the way I understand it, the investigational product is a single device with two medications, and we're adding an inhaled steroid SABA to either an inhaled steroid LABA or an inhaled steroid.

I just wanted to clarify that so we're on the same page, or am I not understanding it?

DR. STONE: This is Kelly Stone, the FDA again. It's on top of the background therapy. They continue their background therapy, and anytime they would use a reliever medication, they would use the combined ICS-SABA. I don't know if that's your question, Dr. Greenberg.

DR. GREENBERGER: How it's presented on the slide I think could be confusing because this is a single product with two medications in it.

DR. STONE: I apologize for that confusion.

DR. GREENBERGER: The other point I wanted to make is regarding the TREXA study. The data are from the U.S., the way it's presented in the article, and I think that they used two different inhalers -- correct me if I'm wrong -- as opposed to this investigational product, which is a single unit.

DR. STONE: Yes. I don't know the answer to that off the top of my head, Dr. Greenberger. We're certainly happy to defer that question to the applicant.

DR. PIPER: Ed Piper, AstraZeneca. I think I can clarify that. In TREXA, you're correct. It was two inhalers, beclomethasone and albuterol in patients who were instructed to take a dose of the beclomethasone at the same time as they took a dose of albuterol. So in that instance, it was two inhalers.

I used the example to show the principle of the combined rescue preparation being effective compared to albuterol, and to be clear, BDA is

indeed a fixed-dose combination product and a single inhaler of budesonide and albuterol. Thank you.

DR. GREENBERGER: Thank you.

DR. AU: If no further follow-up, Dr. May?

DR. MAY: I have a question for Dr. Stone. In the summary slides, you indicated that the results for the kids are inconclusive and that the long-term risks are unknown. But wouldn't that be expected for the study, given the small sample size for this? That's my first question and then after that I have one more.

DR. STONE: Yes, we agree with that statement. It would be --

DR. MAY: So the other question -- I'm sorry. Go ahead.

DR. STONE: No. I was just saying it would be expected with the small sample size.

DR. MAY: And the design, yes.

The other question that I have is, would it be possible to bring up table 7 of the FDA briefing document? That's the event rates in each of the

subgroups. If not, I can repeat from the table the numbers that I'm looking at and that I have a question about.

DR. STONE: I apologize. We're checking to see if we can pull up that figure.

DR. MAY: Maybe I should just get started, and then if you bring it up, that would be great; and if not, that's fine, too.

As I think was pointed out previously, the number of events in the younger age groups are relatively small. I was struck by the amount of borrowing that is necessary to reverse the results, in some sense, that were seen for the kids. Nevertheless, the rate of event in the 12 to 18 age group is 9 out of 34, which is 26.5 percent, which happens to be almost exactly the event rate that is seen in the adults in the AS group.

So number one, I was positively struck by the event rate in that group is not higher, but the numbers are really small. So the AS group for the younger age group from 12 to 18 have an event rate of 7 out of 34, which is 20.6 percent. So our best

estimate for the background rate of events is, for the AS group, the 26.4 percent that is seen in the adults.

So if I'm not mistaken, even though a large amount of Bayesian borrowing is required to reverse the results, I think it would take only two events in the 12 to 18 age group to result in a null effect. I know that, based on hazard ratio, it's a a little bit more complicated than just the percent of events, but it is just that we are talking about very small numbers here.

And, yes, we see what we see, and that's in the opposite direction, but if I'm not mistaken -- and that would maybe be a question for the statistician -- in general, approximately only two events would have to be different; two additional events in the AS group for the kids, for the 12 to 18 age group, more or two events less in the high-dose group to result in a hazard ratio that is approximately 1.

Am I correct on that?

DR. Y. KIM: This is Yongman Kim, FDA. We

agree with the observation, so based on small sample size and very rare events, maybe one or two events in the opposite direction maybe changes the estimate direction. That means there's a lot of uncertainty in this estimate in this population.

DR. MAY: Yes. Thank you, and that was it for my end.

DR. AU: Thank you.

Dr. Cabana?

DR. CABANA: Hi. This is Dr. Cabana.

Dr. Stone, this builds on Dr. May's question. This is slide 11 of your presentation on the sample size calculation. This sample size calculation, it's been described -- well, the sample size for adolescents has been described as small, but looking at this slide, it looked like 1,000 patients were supposed to be recruited over the age of 12.

Were there any assumptions made about what the distribution of adults and adolescents would be or were they all just lumped together, and it was just bad luck that we only ended up with

90 adolescents?

Because if you look at the original sample size calculation, it looks like there could have been many more adolescents, and was there any assumption about how the recruitment would go and what the sample size should have been when doing this sample size calculation? It seems like they were just all lumped together. Thanks for clarifying.

DR. AHN: Hi. This is the primary statistical reviewer, Dong-Hyun Ahn.

So yes, a thousand patients per group was planned for adolescent, adult, and other patients combined, and there was no specific plan for how much from each adolescent or adult patients were to be recruited at the design stage. So it turns out that only a small portion of adolescents from the planned population sample size was recruited in the MANDALA trial.

DR. CABANA: So just to clarify; two points. This was never really powered for -- the way this is structured, it was never really powered for a

specific analysis for adolescent subjects between 12 and 18. Number two, it seems like it was assumed that all these patients, these 1,000 patients, would be lumped together, adult and adolescent subjects, so there was never any planned a priori analysis of adolescent patients between 12 and 18 separately. Thank you.

DR. AHN: Yes, that's correct.

DR. CABANA: Thank you. That helps explain why the distribution was this way. Thank you for clarifying.

DR. AU: Thank you

Why don't we take the last question, clarifying question, from Dr. Dykewicz?

DR. DYKEWICZ: Yes. Thank you.

We've been discussing, not only in this presentation but the sponsor's presentation, extrapolation of data in the pediatric and adolescent group from budesonide/formoterol to the current product under consideration, budesonide/albuterol.

Now, of course, an assumption would be that

the inhaled corticosteroid component of both products is responsible for the bulk of the exacerbation risk reduction, but the question that I'm wrestling with, and I wonder whether the agency has considered this, is we are looking at the difference between a product that has a long-acting beta agonist versus a short-acting beta agonist, and the possibility the short-acting beta agonist's nature plays some role in the protective effect of the combination product.

So my specific question is whether the agency has similar or any other additional reservations about the extrapolation of budesonide/formoterol data to budesonide/albuterol. Thank you.

DR. SEYMOUR: Hi. This is Dr. Seymour, the division director. Thank you for that question. I think we're really focusing on this development program. With inhaled products, they're each unique, they have unique delivery, so we're not necessarily going to be able to glean a whole lot from the literature for the ICS LABA to directly

inform the efficacy data for this product. It's important context to understand, but I don't know that we can leverage it for the efficacy instruction in this program.

DR. CABANA: Thank you. No questions.

DR. AU: Thank you very much.

We'll now take a lunch break, and I apologize for running us a little bit long for that, but we will convene at 1 p.m. Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin around 12:45 Eastern to ensure that you are connected before we convene at 1:00 p.m. Thank you very much. We'll see you shortly.

(Whereupon, at 12:17 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. AU: This is David Au. I hope everyone had an enjoyable lunch. I think we should go ahead and get started again in 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's important to understand the context of the 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 --

(Audio interference.)

DR. STEVENSON: This is Takyiah speaking; a friendly reminder to please mute your lines, your phones, when you're not speaking. Thank you.

DR. AU: -- Thank you. I'll continue.

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

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

The FDA and this committee places 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 for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is now connected. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. Thank you.

DR. DICKENS: Hello. My name is Michelle Dickens. I am a nurse practitioner and a certified asthma educator, and work in Springfield, Missouri, for a hospital system called CoxHealth. For my disclosures, I am a speaker for AstraZeneca for severe asthma, and I have participated in the advisory board for this product. I've also in the past participated as an advisory board member for a

different company, Boehringer Ingelheim.

In the course of evaluating this application, you will be presented with data from several clinical trials, however, my role today is to take you out of the clinical trial and into the clinic. I hinted at this in my written comment, but I felt it warranted a few minutes to give you a glimpse of the reality of asthma care from the trenches.

For the past 12 years, I have worked as a nurse practitioner and asthma educator in an asthma specialty clinic. My days are spent in direct patient care. I counsel asthma patients of all ages about how to manage their disease, and I prescribe medication therapy.

I consider myself to be skilled at explaining the need for controller medicines, the risk of oral steroids, and the importance of trigger avoidance, and I've been told by patients and students that I'm a good educator, and I have the luxury of spending at least 20 to 30 minutes with each patient, educating them about their

disease. But at the end of the day, am I successful?

Judging by the refill patterns of my patients for their asthma controller medicine, I'm better than the average. Unfortunately, that might not be saying much because the average refill rate is only about 35 percent; a solid F if we were getting graded as a community.

Now, let's think back to my days in primary care. I spent 10 years in family practice in a rural health clinic. It's where I developed my passion for asthma care. In a 15-minute visit, I was expected to address my patients' hypertension, diabetes, and their asthma. Is it any wonder that even the most basic message about what it means to have good asthma control or how to use the asthma medications get lost or never addressed? This is the challenge we face in asthma care.

While I may see the most severe asthmatics in my specialty clinic, the majority of those so-called mild patients are being managed in the primary care setting. But are they really mild or

just underestimated? Because now we know that these mild asthmatics have exacerbations at a rate similar to my severe ones. Over half of the mild asthmatics will have a significant flare up in the next year, and clearly we are failing our asthma patients.

However, we're not failing in asthma care because we have shortages of good medicines or well-meaning healthcare providers. We are failing because we have refused to accept the reality of how patients treat their asthma. It's time for a reality check about asthma.

Our enemy is a chronic disease that by nature waxes and wanes over time. Despite our best efforts to educate patients on the importance of taking a controller, even when they're feeling well, they simply don't do it. We blame the patient, labeling them non-compliant. Instead, we should blame ourselves for being non-observant.

The 2020 NAEPP asthma guidelines update specifically addresses the use of short-acting bronchodilators and inhaled steroids for as-needed

combined therapy in mild asthmatics as an alternative to the traditional regimen of daily ICS and as-needed product. I'm a big supporter of this approach, and I've been trying to implement it for my appropriate patients in my practice. However, this requires the patient to use two different inhalers during each dose.

It sounds simple enough, but in the real world, I'm finding that patients get confused about the plan, and they often are reverting back to just using the SABA because it gives quick relief. Once again, we would label these patients as non-compliant with our present therapy.

We need a new treatment paradigm, one that is patient-centered, and that is what this new inhaler can do for us. These medicines are not new. We've had them in our toolbox for decades, but now we're thinking outside the box, using an innovative approach to take the tried-and-true medications in our arsenal and rethink about how best to use them. This inhaler tailors our treatment to match the way that patients behave in

the real world, instead of expecting them to conform to our ideas.

Patients will continue to reach for their short-acting beta agonist for rescue. If we replace it with the combination of a short-acting beta agonist and inhaled corticosteroid, we address both the symptoms and the underlying inflammation. It is a simple but elegant solution that is a win for everyone. The patient gets quick relief while we succeed at treating the airway inflammation, and as you've heard from the clinical trial data, this reduces exacerbations. This could be our new reality, where we translate the success of a clinical trial into success in my clinic.

Thank you very much for allowing me to present.

