FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

JOINT MEETING OF THE

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

AND THE

PEDIATRIC ADVISORY COMMITTEE

DAY ONE

Rockville, Maryland

Wednesday, December 10, 2008

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P R O C E E D I N G S

(8:30 a.m.)

DR. SWENSON: Good morning, everyone. We'll need to bring this meeting to order.

I'm Erik Swenson, acting chairman of this rather august and large committee. And co-chairing with me is Marsha Rappley here.

We'll need to begin, and I need to first read a statement here. For the topics that we'll be discussing today, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express views without interruption.

So as a gentle reminder, individuals are please asked to speak into the record only when they're recognized by the Chair, and we'll look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. And I should reiterate that's quite important, because we're all coming to as best knowledge as possible in these two days.

I would also like to identify the FDA press contacts, Ms. Sandy Walsh and Karen Riley. And if you're here, could you please stand up? Good.

I would like to remind everyone present to please silence cell phones and other electronic devices if you haven't already done so.

And again, committees are reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thanks very much. And I'll turn it briefly over to Kristine Khuc.

Before that, let's have an introduction of all the Committee members, and if we could start at my far right-hand side.

DR. GOLDSTEIN: I'm Brahm Goldstein. I'm a pediatric critical care physician and one of the industry representatives.

MR. BURLINGTON: Bruce Burlington, consultant, and I'm a industry rep.

DR. KRAMER: Judith Kramer. Excuse my laryngitis. I'm associate professor of medicine at Duke University, and a general internist, with a background in randomized controlled trials and observational studies.

DR. D'ANGIO: Carl D'Angio. I'm an associate professor of pediatrics at the University of Rochester, and I'm a neonatologist

and vaccine researcher.

DR. MARGOLIS: I'm David Margolis. I'm a professor of dermatology and a professor of epidemiology at the University of Pennsylvania.

DR. HENNESSY: Good morning. My name's Sean Hennessy. I do pharmacoepidemiology research at the University of Pennsylvania.

SPEAKER: If I could just interrupt for a moment. We are having a little difficulty understanding your words. Can you -- we heard you quite clearly. But prior to that, it's not coming back. We can't understand it too well; maybe a little echo or something. So could people just speak more slowly and clearly into the mic, that would help.

Thank you.

DR. BRANTLY: My name is Mark Brantly. I'm professor of medicine at the University of Florida, and a pulmonary and critical care physician.

DR. NOTTERMAN: My name is Daniel

Notterman. I'm a pediatric intensivist and a molecular biologist. I'm in the Department of Molecular Biology at Princeton University.

MS. CELENTO: Amy Celento, patient representative, Pediatric Advisory Committee.

DR. HUDSON: Melissa Hudson, pediatric oncologist from St. Jude Children's Research Hospital in Memphis.

DR. KRENZELOCK: Good morning. I'm Ed Krenzelock. I'm director of the Pittsburgh Poison Center and Drug Information Center at the University of Pittsburgh Medical Center, and a professor of pharmacy and pediatrics at the University of Pittsburgh.

DR. KNOELL: Good morning. My name is Daren Knoell. I'm an associate professor at The Ohio State University, and appointed in pharmacy and internal medicine.

MS. VINING: Good morning. I'm Elaine Vining. I'm the consumer representative for the Pediatric Advisory Committee.

DR. SHATIN: Good morning. Deborah

Shatin, consultant, Drug Safety and Risk Management Committee.

DR. CNAAN: Avital Cnaan. I'm a biostatistician. I direct multicenter studies at Children's National Medical Center.

DR. ROSENTHAL: Good morning. My name is Geoff Rosenthal. I'm a pediatric cardiologist and epidemiologist at the Cleveland Clinic, and I'm a member of the Pediatric Advisory Committee.

DR. MARTINEZ: My name is Fernando Martinez. I'm a professor of pediatrics at the University of Arizona, and I'm the director of the Arizona Respiratory Center. I'm a pediatric pulmonologist.

DR. RAPPLEY: Marsha Rappley. I'm from Michigan State University. I am chair of the Pediatric Advisory Committee, co-chair today. My area is developmental and behavioral pediatrics.

DR. SWENSON: Erik Swenson. I'm professor of medicine in the Division of

Pulmonary and Critical Care Medicine at the University of Washington, and have served on this Committee in the past.

MS. KHUC: Kristine Khuc, designated federal official for the Pulmonary-Allergy Drugs Advisory Committee.

DR. SCHOENFELD: David Schoenfeld. I'm a professor of medicine at Harvard Medical School, and I'm a biostatistician.

DR. HOIDAL: John Hoidal, University of Utah, pulmonary critical care physician.

DR. GARDNER: Jacqueline Gardner, professor of pharmacy, University of Washington in Seattle.

DR. JOAD: Jesse Joad, professor of pediatrics at University of California-Davis. I'm a pediatric allergist and pulmonologist.