Clarifying Questions (continued)

DR. AU: Thank you very much.

The open public hearing portion of this meeting is now concluded. We will no longer take comments from the audience. 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 take an opportunity to take any remaining clarifying questions. Please use the raise-hand icon to indicate that you have a question and remember to put your hand down after you've asked the question. 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 end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

We'll start with Dr. Kim.

DR. E. KIM: Edwin Kim, University of North Carolina. This is a question for Dr. Stone.

If I'm understanding the proposal, the company is looking to advocate for the high dose

regimen for adults, and my question comes back to the children. Is there a precedent to extrapolating data to, I guess what I'm going to call a secondary outcome, the lower dose that was analyzed versus the high dose, which is what's being proposed for adults? Thank you.

DR. SEYMOUR: Hi. This is Dr. Seymour from FDA, the division director. They have data that they've obtained in the pediatric 4 to 11 age group with the lower dose, so I don't think we necessarily would be relying on extrapolation from the higher dose to the lower dose. I believe the lower dose was also studied in the adult population, and there was success with that dose as well. So there is that information as well that we have in the adult population to look towards.

DR. E. KIM: This is Edwin Kim from North Carolina again with a follow-up. Where that question is coming from was, if I understood the data, there was benefit in the adults for both high- and low-dose regimen, although the higher dose seemed to have a stronger benefit.

Representatives earlier had given arguments for why they studied the lower dose and not necessarily the higher dose, and I'm, again, trying to just clarify when extrapolation -- when borrowing of data is going to be done, is this borrowing from the lower dose data accumulated in the adults, which seemed to have lesser efficacy, or is there somehow -- and this may show -- maybe not -- being completely comfortable with the sort of Bayesian borrowing concept. Thank you.

DR. SEYMOUR: This is Dr. Seymour again. I don't think I have much to add, really, other than they did study the lower dose in the adult population. With inhaled corticosteroids, in general, I would say that, typically, in the 4 to 11 age group, we do see the lower dose as the dose that's approved. So there is that historical information about use of ICS and pediatric patients as well.

DR. E. KIM: Okay. I think the sticking point for me is just the use of this as a rescue versus a controller, but understood. Thank you.

No further questions.

DR. AU: Thank you.

Dr. Holguin?

DR. HOLGUIN: Yes. Fernando Holguin, University of Colorado; a question for Dr. Kelly Stone or the biostatistical team.

I know there are several methods for Bayesian extrapolation or borrowing, and there's also the risk of potentially introducing biases and overinflating type 1 error. So since this is such at the heart of the discussion, I could use a little more information as to the methodology used for Bayesian extrapolation.

DR. TRAVIS: Hi. This is James Travis. I'm the lead statistician for the pediatric and maternal health team. I'd like to ask what particular type of information you're looking for on the method? We provided additional information on the details in one of the appendices in the briefing document, but I think there's a lot to look at, and it would be helpful if you can focus the question a little bit more.

DR. HOLGUIN: Well, the question is, depending on the methodology that you use, you may end up with a different estimate or potentially introducing biases, and it's sort of a simple way to ask whether those were taken into consideration, and --

DR. TRAVIS: Well --

DR. HOLGUIN: I'm sorry.

DR. TRAVIS: Sorry. Go ahead.

DR. HOLGUIN: How you selected data to borrow; is that just done at random, for example? Are the rates of the historical data and comparative data the same, and things like that? Thank you.

DR. TRAVIS: Yes. Thank you for your question. Yes, it's a general concern with using these methods. You do get some kind of influence on the point estimates based on the proximity between the prior mean and the observed mean. The mixture prior model tries to reduce it. It doesn't completely eliminate the bias and, yes, it's definitely a concern. But I think the advantage of

this type of method is it allows us to quantify the amount of borrowing, and I think that compensates for the disadvantages in this case.

DR. HOLGUIN: Thank you. No further questions.

DR. AU: Thank you.

Dr. Carlson?

DR. CARLSON: Hello. This is Dawn Carlson, and I have a question for Dr. Stone, and it's really based on the discussion prior to launch about the extrapolation. My understanding is that it was based on the adults in the MANDALA trial, not any external studies.

Then the second question was that when there was a recommendation to do the Bayesian methodology for extrapolation, was there any estimate? I know there was no agreement on the amount, but was there any estimate of what degree of extrapolation might be required, given the small sample size?

DR. STONE: This is Kelly Stone, FDA. There was a discussion about using a Bayesian borrowing approach, but there was no discussion about the

amount of borrowing that would be appropriate.

Your first question I think had to do with whether the data would come only from the adult population in this study or from external data, if I understood correctly, and it would just be based on the adult data from the MANDALA trial.

DR. CARLSON: Okay. Thank you. That completes my questions.

DR. AU: Ms. Oster?

MS. OSTER: Yes. I just wanted to clarify that if we need 478 borrowed adults to get to a 96 percent confidence level for the 4 to 12 year olds, that the thousand population that you had was adequate; or is it, in the ideal world, you really would want to look for more people?

I think it's a very direct question, is do we even have enough people in the sample size for the borrowing rate needed?

DR. AU: Can I ask to whom is that question directed?

MS. OSTER: Oh. Dr. Stone.

DR. AU: Okay. Thank you.

DR. STONE: Yes, this is Kelly Stone for the FDA. I'm sorry for the delay unmuting.

We think that there's enough data, adult data, from the MANDALA trial to allow extrapolation if it was determined that it was appropriate. I don't know if that answers your question, but we do think that there is sufficient data amongst the adult population in the study to extrapolate if that was deemed to be appropriate.

MS. OSTER: And that's across demographics as well.

DR. STONE: Across demographics as well, exactly.

MS. OSTER: Thank you.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: Dr. Tracy here. I'm not exactly sure who I would direct this to, but we talked about this being a novel indication, but the products themselves really are not that novel. They've been around for a long time, and there's a long history of clinical and regulatory background

to support that.

I was just wondering, is there anything in particular, when you combine these two agents within a single dosing device, that warrants additional consideration? And again, I'm not sure exactly who that would go to, but I'm assuming it's safer, and we've looked at the safety stuff. But are there any other things we need to be thinking about? Thank you.

DR. PIPER: Ed Piper, AstraZeneca. May I offer a comment, Mr. Chair?

DR. AU: Yes, please go ahead.

DR. AHN: Hi. This is Dong-Hyun Ahn, the clinical pharmacology team leader from FDA. Yes, from a clinical pharm perspective, if you combine two active ingredients into one inhaler, or one deep inhalation device, we also ask applicants to do a drug-drug interaction study to see, at least at the systemic exposure level, if one drug or one active ingredient can affect the system PK of the other one.

Does that answer your question?

DR. TRACY: Yes, thank you. That's exactly what I was looking for. Thank you. No follow-on questions either.

DR. AU: No additional comments.

Let's go to Dr. Hunsberger.

DR. HUNSBERGER: Yes. This is Sally Hunsberger. This is directed at probably the FDA. I just wanted to understand a little more what the goals or objectives were of the FDA when they ask for a company to include younger kids but allowed such a small sample size. So was it really just to get some safety information? Because clearly, with that small sample size, you won't get any efficacy information.

So I'm just trying to understand statistically or what you were thinking when you asked for these participants to be included.

DR. SEYMOUR: This is Dr. Seymour. I'll try and address your question. This program dates back a number of years, and I think when we initially had conversations with the sponsor about the development program, they initially were proposing

to do a trial, probably MANDALA-like, that was going to be in patients 12 years of age and older. And we sort of questioned what the plan was their pediatrics program, and I don't think at that time they'd really developed one yet.

Given the familiarity with these moieties and the idea of how this product would be used, at that time we said, "Why don't you consider conducting the trial in the entire age group?" So I think they took that advice and came back with a proposal and, ultimately, we did agree to what the applicant proposed in terms of the sample size in the 12 and older, 12 to 18 and 4 to 11 years of age.

But at that time, I don't think we fully appreciated the difference in this development program compared to other asthma products, which thinking about it, other asthma programs are generally looking at FEV1 as a continuous endpoint; so this power, this number of patients with a continuous endpoint, might have been a sufficient number of patients to have a little bit more

statistical confidence. But here, I don't know that we would have anticipated that we would be looking at a handful of events in 4 to 11 years of age and 12 to 18 years of age to really be making a decision on.

So in hindsight, maybe having more data in these age groups would have been a good idea, but this is a novel program, and I think including patients from 4 years of age and older is not something we've typically done with our development programs, but it's gone back to, really, some familiarity with these moieties and dosing that we already knew, and knew that they were effective for other uses in asthma.

So this is the data we have, and we have to make a decision about this, and it's really, I think, a good opportunity to take the question of extrapolation and asthma in adolescents and children 4 to 11 years of age to you to get your opinion on, and whether this is enough data or not to support a favorable benefit-risk.

DR. AU: Thank you. That's very helpful.

DR. PIPER: Ed Piper, AstraZeneca. May I make a comment building on Dr. Seymour's point, please --

DR. AU: Yes. Please go ahead.

DR. PIPER: -- saying to Dr. Seymour that one of the pieces of data we have that might be helpful we haven't shared yet is what we learned about lung function and changes in lung function in the MANDALA study, in the two populations of interest. So I'm just going to briefly pass you to Dr. Church just to show you two slides on that data that might be relevant. Thank you.

DR. CHURCH: Alison Church, AstraZeneca. Slide up. Lung function was measured at weeks 12 and 24, and was an exploratory endpoint in the overall population, and we did a post hoc analysis in the adolescent population.

Slide up. I'll just describe the data. At week 12, we saw a 202 milliliter improvement in FEV1 with the lower dose of BDA, the 80/180, versus albuterol with a p-value of 0.02. At week 24, that value was 196 with a p-value of 0.048. For the

BDA 160/180 dose versus albuterol, we saw an improvement of 70 mL with a p-value of 0.41, and at week 24, the improvement was 149 mL with a p-value of 0.14. We also have additional lung function data in children. Again, looking at the lung function at week 24 and week 12, we saw an improvement of 131 milliliters with a p-value of 0.104, and at week 24 of 183 with a p-value of 0.056. Thank you.

DR. AU: Thank you.

DR. PIPER: It's helpful to share the lung function data that we haven't previously shared, given that is a high relevant endpoint in these subpopulations. Thank you.

DR. AU: Any follow-up, Dr. Hunsberger?

DR. HUNSBERGER: No. Thank you. That was very helpful; appreciate it.

DR. AU: Yes. Great. Thank you.

Dr. Jones?

DR. JONES: Yes. Bridgette Jones. I had a question -- I think it's for the sponsor -- about the proposed dosing regimen.

You proposed 2 inhalations of 80/90 in 12 or greater and 2 inhalations of 40/90 in 4 to 12, not to exceed 6 doses in 24 hours. Can you talk about how you came up with the maximum 24-hour cumulative dose?

DR. PIPER: Ed Piper, AstraZeneca. Yes. The maximum dosing that we chose is consistent with the albuterol label, which allows 12 doses in a 24-hour period, and that was what we studied in the MANDALA trial. That was the maximum dose we advised that patients should take. And as you've seen from the data I showed you on the pattern of use, that was a dose that was used very infrequently, presumably at the time of the worst -- in the run-up to an exacerbation. So yes, it was based on the albuterol data and existing label, and was studied in MANDALA. Thank you.

DR. JONES: Thank you.

DR. AU: Great.

Ms. Oster?

MS. OSTER: Yes. We've been talking about age and not weight or size, and we all know, unlike

adults that stay the same size, that children are growing.

Can you comment on the limitations of age and the potential of incorrect dosing because of their weight and size and how that was looked at? And that would be a question for the sponsor.

DR. PIPER: Ed Piper, AstraZeneca. This is an inhaled medicine, so the site of action is local in the lungs, so weight is less of a concern than it would be for a drug with systemic bioavailability. Thank you.

DR. AU: Thank you. Any follow-up?

(No response.)

DR. AU: If not, Dr. Weinberg from the sponsor?

DR. WEINBERG: No. Thank you, sir.

DR. AU: Very good.

Dr. Schwartzott? I'm sorry. Ms. Schwartzott?

MS. SCHWARTZOTT: Yes. I'm the patient representative, Jennifer Schwartzott, so I have questions that are a little bit different from the

doctors.

I would like to see some data relating to the moderate to severe side effects and/or adverse events in the pediatric patients. I'm concerned about the difference in the safety risk with those from the young children compared to the adolescents.

DR. PIPER: Ed Piper, AstraZeneca. I'm going to pass you to our pediatric lead, Dr. Church, who will take you through some of the adverse event data observed in the trial in pediatrics and adolescents.

Dr. Church?

DR. CHURCH: Alison Church, AstraZeneca.

For adolescents, no AEs, preferred term, was reported by more than two subjects in any treatment group. The adverse events reported were consistent with those expected in a population of adolescents with asthma. There were no AEs leading to discontinuation of treatment, nor AEs considered related to investigational product reported in adolescents.

In children, the only AE, preferred term, that was reported by more than two subjects in any treatment group was for influenza, which was reported by three subjects in the albuterol group and two in the BDA 80/180 group. One patient in the BDA 80/180 group discontinued treatment due to AEs, or adverse events, of oropharyngeal pain and cough, and two subjects reported adverse events considered related in the BDA 80/180 group. One patient reported an adverse event of cough and the other and adverse event of cough and pharyngitis that were considered related by the investigator. Thank you.

MS. SCHWARTZOTT: Can I ask a follow-up question, then, about that?

DR. AU: Please do.

MS. SCHWARTZOTT: Okay. In regards to heart rate, tachycardia, was that an issue with any of the side effects? I know that it can be a problem with patients that can't take the albuterol on its own.

DR. PIPER: Ed Piper, AstraZeneca. No,

tachycardia was not an adverse event that we observed during the trial. Thank you.

MS. SCHWARTZOTT: Thank you. That's all I have.

DR. AU: Alright.

Let me ask, Dr. Holguin, your hand is still up. Do you have an additional question?

(No response.)

DR. AU: I'll take that silence as a no, and we'll go on to Dr. Cloutier.

DR. CLOUTIER: Thank you very much.

This is Michelle Cloutier. I have a question related to safety of the fixed combo in 4 to 12 year olds. When you look at the frequency of doses, you pointed out the very large percentage of children who did not use -- I think it was 40-45 percent of children did not go for the rescue medication during the day. But the next most common were 4 puffs, or 2 to 4 puffs, which is 1 to 2 inhalations per day. Did you look at all -- in terms of those 2 to 4 puffs, what number of those were related to prevention of exercise-

induced bronchoconstriction?

The reason that I ask that is children often -- these school-age children in particular -- use bronchodilator prior to recess, and many of them use albuterol, for example, prior to sport. Is it possible that these children, who have mild asthma, whose asthma is well controlled, may be unnecessarily exposed to inhaled corticosteroid when they're using protection in terms of exercise?

I think that's a question for Dr. Piper.

DR. PIPER: Ed Piper, AstraZeneca. Thank you, and you're right. Just to help the whole panel, in the MANDALA study, patients were permitted to take BDA or albuterol in response to to symptoms as they would for normal rescue. They were also permitted to take it if they were aware they were at risk of bronchoconstriction from known triggers, particularly exercise.

So when we look at the data that shows the pattern of use in the 4 to 11 year old group, we have to look at that and recognize that there are

two components to that, patients taking in response to symptoms and those taking it prophylactically. So we saw it as being quite reassuring data that patients were not overusing the product, taking into account both those opportunities to use the product were available in the protocol, so we didn't have that concern.

DR. CLOUTIER: But just in follow-up to that, Dr. Piper, how do you know that in these children -- many of whom had many days that they wouldn't need any rescue medication -- that they have very well-controlled asthma, but they're using it for exercise prophylaxis and don't actually need the inhaled corticosteroid; and therefore, a cumulative dose over the course of many, many years would be an unnecessary exposure for those children to ICS?

DR. PIPER: Yes. Ed Piper, AstraZeneca. I think our concern was that for a rescue preparation, we would expect that patients would want to use the product in the same way that they used their existing rescue, and the concept of

having a rescue inhaler like BDA that was used both in response to symptoms and prophylactically would seem to be appropriate; the concept that a patient would have to carry two different rescue inhalers, one albuterol and one BDA, seems to us to be overly complex. And as I said, looking at the pattern of use that included prophylactic use for exercise, we didn't see a concern around the amount of products being used as I described earlier.

So that was our perspective on the topic, but what you raised is clearly relevant and appropriate to consider in the round [indiscernible]. Thank you.

DR. CLOUTIER: Thank you. That's my question.

(Pause.)

DR. AU: I'm sorry. This is David Au. I dropped briefly. I just wanted to check back.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sorry. Sally Hunsberger. I actually did have one follow-up question to my original question.

The company presented, what I understand is new data, and I guess I just wondered if the FDA had any comment on that data since we didn't see a slide on it, and the numbers were just quoted. And I'm wondering if they saw it and if you have any comments on that lung function data.

DR. STONE: This is --

DR. PIPER: Ed Piper, AstraZeneca. We'd be very willing --

DR. STONE: Oh, go ahead.

DR. PIPER: -- sorry. We'd be very willing to share the data. We have a slide on it, but we don't have control of the slides. So if it was of interest to the panel and you wanted to see the slide, we'd be happy to share it with you.

DR. STONE: This is Kelly Stone from the FDA. We have not seen this data, so we can't comment on it, and it certainly hasn't been a consideration in our evaluation of this program. This is new data to us.

DR. AU: Thank you.

DR. PIPER: Should we share the data,

Mr. Chair?

DR. AU: Sure. Why don't you go ahead and share it.

DR. PIPER: So I'll hand it to Dr. Church to share the data.

DR. CHURCH: Slide up. This data was shared, as I understand it, in the submission documents, in the modules that were submitted, and it should be in the CSR.

This is the lung function data where I read out the numbers. So again, this is in the adolescents at week 24, at week 12 on the top and week 24 on the bottom, with the 80/180 dose on top in the first row and the 160/180 dose in the second row. So again, as you can see, there were improvements in FEV1 with BDA 80/180 compared to albuterol. The p-value was less than 0.05 for the 80/180 dose comparisons, where that was not the case for the 160/180 dose.

Next slide. I can also share the data in children. At week 12, an improvement of 131 milliliters was observed, and at week 24,

183 milliliters, both of which had p-values greater than 0.05. Thank you.

DR. PIPER: Thank you for the opportunity, Mr. Chairman.

DR. AU: Yes.

DR. SEYMOUR: This is Dr. Seymour from the FDA. Can I make a comment on that?

DR. AU: Yes, please do.

DR. SEYMOUR: I think we would ask the committee to consider the utility or the usefulness of that spirometry data for the exacerbation endpoint and indication here. We do have a dedicated trial that looked at lung function with DENALI, so we already have some assessment of lung function from this product; so just something to consider.

DR. AU: Thank you.

Dr. Stoller?

DR. STOLLER: Yes. This is Jamie Stoller. With regard to recognizing the comments about the spirometry data, a question for the sponsor. As I looked quickly at the 12 to 18 data and the

magnitude of effect, are you surprised that the magnitude of effect was smaller for the larger dose than for the smaller dose?

DR. PIPER: Ed Piper, AstraZeneca. As we described before, the 80/180 and the 160/180 in adolescents is not dose ordered. That is a surprise to us. I think I gave you the reasons why we consider it to be, actually, the lower of small numbers of patients and small number of events before the lunch break. I think looking, again, at the overall data that is powerfully in support of the 160/180 dose in the overall patient population on the primary endpoint and all the secondary endpoints, I think we feel comfortable that that is the right dose to be recommending that is considered for adolescents as well. Thank you.

DR. AU: Thank you. No follow-up?

DR. STOLLER: No, just to follow up, and sort of an editorial comment, perhaps in anticipation of responding to questions later, one of the things that troubles me, in general, is the data really vacillate, sometimes favorable,

sometimes unfavorable. It sort of ascribes to small numbers, and the volatility of the data in small numbers is apparent. I'll stop with that, so no further comment.

DR. AU: Thank you, Dr. Stoller.

Dr. Cabana?

DR. CABANA: I think Dr. Stoller asked the question I wanted to ask as well, too, about the small numbers, so it's also very troubling as well. If it's the law of small numbers, it seems like you just can't pick which small group that you like. That's just a comment. Thank you.

DR. AU: Thank you.

Dr. Holguin?

DR. HOLGUIN: Yes. Fernando Holguin. I was just wondering for the sponsor, were both arms -- the high and lower dose in adolescents, were there similar amounts of exposure data in terms of like data points that were during the analyses? Is it possible those in lower dose, you had fewer data points exacerbation-wise or lung function treatment?

DR. PIPER: Ed Piper, AstraZeneca. I don't believe that's the case. The number of adolescents are similar between the treatment groups, so I don't think that there is less data, per se, by dose group. We stratified by age for the adolescents, both, hence, the equal number of patients in the adolescent cohort, so I don't think that's a factor.

DR. HOLQUIN: Thank you. No further questions.

DR. AU: Can I ask one last round for the committee at large? Are there any more clarifying questions for either the FDA or the sponsor?

(No response.)

DR. AU: If not, then I think we can move on.

We will now proceed with the FDA charge to the committee from Dr. Kelly Stone.

Oh, I'm sorry. Before we do that, Dr. Stoller, do you still have your hand up or was that from the carryover?

DR. STOLLER: I'm sorry. I'm neglectfully

not lowering my hand. No further questions.

DR. AU: Okay. Great I just wanted to make sure. Thank you.

So we will now proceed to the FDA charge to the committee from Dr. Kelly Stone.

FDA Charge to the Committee - Kelly Stone

DR. STONE: Thank you, Dr. Au.

I'd like to thank the committee and the applicant for the discussion up to this point. Just to re-emphasize, BDA is a new combination product, budesonide and albuterol. It's a new proposed indication to prevent progression to exacerbations, severe exacerbations, and it would be the first use of an ICS for reliever treatment

For the adolescent, and for the pediatric subgroup, in general, there is great uncertainty in terms of the effect of this product for the intended use, and the focus of the discussion really comes back to where it's been, which is how comfortable are the members of the committee in extrapolating data and what is the basis for extrapolation of that data? And we're particularly

interested in whether there's less uncertainty in the adolescent 12 and above group compared to the 4 to less than 12 age group.

So the questions that we're asking the committee to discuss, again, to help inform our analysis of this development program are, one, discuss the data to support the efficacy of the fixed-dose combination for the proposed indication that's highlighted here.

In particular, for adolescents 12 to less than 18 and young children 4 than less than 12, discuss if extrapolation of adult data to pediatric patients is appropriate based on the available data; and if so, discuss the appropriate degree of extrapolation in these age groups. And we're particularly interested in whether full extrapolation, as would be needed here, would be appropriate, based on available data.

The second discussion point is to discuss the safety of BDA for the proposed indication, discussing any specific pediatric concerns. And there have been some raised in the discussions at

this point, but we'd like to hear if there are any additional safety considerations that would need to be considered, particularly for the younger children.

Then there are three voting questions that we're going to ask the committee to vote on. The first, do the data support a favorable benefit-risk assessment for use of BDA in patients greater than or equal to 18 years of age with asthma? And if not, we'd like to hear what additional data may be needed to support that indication in that age group.

Question 4 is a voting question, again, do the data support a favorable benefit-risk assessment for BDA in patients 12 years of age to less than 18 years of age with asthma? And if not, what additional data are needed?

Then finally, in the youngest age group, 4 to less than 12 years of age, do the data support a favorable benefit-risk assessment for the proposed indication? And if not, what additional data would be needed?

We look forward to hearing discussion on the discussion questions, as well as feedback on the voting questions, and I will turn it over at this point to Dr. Au. Thank you so much.

Questions to the Committee and Discussion

DR. AU: Thank you, Dr. Stone.

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 would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except after specific request of the panel.

After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question to discussion. We will start with question 1.

Discuss the data to support the efficacy of fixed-dose combination, budesonide and albuterol sulfate, metered dose inhaler, BDA, for the

as-needed treatment for prevention of bronchoconstriction and for the prevention of exacerbations in patients with asthma 4 years of age and older. For adolescents 12 to 18 and young children between 4 and 12, discuss if extrapolation of the adult data to pediatric subjects is appropriate, and if so, discuss the appropriate degree of extrapolation in these age groups.

Are there any questions about the wording of the discussion question?

(No response.)

DR. AU: Okay. If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

We'll start with Dr. Stoller.

DR. STOLLER: Yes. Thank you, Dr. Au. This is Jamie Stoller. I have a predicate comment and then really a question for my pediatric pulmonary colleagues on the committee, on the panel. The predicate comment is, the whole issue of extrapolation is predicated on a couple of issues. One is the disease similarity, if you will, but

another dimension of it is the extant data, recognizing that the extant data from both TREXA and STAY don't exactly apply here, a different beta agonist, formoterol, rapid-acting but long acting, as opposed to albuterol.

As I read those studies, again, TREXA in ages 5 to 18, and STAY in ages 4 to 11 -- and this was alluded to earlier, I believe -- the data are sort of conflicting. At least as I read it, TREXA on the primary outcome measure, which was time to first exacerbation -- not treatment failure as was shown, but time to first exacerbation -- actually did not achieve significance in the as-needed group, and STAY in the younger patients appears to have done so.

So I'm interested in my pediatric pulmonary colleagues' sense of this predicate data as it applies to plausibility and extrapolation, recognizing again that extrapolation is a function. not only of disease characteristics, of endotype issues, but also of available data, albeit extended to this trial. I hope my question's clear.

DR. AU: Do we have any volunteers from our pediatric colleagues?

DR. CLOUTIER: This is Michelle Cloutier.

Dr. Stoller, that is exactly the areas that I'd like to address, and maybe this would help. I look at the four criteria that the FDA proposed for extrapolation of data to the 4 to 12 year olds. The first is that the disease is the same in adults and pediatrics, and while there are similarities in the disease between children and adults, there are also some significant differences that were not mentioned or discussed.

The first of these is that there's a male predominance in children compared to a female predominance in adults. Some of that is related to structural differences and airway dysanapsis in boys, which resolves as their airways grow later on but clearly can affect their response to a bronchodilator.

The second is that the most important trigger in young children are viral respiratory tract infections, while in adults, as shown in the

MANDALA study, it was allergens and exercise. And the last, which relates to response to therapy, lies in that young children are more likely to have a low Th2 response in early childhood as compared to later on. So I think these differences could, in fact, speak to the disease not being the same in young children as it is in adults.

In terms of the second element, response to treatment is the same, I think all of the studies that have looked at the addition of an ICS -- now I'm talking about young children, again, 4 to 12 -- the use of [indiscernible] has not shown to be more effective than what we're currently recommending, which is daily ICS with SABA rescue. So I'm not sure that the response -- it doesn't look like the response is the same.

I think the TREXA data is really important. It's one of the things they didn't mention about TREXA, is that the mean age of participants in TREXA was 10 and a half, which means they did not have very many 4 to 12 year old children. They were much more skewed to older children, which is

one of the reasons why the expert panel did not support that therapy in young children because of low certainty of evidence.

So the third is the high confidence in the evidence, and I think you point that out beautifully; it's all over the place. And I think there are very much significant knowledge gaps, particularly in children 4 to 12. And I'll leave that at that, and I'll lower my hand as well.

DR. AU: Thank you very much.

Dr. Stoller, did that response satisfy you or would you like to hear from other of our pediatric colleagues?

DR. STOLLER: Oh, no. That was very helpful. I invite other comments, but that was very helpful. Thank you.

DR. AU: Let me ask if there are any other comments to this before moving on to the next participant.

(No response.)

DR. AU: Hearing none, let me go to Ms. Oster.

MS. OSTER: I just want to make the comment in support of what we just said. One comment that is jumping out at me is if it's small data, and now we're being asked then to extrapolate the data, why didn't we just get more data? I think that for the children, because we didn't hit the data size that was acceptable, it does not mean the result is we have to extrapolate the data. So that's just my comment there.

DR. AU: Alright. Any comments on that?

(No response.)

DR. AU: Great.

Dr. Kaizer?

DR. KAIZER: Yes. It's Alex Kaizer from the University of Colorado, and just a few comments on some of the statistical aspects of the trial. I think it echoes a lot of what people have already raised and addressed. I think one of the challenges we have is that, as been stated, it's not like this study was designed to be powered in children or adolescents. So regardless of the outcome, we would have been underpowered to

probably detect a significant effect in those groups.

I think one of the things that makes it more difficult in this case is, as people have said, the effect estimates jump around. For those adolescents, it's unexpectedly large for the higher dose group, performs better for the low-dose group, and then for the children group, it very much looks null for the point estimate. For all of these, though, as has been mentioned, the confidence intervals are extremely wide.

In a perhaps more ideal situation, all of these point estimates may have appeared -- well, not significant, but aligned with the overall estimate, and we still have, though, the issue at hand that the confidence intervals would be extremely wide, potentially alluding to the chance of an effect appearing with the benefit towards just the albuterol group.

So I think that's one of the challenges statistically here, is that we really do need to lean into a lot of the context, scientific, and

clinical understanding of the disease here because the study as designed was not meant to be statistically powered to address those concerns.

I think, really, the only way to address that, I think that Ms. Oster was getting at, is that we would need more data to confirm the effect beyond the sample size, knowing that with small numbers like this, a single person's change in the outcome can lead to very different effect estimates, with the caveat, again, being there are large confidence intervals.

I think also just the use of the Bayesian information sharing approaches does help to illustrate what would have been needed to move the needle, so to speak. I personally do research on these methods to develop new statistical techniques for what is called information sharing or borrowing, and one of the things to note is that one of those criteria we use is what we call exchangeability, or is the effect estimate we're trying to pull together similar or not?

When we see differences in those effect

estimates, as we do here, we may be wary statistically to borrow too much or read too much into pooling that data together, where at one extreme we have these results now, which seemed very disparate and challenging to interpret, and at the other extreme we have the overall trial results, which suggests benefit. And if we ignored these potential differences by age, it would lead us to suggest that we should see some benefit for the overall treatment.

I know it doesn't clarify what we should do, but I think it helps to illustrate that we would need to borrow a significant amount of adult data, given the small sample size of both children and adolescents. But then depending on how clinically relevant we think that would be, it could be useful to extrapolate or incorporate that information in a meaningful way. Thank you.

DR. AU: Thank you so much.

Any additional comments to that?

(No response.)

DR. AU: Let me go on to Dr. May.

DR. MAY: Yes. I was just wondering, it seems to me -- and just following up from Dr. Kaizer -- that the data that we see for the kids are really not that supportive, or are not only inconclusive but they are all over the place because of the sample size.

I was wondering if there were no kids included at all, the disadvantages that would have been to not have any information with regard to safety. But even here the safety data is limited because of the limited sample size, but would we decide to go forward solely on the data of adults if we had no data for the kids whatsoever? I think, besides the safety data, this is the comparison; that the estimates are all over, and it might have been as well as not having these data at all.

So I'm wondering is there any precedent for having a combination drug that had no data for kids but was approved for kids, based on the adults' data and based on the fact that it was thought to be the same disease, the same process, and for the

same outcome? And that's my question.

DR. SEYMOUR: Dr. Au, this is Sally Seymour from the FDA. Would you like me to respond?

DR. AU: Yes, that would be useful. Thank you. I appreciate that.

DR. SEYMOUR: Thank you for the question, Dr. Jones. In my time here at FDA, I cannot think of any example of a product that was approved, an inhalation product, based upon adult data only to include an indication in children. Keep in mind, for extrapolation, we're generally referring to efficacy data, so even if we do a full extrapolation for a PK program for a systemic product, we generally also get safety data. So there is some data and children beyond the adult data.

Does that answer your question?

DR. AU: Just to clarify, that was Dr. May and not Dr. Jones.

DR. SEYMOUR: I'm sorry.

DR. MAY: And yes, that answers my question. No problem. Thank you.

DR. AU: This is David Au. I'll follow up on that. That was similar to the spirit of my question, and I don't think anyone was able to really hear it because of my previous phone, which is if we're going to rely on data from outside the trial results, why even include the patient population to begin with? It does seem like we're being asked, at least in my opinion, for a leap around what is kind of existing data in the heterogeneity of point effects that are demonstrated. So I appreciate that comment, Dr. May.

Are there any other other follow-up points or discussion points from Dr. May's point?

(No response.)

DR. AU: Otherwise, let's go to Dr. Jones.

DR. JONES: Yes. This is Bridgette Jones. I just wanted to go back and talk a little bit more about the criteria for extrapolation, especially as it relates to whether or not the disease is the same in adults and children.

I think most of us are aware that asthma is

a disease that has variable phenotypes, so I think certainly that there are differences in the prevalence of different phenotypes in adults versus kids, but I think, overall, from a treatment standpoint, if you look at the asthma national guidelines, for the most part, many of the treatments have consistently been very similar between children and adults.

So I don't think that we have any biological or scientific evidence that drug targets -- and affected drug targets especially for inhaled corticosteroids and short-acting beta agonists -- would be that dissimilar between children and adults alike.

So I think based on what we know and we observed over the decades, you would expect that they would behave similarly, targeting smooth muscle relaxation and inflammation in children, as well as in adults, even though the underlying etiology that's causing the inflammation may not be the same.

So I just wanted to discuss that a little

bit more because I think when we're thinking about the disease itself being the same versus the phenotype within that disease, those are two different discussions. Thank you.

DR. AU: Great.

I might ask Dr. Cloutier to comment because she had pointed out some of the differences in children and adults, as well as maybe a specific comment around that the guidelines did not endorse the adoption of therapy for younger kids that were noted in TREXA study, I believe.

DR. CLOUTIER: Thank you, Dr. Au. This is Michelle Cloutier.

I was the the chair of this expert panel that made the 2020 Focused Update recommendation. I think that the committee, in looking at these updates -- and remember it was a Focused Update; there were very specific questions, but there were specific questions related to intermittent ICS.

Now, the results from MANDALA were not available, but the studies that were used for this specific question were the TREXA study and

Turpeinen study. The questions related to growth included the Camargos study from I think 2000, as well as one other study; Collette [ph] I think is the name. But the whole idea behind TREXA really was to determine the added value of ICS plus albuterol in young children with mild asthma in terms of exacerbations, and it clearly demonstrated two things. One was that ICS plus albuterol did not have added value to daily ICS, and it did not reach statistical significance when compared to albuterol alone, and that is the reason why the NAEPP guidelines does not recommend this therapy in young children.

Now, there is a big difference between the NAEPP and GINA, and I think one of the ways that's best able to explain the reason for that is the NAEPP expert panel made a conscious effort not to extrapolate data across ages or asthma severity and to limit expert opinion. GINA uses evidence when evidence is available, but also uses expert opinion -- that's informed expert opinion -- and does extrapolate. That's the difference. That's

one of the major reasons for the difference in this particular recommendation between the two documents.

Does that answer the question and help?

DR. AU: I think that adds robust to the discussion, and I want to thank you for that clarification.

Do others have comments or on this point?

(No response.)

DR. AU: Great. Let's move on to Dr. Tracy.

Dr. Tracy?

DR. TRACY: Thank you. Dr. Tracy here.

This is a little bit of a follow-on. I find myself in this incredible conundrum with data that's all over the place -- in all likelihood because of the small sample size -- so we're forced to make a decision that we almost can't make, or in this case a non-decision, and we can't look at these really three fairly different groups of adults, the adolescents, and the kids. Going back to the GINA versus NIH guidelines stuff, I think expert opinion does play a role here, and I think

this is a little bit of a contrarian, but maybe we have to figure out some way to kind of split these out some way.

My general sense, as I mentioned in my prior comments, if you take it in their singular form, these are not new drugs. Do they affect everybody? Well, what we're doing here is we're kind of comparing populations, where in reality most of us who do this for a living, it's individuals that we take care of. There are an awful lot of adolescents that would very much benefit from a product like this, and just because the powering was not sufficient to answer the question, I'm not sure it's doing our patients a service by putting the kibosh on this.

On the younger kids, there's obviously less data for that, and obviously it's probably less clinical experience. And as far as the safety goes, which will be in the next question, I think that those things are fairly well laid out, and that's a little bit different. But I think we're getting kind of caught up here in the weeds a

little bit, I think, but it's just my thoughts. Thank you.

DR. AU: Great.

Any additional comments from the panel members?

(No response.)

DR. AU: Dr. Greenberger?

DR. GREENBERGER: Thank you. I want to just re-emphasize how important the unmet need is here, however, I'm going to say, clearly, that there are differences in treatment responses between adolescents and children versus adults, and the literature has enough examples of that, including quintupling fluticasone, as people know.

So I think it might be that the therapeutic differences are of such importance with this disease, asthma, and heterogeneity responses are significant that extrapolation of the adult data to children is not appropriate. That's my comment.

DR. AU: Any follow-up?

Dr. Dykewicz, can I give you the opportunity to speak? I know you raised your hand and lowered

your hand, but I just wanted to give you the opportunity.

DR. DYKEWICZ: Thank you.

Well, one of the issues that we're deliberating about --

DR. AU: I'm sorry to interrupt you. Could you state your name for the record, please?

DR. DYKEWICZ: I'm sorry. Mark Dykewicz.

One of the considerations that Dr. Cloutier had raised was, of course, the distinctions in terms of reasons for exacerbations in the pediatric group and the adult group. And I'm thinking in a larger perspective here about the importance of that, and in terms of adults, in the particular MANDALA study, was there any data that was looking at what the cause of the exacerbations that did occur were? Thank you.

DR. AU: Any comment on that? My understanding, at least -- and I should be corrected if I'm incorrect -- is that at least in the older age groups, it seemed to be more kind of allergy or kind of driven, which is the children,

but I would welcome comment otherwise.

(No response.)

DR. AU: Borrowing any other comments, let me move to Dr. Holguin.

DR. HOLGUIN: Yes. Fernando Holguin, University of Colorado. Thank you, Mr. Chairman. My question was following -- or comment was following -- Michelle Cloutier.

When you say that there was no benefit from intermittent ICS bronchodilator therapy in young children, were you considering the fact that maybe they're a lot less exposed when compared to daily ICS? Wouldn't that be a benefit in itself, given this equipoise in that regard? Thank you.

DR. AU: Let me see. That was more directed to Dr. Cloutier; is that correct?

DR. HOLGUIN: Yes.

DR. AU: Let me see if I can summarize. Was that more a question around the addition of ICS --

DR. HOLGUIN: When we say that there's no benefit in that particular population and we are using daily ICS as a comparison, the fact that

you're treating kids intermittently, wouldn't that be a benefit not exposing them to daily ICS for perhaps a comparable level of controller effectiveness?

(Pause.)

DR. CLOUTIER: I'm sorry, Dr. Au. This is Michelle Cloutier. I did not understand your question. I'm sorry.

DR. HOLGUIN: You were saying earlier that when looking at the TREXA data, the guidance decided not to recommend intermittent therapy in the younger kids. And I was wondering whether comparing to daily ICS that was factoring total ICS corticosteroid exposure and its effect on growth -- because it seems to me that if you treat these kids with intermittent dose, perhaps you save them from being exposed to daily ICS.

DR. CLOUTIER: Yes. That's a very good question, and it's an important one. The problem is this. The data on growth, although I think all of us believe that there is a clear effect of ICS on growth, the CAMP study demonstrated that the

effect on growth occurs within 3 months and appears to just last. It doesn't increase, and it appears to be about a sonometer, a little bit more in the boys, a little bit less in the girls, but around a sonometer. In TREXA, there was a concern about growth suppression in the children who were treated with daily therapy, but that was one of the risk-benefits, a known risk-benefit of ICS, which is relative to growth.

There are, however, additional studies, which don't always show that growth effect, so there is some -- that was, I think, Carmargos' study that I mentioned, as well as I think Collette's study.

So I think this is one of these things in terms of guidelines, where with an individual patient, you would discuss that, and you shared decision making to determine the therapy. But we're talking about a population base, and the difference in growth, Turpeinen's study did not show that difference, but showed a marked difference in exacerbation in children treated

daily.

So there is some there's some inconsistency, and it may be related to the actual ICS, that maybe they're specific for that, and it may also be specific to actual patient adherence to therapy and what they actually do use. That's the best I can do to answer that.

DR. HOLGUIN: Thank you, Dr. Cloutier, I appreciate it.

DR. AU: Can I move on to Dr. Kaizer?

DR. KAIZER: Alex Kaizer from the University of Colorado. I guess a question, and I think it's directed more towards the FDA, potentially. But it sounds like the trial originally was designed to not go down as far as 4 years of age.

So I'm just wondering in the case of 12 to 18 year old adolescents who weren't prioritized through power as a comparison, in the university where we're doing the study, and it was designed to be 12-plus, let's say, and we see the same effect overall that we saw here of a benefit, is it practice, or historic work at the FDA, that

you take that overall headline effect that shows potentially benefit for the high dose, but then it's underpowered for that adolescent age range, would you still use that overall days and essentially extrapolate within that 12 to 17 year old range?

Or if the study was designed for that overall effect estimate, do you try to use that for an approval to say even though the evidence is underpowered at 12 to 17, historically that's been still ignored or noted in an approval of a drug?

DR. SEYMOUR: Hi. This is Dr. Seymour from FDA. Historically, for asthma trials, we've enrolled patients 12 years of age and older, and it's generally never powered for the 12 to 18 year age group to stand on its own and be statistically significant. So we never ignore that data, but we look at that data and generally have extrapolated if results are consistent and if there's no concerning data in that 12 to 18 year age range.

There's only one instance I can think of where we had conflicting results in the 12 to 18

year age range, where they actually had higher risk of exacerbations and hospitalizations, where we made a decision that there was enough concerning data in the 12 to 18 year age range, even though it probably wasn't powered for efficacy, but there is a safety concern, so we didn't approve down to 12.

But generally speaking, the 12 to 18 year age range is included with the adults, and we look at it, make sure it's consistent, supportive, and we'll approve for the full age range unless there's some reason not to.

DR. KAIZER: Thank you. That was very, very helpful.

DR. AU: And I apologize for mispronouncing your name, Dr. Kaizer.

Ms. Oster?

MS. OSTER: I'm good.

DR. AU: Okay. Great.

MS. OSTER: No, I'm fine.

DR. AU: Okay. Thank you.

How about Dr. Stoller?

DR. STOLLER: Yes. This is Jamie Stoller,

and I want to frame my comments here. As an adult-one doctor, I had to read TREXA for the sake of gearing up here, and I want to make a comment and make sure it jives with my pediatric pulmonary colleagues.

In response to Dr. Holguin's question, as I understood his comment, there is clear advantage to sparing steroid dose by using it intermittently, but when I look at TREXA, in table 2 in particular -- I'm looking at it in front of me -- the rescue approach of beclomethasone and albuterol actually failed to achieve significance for the primary outcome measure, which was time to first exacerbation.

We were shown the data on treatment failure, which was not the primary outcome measure in the study, as I recall. So while I agree with you that would be a benefit -- and again, extrapolation is not based on predicate data from other studies -- I understand that, but the whole plausibility of extrapolation has to do with both the disease entity, as well as ambient data. And the only data

that informs beclomethasone and albuterol, as far as I see, the most compelling data comes from TREXA, which again I invite dissension from my colleagues who may know this data better than I. But as I read it, it looks like it's not consistent with rescue approach alone in the regimen that's being used here, albeit in two different inhalers, not one.

So happy to be corrected on that, but I think it's a nuanced point, which at least in my mind has a lot to do with extrapolatability in this context, and I'll stop there.

DR. AU: Let me invite dissent since Dr. Stoller opened that opportunity.

DR. HOLGUIN: Fernando Holguin, University of Colorado.

Thank you, Dr. Stoller. I think although it being a secondary outcome, treatment failure is actually quite important because a composite outcome, that probably included lung function, symptoms, and exacerbations as well, so I won't dismiss it as less significant.

DR. AU: Right.

Any additional comments? I really do enjoy this robust discussion.

(No response.)

DR. AU: Sorry. Additional comments?

Dr. Holguin, you had your hand up?

(No response.)

DR. AU: Dr. Holguin?

DR. HOLGUIN: No, I don't have my hand up.

DR. AU: Did anyone else have any other comments? I'm going to try my best to summarize this very robust discussion, and I'm going to beg the committee's forgiveness if I miss anything, but I do invite additional correction or nuanced discussion.

So let me try to summarize. I'm going to start with Dr. Tracy. He says that we are in a conundrum and that there is a population of patients that would potentially benefit from this type of approach, and this was also echoed by others in the committee, and that we are looking at population averages as opposed to an individual

patient in front of us.

At the same time, though, as has been pointed out by multiple members of the committee, there's a large degree of heterogeneity in the treatment effects that we have noted between the adolescents, as well as the children 4 to 12 years old, and that we're being asked to make extrapolations because the data itself is so heterogeneous and actually includes unity -- includes 1 -- in the point estimates.

So then we're asked to make decisions around are the diseases similar enough among children and adolescents, similar enough to adults, to make that extrapolation in ways that are robust and will serve the public interest?

So we talked a lot about the similarities between adult asthma and pediatric asthma or both the adolescent and children together, really mostly driving it around how we approach treatment, and that the phenotypes are different, and that there are sex differences, there are trigger differences, there are differences in Th2 response, but that the

overall effect still unifies around a treatment approach.

That said, the external data that we're asked to consider in support of this application has some issues with whether or not that data actually supports the primary outcome that was being sought in that trial.

So the sum is that I think we're faced with very small numbers of patients in both the children and the adolescents. The data would suggest that the reliability of the estimate has to do a lot with, actually, the number of subjects, and that the question around extrapolation is really kind of predicated on the similarities between asthma as a phenotype, or as multiple phenotypes, versus the convergence on similar treatment approaches.

Let me pause there and ask whether or not I've done the discussion some justice and whether or not anyone else has comments to it.

(No response.)

DR. AU: Okay. If there are no more discussions or comments on the summary, I think we

can move on to question 2.

MS. OSTER: Randi Oster has her hand up.

DR. AU: Oh, I'm sorry. I did not see that.

MS. OSTER: Okay. That's fine.

Yes. I just wanted to thank you for your summary, but I do want to emphasize that we are faced with small numbers, and we are faced with the reliability of the estimates that we've given, and we are asked to extrapolate the data. But at the end, if we are wrong, because the data is small, because the assumptions are off, it is the children and their growth that has to live with that.

It hasn't been made clear to me why we can't just expect larger sample sizes, and so why this is an important issue, and I can feel for that mother who has, as they said earlier, that point in time that you have to solve it, they need to understand the longer range, what this can be doing.

That is our job, to put drugs out there that when they have the label, as what Dr. Piper had said, it will just be on the labeling. At the point in time of having an asthma attack, no one's

paying attention, so it's our job to make sure we have the data. And I just want to make sure that's added into your summary. Thank you.

DR. AU: Great. Thank you so much. I appreciate that.

Any other additions?

(No response.)

DR. AU: Great.

I think we can move on to question 2.

Question 2, discuss the safety data for BDA for the proposed indication. Discuss any specific pediatric safety concerns.

Let me first pause and ask if there are any questions around or comments around the concern of how the question is worded?

Dr. Cabana, do you have a question or concern about the wording?

DR. CABANA: Sure. In terms of safety concerns, I guess to clarify it long term or short term, we only have short-term data. But are we also supposed to consider long-term safety concerns as well, too?

DR. AU: Can I ask the FDA for their comment on that?

DR. STONE: Yes. This is Kelly Stone, FDA. I think we're asking for both. If this were approved, it would be used long-term. And we have data, some data, from short-term studies, but we also want to understand from the committee how you would anticipate this would be used and if there are any long-term safety concerns from the new indication.

Does that answer your question, Dr. Cabana?

DR. CABANA: Yes. Thanks, Dr. Stone. I appreciate the clarity. Thank you.

DR. AU: Great.

Any other questions or comments about the wording of the question?

(No response.)

DR. AU: If there are no more questions or comments concerning the wording of the question, we'll now open the question to discussion.

We'll start with Dr. Evans.

DR. EVANS: Thank you. I'm sorry. I was

unmuting. I think on balance, the short-term safety data appears to be quite robust in all the areas that were tested. We really see very little in terms of a safety adverse events signal, and very reassuring is that both components of this combination have long-term data available, and I find that largely reassuring.

The only concern that I'm really left with is whether we're going to encounter kids who have unnecessary exposures to ICS, and we've talked about this a little bit already today in terms of the patients who maybe have low Th2 phenotypes. The particular concern I have is the notion of an indication where people will be using this prophylactically for exercise-induced bronchospasm, whereas normally they might have only used bronchodilator.

So that's the principal safety concern I raise here on the backdrop of a really favorable safety profile, at least short term, in the presented studies. And that's it. Thanks.

DR. AU: Thank you.

Any additional no discussion on that point?

Ms. Oster?

MS. OSTER: Yes. This is Randi Oster, the consumer representative. The two safety concerns that I want to discuss or have addressed, the first one is bone density. It's not clear to me that we understand the long-term issues of that.

The second is, in the MANDALA study, from the adolescents from 12 to 18, there was only one person that was identified with a severe adverse event, and that was anxiety and depressive disorder. In the sample size of 34, if this goes much larger into the community, how does that ramp up, and then what do we do about that, and have we addressed that adequately with this small sample size?

DR. AU: Does the panel have any comments on that?

(No response.)

DR. AU: This is David Au. I'll comment.

I think it's the same challenge that we have around the efficacy data, which is that the low

numbers do not allow us to really talk with confidence about whether or not there is a high degree of certainty.

I do you agree with Dr. Evans that as individual components, we have had a long history of these two compounds, but the combination and how they might use, and how they might accumulate, I don't think it's fully known. But I'd welcome comments from others along that line.

(No response.)

DR. AU: Otherwise, I'm happy to move on.

Let's go to Dr. Jones.

DR. JONES: This is Bridgette Jones. Yes, I think, as was previously mentioned, the short-term safety data I think is reassuring, but the real question is [inaudible - audio gap] -- exposure and how it will be actually used in the real world. The overall dosing regimen and proposed indication is pretty broad. It's indicated for asthma or prevention of bronchoconstriction.

So when I think about prevention of bronchoconstriction, I think specifically about

children using it prior to exercise and exertion. And I agree with others in being concerned about children being exposed to inhaled corticosteroids at times that they really don't need to have that as a treatment. I do think, certainly, there would be need for long-term safety follow-up, but just the broadness of the dosing regimen and the indication does give me some concern about the long-term exposure.

DR. AU: No additional comments?

Dr. Greenberger?

DR. GREENBERGER: Thank you. This is to follow-up on Randi's question about anxiety. Undertreated asthma --

DR. AU: I'm sorry to interrupt you. Could you please state your name for the record? I'm sorry about that.

DR. GREENBERGER: Paul Greenberger.

DR. AU: Thank you.

DR. GREENBERGER: Can you hear me?

DR. AU: Yes. Sorry about that.

DR. GREENBERGER: Undertreated asthma causes

burden on families, and certainly children and adolescents. The lack of a quick fix or a good product to intervene to control and delay the time of the exacerbation or prevent exacerbations is extremely important. That in itself causes anxiety. I look at the numbers of anxiety identified here. That needs to be compared with probably the alternative, which is not some investigational product like treatment, for example. So I'm not concerned about that number in itself.

DR. AU: Dr. Kim?

DR. E. KIM: Hi. Edwin Kim, University of North Carolina. I guess I have more of a comment than a question.

It's been brought up a few times these are two medications that are well known, and we understand the risk of them. I think one piece that's reassuring to me is although it's short-term data, it doesn't seem that there's any indication of new adverse events that we did not predict or did not know. So in some ways, I do think that we

can and should give some level of credit to the prescribers who have been using these medications for long periods of time, and have, I think, some sense of how to manage it.

Again, some guidelines around, I think, the pretreatment, as it's been discussed, would seem to be very important to manage ICS cumulative dose, but for me, at least, not seeing or having any indication of some unexpected or some new adverse event from the combination is reassuring.

DR. AU: Great. Thank you.

Dr. Schwartzott?

MS. SCHWARTZOTT: This is Jennifer Schwartzott, and I'm the patient representative. I'd like to give the patient perspective.

As a lifelong patient, I understand the unmet need and the limitations of albuterol on its own. I was uncontrolled for years and years, and it's a very very scary situation, especially when you're a child. I go back all the way to I can't remember when.

Personally, I've learned how not to breathe.

As an adult, I sometimes couldn't afford the multiple inhalers, and even recently have had to fight with my insurance company to cover my Xopenex, Dulera, and the nebulizer treatments. And the meds don't always help anyway, so you just learn how to deal without some of these things.

I do believe we need this in the arsenal as an option for many people. I do understand that this drug is something that will change lives, but I also understand the concern that the data is all over the place and that the small data groups are concerning. But I am leaning towards striving to move forward with the adult benefits outweighing the risk. Adults have informed consent and can decide if this is an option for them or if they want to go another route.

The adolescent group, I'm having some problems making a decision. There is a lack of data, but the benefits very possibly outweigh the risks. I'm not an expert to understand all the data, but as an adult with loved ones with asthma, I feel that with medical and parental supervision

and future follow-up with the FDA, it is worthwhile and safe to proceed with the treatment for the adolescents.

As for the pediatric group, I don't think there's enough data. We do not have enough information to make an informed decision to approve it, and this age group is too much at risk. More data is needed to prove the safety, and as much as I feel for the children, and the doctors, and the parents, I just don't feel we can move forward with that group, although I think further study is warranted. That's what I had to say.

DR. AU: Thank you, Ms. Schwartzott.

Dr. Holguin?

DR. HOLGUIN: Yes. Fernando Holguin. I know there are some concerns about long-term ICS exposure, and to highlight the MANDALA study, the pattern of utilization in kids was similar to adults, and the majority of kids used -- I think the average was 2 inhalations per day. In fact, I think 30 to 40 percent did not use at all inhalers, so I'm not that concerned about long-term ICS

accumulation with this approach..

DR. AU: Great.

Are there any other points that people would like to make?

(No response.)

DR. AU: Let me see if I can summarize this discussion.

The question that we are asked is really to discuss the safety data for BDA for the proposed indication and discuss any specific pediatric safety concerns, and I think most of our discussion focused on that. I think the discussion focused both on short-term as well as long-term safety concerns.

Overall, I would say that I think I heard consensus that these are two known substances that have been used separately for a long period of time, and that there was general relief that there was no new adverse events or unexpected adverse events that would occur; that there were issues specifically around long-term bone density, as well as the one SAE that occurred due to anxiety and

depression, although it was pointed out that the other treatment of asthma also produces a fair amount of anxiety and concern both for the patient, as well as the family.

I think there was also consensus around the desire not to expose children to excessive amounts of inhaled corticosteroids, although the data from the trial would suggest that the average dose would not be all that different or at least some of the panel members did not have concern around excessive doses of inhaled corticosteroids, at least over the short run.

I do think that there was also consensus around that the number of -- and this is really a conversation focused more on adolescents and children, which is that the numbers were really inadequate to determine whether or not there was any true safety signal just because the event rate was relatively low, and the numbers in the overall population of those two groups were small.

So let me pause and ask if there are any additional questions.

Dr. Evans, your hand is up, and I don't know if you wanted to add something before this or whether or not it was just errant.

DR. EVANS: Sorry about that.

DR. AU: Okay. Great.

Can I ask for the committee to comment on my summary? Did I miss anything of substance?

(No response.)

DR. AU: Great.

If there's no further discussion on this question, we will now take a quick 15-minute break; about a 15-minute break. How about that?

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. Why don't we reconvene at 3:10 Eastern Time? So a little bit more than 15 minutes from now. Thank you, all. It's been a great discussion so far.

(Whereupon, at 2:52 p.m., a recess was taken.)

DR. AU: Welcome back, everyone.

We will now move on to the next question,

which is a voting question. Takyiah Stevenson will provide the instructions for the voting.

DR. STEVENSON: Questions 3 through 5 are voting questions. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed.

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 roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

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

(No response.)

DR. AU: Let me read question number 3, which is a voting question.

Do the data support a favorable benefit-risk assessment for use of BDA in patients equal to or greater than 18 years of age with asthma? If not, what additional data are needed?

Are there any issues or questions about the wording of the voting question?

(No response.)

DR. AU: If there are no questions or comments concerning the wording of the question, we will now begin voting on question 3.

DR. STEVENSON: We will not move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. STEVENSON: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However you should also address any subparts of the voting question, if any.

There are 16 yes, 1 no, zero abstentions.

DR. AU: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may provide justification of your vote, if you wish to.

We'll start with Alex Kaizer.

DR. KAIZER: Alex Kaizer, yes.

DR. AU: Dr. Jones?

DR. JONES: Bridgette Jones. I voted yes.

DR. AU: David Au. I voted yes.

Dr. Kim?

DR. E. KIM: Edwin Kim, University of North Carolina. Yes.

DR. AU: Dr. Holguin?

DR. HOLGUIN: Fernando Holguin voted yes.

DR. AU: Dr. Stoller?

DR. STOLLER: Jamie Stoller. I voted yes.

DR. AU: Dr. Tracy?

DR. TRACY: Dr. James Tracy. I voted yes.

DR. AU: Ms. Schwartzott?

MS. SCHWARTZOTT: Jennifer Schwartzott. I voted yes.

DR. AU: Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz, yes.

DR. AU: Dr. Cataletto?

DR. CATALETTO: Mary Cataletto. I voted yes.

DR. AU: Dr. Cabana?

DR. CABANA: Michael Cabana. I voted yes.

DR. AU: Dr. Cloutier?

DR. CLOUTIER: Michelle Cloutier. I vote yes.

DR. AU: Dr. Greenberger?

DR. GREENBERGER: Paul Greenberger. I voted yes.

DR. AU: Ms. Oster?

MS. OSTER: This is Randi Oster, consumer representative. I voted no. I voted no for the reason that I wanted to emphasize the need for analysis of triggers, which was not included in the study, as Dr. Piper talked about, as well as at the age of 18, there is still growth for young men especially, and that the growth, there was no formal growth study.

DR. AU: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. I voted yes. I thought the efficacy data were strong and there are no safety signals, so for this population, I voted yes.

DR. AU: Dr. Evans?

DR. EVANS: Scott Evans. I voted yes for the reasons just stated by Dr. Hunsberger.

DR. AU: And Dr. May?

DR. MAY: Susanne May. I voted yes. Ditto with regards to the reasons as Dr. Hunsberger.

DR. AU: Thank you very much, and I apologize for my coughing bit.

The consensus, by a large majority, was favorable, mainly because I think in this older age group, there was a robust efficacy signal, and that, overall, there were minimal safety concerns; although to acknowledge Ms. Oster and her dissent around safety signal for growing young men, as well as triggering events. Thank you.

We will now move on to question number 4,

also a voting question.

Do the data support a favorable benefit-risk assessment for use of BDA in patients greater than the age of 12, greater than or equal to 12 to less than 18 years of age with asthma? If not, what additional data are needed?

Are there any issues or questions about the wording of the voting question?

DR. CLOUTIER: This is Michelle Cloutier. Is this asthma of all severities or is it specific?

DR. AU: Can I ask the FDA to clarify, please?

DR. STONE: Yes. This is Kelly Stone, FDA. The indication doesn't specify severity, so it's without distinction of severity. It's in line with the proposed indication. After the vote, if there are concerns about severity, comments can be made to clarify your vote.

DR. AU: Great.

If there are no more questions or comments concerning the wording of the question, we'll now begin voting on question number 4.

DR. STEVENSON: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. STEVENSON: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down a list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

There are 8 yeses, 9 noes, zero abstentions.

DR. AU: Thank you.

I will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of

your vote, if you wish to.

We'll start with Dr. Kaizer.

DR. KAIZER: Alex Kaizer, and I voted no. The reason I voted no was that there was enough heterogeneity in the data presented, and potentially with past studies, that made it challenging to be highly confident that we could extrapolate these results. I think, essentially, what would help drive confidence in extrapolation is just more data or more observations to further identify that the effect sizes aligned with the adult population, as we would hypothesize, and being more confident that, potentially, long-term safety outcomes could be followed out further.

DR. AU: Dr. Jones?

DR. JONES: This is Bridgette Jones, and I said yes. I voted yes that there is a favorable benefit-risk assessment due to the reassuring short-term safety data that was presented in the study, and no major safety signals were identified. I think based on the concepts of extrapolation in a disease like asthma, which is similar, although

they're varying phenotypes in both children and adults, I do think that full extrapolation is appropriate in this age group, and that you would expect similar outcomes for a favorable risk-benefit as in adults.

I do think there's a need for more long-term safety data to determine overall exposure long term, frequency of use, and also think there needs to be further consideration around the specific parameters for approval as far as how the medication is being used and in what instances it's being used in asthma, for example, in exercise-induced asthma.

DR. AU: Thank you.

David Au. I voted no. I voted no because of similar reasons to what Dr. Kaizer had mentioned, especially around the lack of directness in terms of the differences from any particular point estimate.

I would say that I would give deference to the FDA to make decisions around this particular age group so that it aligns with what has been done

in the past as well, so as not to create more confusion in the practicing field around whether or not a particular drug or set of drugs is indicated for adolescents in particular. But in terms of the data itself, I do not think it supported a favorable benefit-risk just on face. Thank you.

Dr. Kim?

DR. E. KIM: Edwin Kim. I voted no. The risks I think are known and mostly manageable, however, the benefits to me were unclear. Even if one assumed benefit were there from extrapolation, the correct dose I think was also unclear. So for those reasons, I couldn't support a benefit over the known risk. I would need a larger sample size with more clear efficacy, including supporting the higher dose regimen.

DR. AU: Thank you.

Dr. Holguin?

DR. HOLGUIN: Fernando Holguin. I voted yes for the reasons outlined by Dr. Jones.

DR. AU: Dr. Stoller?

DR. STOLLER: This is Jamie Stoller. I

voted no. My usual want is to sort of frame the level of confidence in my vote, and I would say in this particular issue it was, at most, moderate.

What I mean by that is that I have no particular safety concerns in this particular population. My concern regarded the possibility of extrapolation, as has been said; extrapolation, as I intimated, in regards to the similarity of disease, and then the applicability of predicate data -- in this case running from TREXA, both from the fact, as was pointed out, admittedly small sample sizes -- the point estimates in this study were in the wrong direction for the dose that's being proposed; again, tiny numbers, very volatile. And at least from TREXA and the primary outcome measure, the data were not supportive of a budesonide/albuterol rescue combination.

So those are the reasons that I voted no. I'll stop there. Thanks.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: James Tracy here. I voted yes.

I do believe that it was reasonable. As members from the agency pointed out, it's often that adolescent data is pooled with adults. I was reassured by that. From a safety standpoint, I saw no significant safety signals whatsoever. And as I mentioned in the past, the primary drug of concern, of course, is the budesonide, and that's already indicated down to age 12 months. Thank you.

DR. AU: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: Yes. I'm Jennifer Schwartzott, and I voted yes. I feel that the benefits do outweigh the risks, although there are some risks. I do also think that further long-term data collection needs to be done from the FDA for youth under the age of 18, and I felt there was enough there to put it through.

DR. AU: Great. Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz. I voted yes, which was, if you will, a weak confidence yes. Considerations that went into my mind, well,

certainly the data is inconclusive. I did extrapolate -- give some credit, if you will -- to the data that has been generated within this age group for budesonide/formoterol, which has shown benefit for reducing -- well, having an effect on rescue.

I think that gives me some level of confidence that within this age group, we are looking at a disease process that would respond to an inhaled corticosteroid/beta agonist combo. I would also, though, say, based upon a question that I had raised earlier in the discussion, that I do have some uncertainty about whether or not we can extrapolate fully from the formoterol data, and formoterol is a long-acting beta agonist, and it is possible that that data is being driven in a positive way, not only by the inhaled corticosteroid, but also by the long-acting beta agonist, the nature of the drug.

This is also a population of adolescents; that is, it's higher risk for exacerbation and morbidity. There is certainly deliberation about

what the correct dose would be, where we had the 80 dose looking somewhat more favorable, but I also am giving some deference to the FDA precedent for grouping together age 12 and 18 with the adult patients. Thank you.

DR. AU: Great. Thank you.

Can I ask the committee members, if you're not speaking, to place yourself on mute? We would appreciate that.

Mary Cataletto?

DR. CATALETTO: Mary Cataletto. I voted yes. I think the risk-benefits pretty much speak for themselves, however, I would make one exception having worked with this population basically my whole career. It has the potential for abuse, and I think that it requires a whole new education for kids who, if they're going to use this BDA the way they use albuterol, as premedication for exercise, there is a potential that they're going to abuse it. So I would be very careful with that even though I said yes. I think that the exercise-induced asthma section needs to be very

carefully crafted and followed.

DR. AU: Thank you.

Dr. Cabana?

DR. CABANA: Michael Cabana. I voted no. I voted no for the reasons already articulated by Dr. Kaizer and Dr. Kim.

DR. AU: Thank you.

Dr. Cloutier?

DR. CLOUTIER: This is Michelle Cloutier. I voted no for the reasons better articulated by Dr. Au and Dr. Kim than I could articulate. Thank you.

DR. AU: Thank you.

Dr. Greenberger?

DR. GREENBERGER: Paul Greenberger. I voted no. I do not believe that the evidence support favorable benefit in terms of the benefit-risk assessment. I have no concerns regarding risks, but I do not see support of benefit, and that's why I voted no. I would like to see the agency and the sponsor work together to solve this problem and finding if there are good responders in this age

range. Thank you.

DR. AU: Thank you.

Ms. Oster?

MS. OSTER: This is Randi Oster, consumer representative, and I voted no. I'd like to expand the thoughts of my other colleagues and say that I voted no because the exacerbations that cause asthma are caused by irritants, and there is secondary data that says that zip codes are a point point where highways and factories can be a leading indicator.

We have here a wonderful solution that could work, but also could impact the growth rate of this particular age group, and we have small data, and that data was not balanced by demographic. So therefore, I would challenge the FDA as we move forward to really look at, sometimes, upstream thinking and make sure that we have a demographic balance in the data that is presented.

DR. AU: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. My

yes is a very, very soft yes, and I think the main reason I voted yes was just the idea that in the past, the FDA has extrapolated from the adults to this age group. The data in the study clearly don't give us any information about efficacy, so it is purely based on the extrapolation and just because the FDA has done that in the past. So if the FDA ruled differently, I would not be opposed to that, but I think that was my main consideration. The short-term safety I think is appropriate. Again, we don't know the long-term safety. That's all.

DR. AU: Thank you.

Dr. Evans?

DR. EVANS: Yes. Hi. This is Scott Evans. I voted yes. I did so on the basis of a generally favorable safety profile with a robust overall efficacy signal and some hint, at least, of a signal in this particular population, and the fact that I think it's particularly reasonable to extrapolate that efficacy signal to this population. I do wish to emphasize, though, in my

comments, as I did earlier, my concern about using this strategy for exercise-induced asthma. Thank you.

DR. AU: Thank you.

Dr. May?

DR. MAY: Susanne May. I voted no. The confidence intervals for the effect estimates, for the indications that are sought, were stretching from about a half in the positive direction to about 2 and a half to 4 in the harmful direction, which is, to me, consistent with -- or as supportive as no data, and approving may set a precedent for other combination drugs with no data for children, with similar individual safety profiles in adults and children and combined efficacy data in adults.

If the FDA were to consider seeing [indiscernible] that other precedent because of the strength of the adult data, then I could understand that, but otherwise I think there is not sufficient data in the kids to support a positive benefit-to-risk ratio on the primary outcome for

the indication sought, and that was it.

DR. AU: Thank you very much.

We definitely had a divided vote. Again, apologies for my voice.

Along the yeses, it was really a theme of the ability to extrapolate data from not only the compounds being under consideration, but other studies outside of it that support the general consideration of this combination for this particular age group.

There were some voices around the softness around the yes, mainly around the idea that there had been some precedent from the agency before about not looking at this particular age subgroup and making decisions independent of studies that included data specifically targeting this group or studies targeted at this subgroup.

I think, overall, there was general recognition that there's reasonable safety data, again, based on extrapolation, but that there were some issues, including making sure that there was no abuse with this approach, and there was a number

of comments around exercise-induced asthma or exercise-induced bronchoconstriction.

In terms of the noes, there was, I think, a clear message around lack of confidence in the data and lack of consistency in terms of dose-response relationships and not being able to actually estimate what is the right dosage. The committee I think differed from some of the yeses in that the external data did not necessarily support the use of this combination in this approach.

Also in the noes, there was an ask for the FDA to look to ensure that there is demographic data collection in future studies. I think within the noes and the yeses, there was a general theme that there is more data that's needed within this particular population in age categories and that the data itself could not directly speak, just because of the relatively few number of adolescents that were included in the study.

Let me pause there and ask if I missed anything from the committee or whether or not you

feel like I've summed that up adequately.

(No response.)

DR. AU: Great.

We will now move on to question 5, also a voting question.

Do the data support a favorable benefit-risk assessment for the use of BDA in patients equal to or greater than 4 years to 12 years and less than 12 years of age with asthma. If not, what additional data are needed?

Are there any issues or questions about the wording of the voting question?

(No response.)

DR. AU: If there are no questions or comments concerning the wording of the question, we will now begin voting on question 5.

DR. STEVENSON: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now

complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. STEVENSON: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however, you should also address any subparts of the voting question, if any.

There is 1 yes, 16 noes, zero abstentions.

DR. AU: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote, if you wish to.

We will start with Dr. Kaizer.

DR. KAIZER: Alex Kaizer, and I voted no. I think the reasons are similar to my reasons for the 12 to 17 year old range in that given the small sample sizes, there's just a lot of uncertainty

around the point estimate. And given that it was very much in the neighborhood of the null around a hazard ratio of 1, I think additional data is needed to either confirm that even though there is a fairly good short-term safety profile, is it truly a lack of efficacy or is it just that it's a small sample and more data is needed to actually confirm that there may be a benefit there for at least some patients, given the potential heterogeneity across phenotypes that others mentioned?

I further think, as well, that long-term safety data may be needed with regard to some of the growth concerns or considerations that were also raised by other committee members. Thank you.

DR. AU: Thank you.

Dr. Jones?

DR. JONES: This is Bridgette Jones. I voted yes in regards to my comment for the other age groups. Again, I think the overall safety profile was reassuring with no concerning safety events. I also think about the fact that the

original discussions and proposal with the FDA was to assess safety. I applaud the FDA and the sponsor's efforts to obtain efficacy in children, in young children especially, but I think it's certain limits, a very small sample size, and then maybe not the most appropriate primary outcome endpoint of exacerbation.

So I think based off of that, we're left with whether or not you can extrapolate based on disease similarities, and what we know about these medications, and how they function in children. So based off of those thoughts of utilizing extrapolation, I still think there are kids in the 4 to 12 age group who would likely benefit from this medication, and I think our job is to kind of make that educated guess, and then the art of medicine occurs in the doctor's office, where we determine which children may benefit from use of certain medications.

So for those reasons, I voted yes. I still think there's a concern for the long-term safety as I mentioned before, so there would definitely need

to be postmarketing safety studies, and then an additional look at more specific parameters of use particularly regarded to exercise-induced asthma.

DR. AU: Great.

This is David Au. I voted no for the same reasons as Dr. Kaizer. Thank you.

Dr. Kim?

DR. E. KIM: Edwin Kim. I voted no. Similar to my argument with the adolescents, I think the risk again here is known and mostly manageable, but I think the efficacy data at the dose studied is inconclusive. And extrapolation, I have some concerns, as was voiced during the discussion, about some of the differences in the youngest asthmatics versus the adults and the different triggers.

Additional studies would just be additional efficacy studies specific to this age group to show that there is some stronger signal than what has been shown so far that could justify further extrapolation.

DR. AU: Thank you.

Dr. Holguin?

DR. HOLGUIN: Yes. Fernando Holguin. I voted no for the reasons that Dr. Kaizer mentioned. But in addition, to me, what's important is the fact that there's less evidence supporting efficacy in other studies outside the trial as well.

DR. AU: Thank you.

Let's see. Dr. Stoller?

DR. STOLLER: This is Jamie Stoller. I voted no [indiscernible]. I think the reasons have been nicely articulated. I would emphasize the need for a dedicated study to get real-world data on use and long-term effects in this young population, and I'll stop there.

DR. AU: Thank you.

Dr. Tracy?

DR. STEVENSON: Excuse me. This is Takyiah speaking. I'm sorry to interrupt.

Dr. Stoller -- I'm sorry. Just a general, friendly reminder to all participants, please remember to mute your phones, in Adobe or on your phones, when you are not speaking.

Dr. Stoller, could you please kindly repeat your name and your vote? I'm not sure if we caught when you stated your vote into the record. Thank you.

DR. STOLLER: Oh. I'm sorry. Can you hear me now? I was unmuted.

DR. STEVENSON: Yes. It was just background noise coming from someone else. So yes, please just restate your name and your vote for the record.

DR. STOLLER: This is Jamie Stoller. I voted no, largely for the reasons stated, and I would emphasize the need for a larger study in this particular population to better ascertain long-term risks and real-world data. Thank you.

DR. STEVENSON: I appreciate that, Dr. Stoller.

I can hand it back to the chair. Thank you, Dr. Au.

DR. AU: Thank you.

Dr. Tracy?

DR. TRACY: James Tracy. I voted no.

Although I had no real concerns from a safety standpoint, where I felt like we could extrapolate with adolescents, I didn't think that would hold quite so true with this age group. Thank you.

DR. AU: Ms. Schwartzott?

MS. SCHWARTZOTT: This is Jennifer Schwartzott, and I voted no. I just do not feel like there was enough data to make a truly informed decision on safety and efficacy, along with the other reasons others have stated.

DR. AU: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Mark Dykewicz. No, for the reasons well articulated by others.

DR. AU: Thank you.

Dr. Cataletto?

DR. CATALETTO: Mary Cataletto. I voted no for the reasons that have been expressed so far.

DR. AU: Thank you.

Dr. Cabana?

DR. CABANA: Michael Cabana. I voted no, similar to the reasons stated by Dr. Stoller.

DR. AU: Thank you.

Dr. Cloutier?

DR. CLOUTIER: I voted no. I think there are too many uncertainties related to the efficacy, and I think it's unclear how to use this combination in children, in young children especially, in asthma of different severities, as well as different indications, including exercise-induced asthma.

DR. AU: Thank you.

Dr. Cloutier, can I ask you to state your name into the record?

DR. CLOUTIER: Oh, I'm sorry. It's Michelle Cloutier, and I voted no --

DR. AU: Thank you.

DR. CLOUTIER: -- for the reasons articulated by others.

DR. AU: Thank you. I think we got your reasons. I think we just needed your official name. Thank you.

Dr. Greenberger?

DR. GREENBERGER: Paul Greenberger. I voted

no. As with adolescents, in the ages 4 to 12, I do not believe we have evidence of a favorable benefit, and I voted no for that reason.

DR. AU: Thank you.

Ms. Oster?

MS. OSTER: This is Randi Oster, consumer representative, and I voted no, and I wish I didn't have to. I remember what Michelle Dickens said about it was a simple and elegant relief, Dr. Seymour called it novel, and Kelly Stone referred to it as unique, and what an opportunity if we could have approved this.

But I want to go back and make sure that for us to do that, that the message is clear. Small data actually slows down the process because we weren't able to say yes today. And from a consumer point of view, when people think of the FDA, they think that it's safe and tested, and that's what we have to deliver so that there is trust.

So going forward, I hope that this message is is an opportunity for when the testing samples are coming in, to push back and say we need more

because we know where this is going to go at the end of the results. Thank you.

DR. AU: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted no. I believe you can't extrapolate from the adult data to this small subgroup. I think we need efficacy data, you need long-term safety data, and also to learn more about how it would be used in this population. So for those reasons, I voted no.

DR. AU: Thank you.

Dr. Evans?

DR. EVANS: This is Scott Evans, and I voted no. The reasons have largely already been stated, but I will also emphasize that I'm sympathetic to Dr. Jones' comments about the art of medicine, and in this case, since both components of this combination are already approved for use in this population, I regard physicians that are caring for these patients still have the opportunity to prescribe them if they perceive their patient to have a potential benefit.

DR. AU: Great.

Dr. May?

DR. MAY: Susanne May. I voted no for the reasons stated by others on the committee and for the reasons stated for the last question as well.

DR. AU: Thank you.

Let me see if I can summarize this for us. There was an overwhelming preponderance of no votes in this case. The yes vote was made, I think, largely because of the art of medicine, and that the safety profiles with the known agents are well described and can be managed; that the ability to extrapolate, based on existing data, was appropriate, and therefore the panel member felt that it was appropriate to recommend approval.

I think the no votes come down to disagreement around the ability to extrapolate, the lack of consistent efficacy data, data that is inconsistent internally around dose and dose-response relationships. There was also an absence of long-term safety data, as well as desire to have a better understanding of how this would be

used in the real world.

Finally, there was a comment around small data or small numbers of patients and how it slows the approval processes and is relatively inefficient, as well as the need for, obviously, additional data within this particular age strata.

Let me pause there and ask if there's anything that I missed in summary that people feel like they should add?

(No response.)

DR. AU: Hearing none, I think we are close to adjournment, but before we adjourn, are there any last comments from the FDA?

DR. STONE: This is Kelly Stone from the FDA. On behalf of the division and the agency, we would like to thank the committee for your comments and your feedback. We're going to take all of the information that you provided in your discussion as we review this program, but we're grateful to you for your efforts in reviewing the program and providing insight. So thank you all, to all participants.

Adjournment

DR. AU: I also wanted to thank the panel members. I thought the discussion was very robust. I also appreciate AstraZeneca and Bond Avillion for their presentations today, and I just want to wish everyone a pleasant evening, and we will now adjourn the meeting. Thank you.

(Whereupon, at 4:04 p.m., the meeting was adjourned.)