MS. HOLKA: Andrea Holka. I'm the patient rep on the Pulmonary-Allergy Drug Advisory Committee, and I am executive director of Attack on Asthma in Nebraska.

DR. KOCIS: Good morning. Keith Kocis

from the University of North Carolina in Chapel Hill. I'm a professor pediatrics, and I'm a pediatric cardiologist and intensivist.

DR. WOLFE: Sid Wolfe. I'm a general internist. I'm with the Health Research Group of Public Citizen. I'm on the Drug Safety and Risk Management Advisory Committee.

DR. ZITO: Julie Zito, University of Maryland, professor in pharmacy and psychiatry, and new member to the Drug Safety Group.

DR. NEWMAN: Lee Newman. I'm at the University of Colorado, Denver. I'm a professor of public health, and a professor of medicine and a pulmonologist.

DR. SCHNEEWEISS: Sebastian Schneeweiss. I am an associate professor of medicine and epidemiology at Harvard Medical School and School of Public Health, and I do pharmacoepidemiology.

DR. FRANCIS: Good morning. I'm Henry Francis. I'm the deputy director of the Office of Surveillance and Epidemiology at FDA, and an

infectious disease physician by training.

DR. McMAHON: Ann McMahon, acting director, Division of Pharmacovigilance II in the Office of Surveillance and Epidemiology. I am a pediatrician by training. Thank you.

DR. SEYMOUR: Sally Seymour. I'm the deputy director for safety in the Division of Pulmonary and Allergy Products at the FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the director of the Division of Pulmonary and Allergy Products at the FDA.

DR. ROSEBROUGH: Curt Rosebrough, director, Office of Drug Evaluation II.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

DR. NELSON: Robert Nelson, in the Office of Pediatric Therapeutics, and I'm a pediatric critical care physician and neonatologist.

DR. MURPHY: I'm Diane Murphy. I'm the director of the Office of Pediatric

Therapeutics, and the office commissioner on pediatric infectious disease specialists.

DR. SWENSON: Thank you very much.

I'll turn it over to Kristine Khuc of the FDA.

MS. KHUC: The Food and Drug Administration is convening today's joint meeting of the Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committees' compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208 and Section 712 of the

Federal Food, Drug, and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC 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 the particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts, when necessary, to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 USC Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contracts/grants; cooperative research and development agreements; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves discussions of the benefit/risk assessment of long-acting beta-2 adrenergic agonists for the treatment of asthma in adults and children. This is a particular matters meeting, during which specific matters related to long-acting beta-2 adrenergic agonists will be discussed.

Based on the agenda for today's

meeting and all the financial interests reported by the Committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 USC Section 208(b)(3) and Section 712 of the FD&C Act to Dr. Fernando Martinez. Dr. Martinez is a member of the Advisory Board for a competing firm, for which he receives between $5,001 to $10,000 per year.

With regard to FDA's guest speaker, the Agency has determined that the information to be provided by this speaker is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Robert Lemanske has acknowledged that he is a consultant for Merck, GlaxoSmithKline, Novartis, AstraZeneca, and Mapp Pharmaceuticals. As a guest speaker, Dr. Lemanske will not

participate in Committee deliberations, nor will he vote. The waivers allow this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30, of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting, and will be included as part of the official transcript.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Brahm Goldstein and Bruce Burlington are participating at this meeting as non-voting industry representatives, acting on behalf of regulated industry.

Drs. Goldstein and Burlington's role at this meeting is to represent industry in general and not any particular company.

Dr. Burlington is an independent pharmaceutical consultant.

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

I would also like to remind panel members to please make your selections for the menu. Please set it aside and we'll collect it at the break.

Thank you.

DR. SWENSON: And now I'd like to introduce Dr. Chowdhury of the FDA, who will proceed with some opening remarks.

DR. CHOWDHURY: Good morning. Good morning, Honorable Co-Chairs and members of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee, representatives from AstraZeneca, GSK, and Novartis, and others in the audience. I welcome you to this meeting on behalf of the U.S. Food and Drug Administration.

Dear members of the Advisory Committee, I particularly thank you for your participation in this meeting. In this brief presentation, I will introduce the objective of this Joint Advisory Committee meeting and the questions that you will discuss and work upon.

There are two inhaled long-acting beta agonist bronchodilators marketed in the United States. These are salmeterol and

formoterol. They are marketed as single-ingredient products and also as fixed-dose combination products with inhaled corticosteroids. Products containing salmeterol and formoterol are indicated for use in patients with asthma, exercise-induced bronchospasm, and chronic obstructive pulmonary disease. Important safety risk of long-acting beta agonist bronchodilators in patients with asthma are asthma-related death and severe asthma exacerbation.

Dear members of the Committees, the objective of this Advisory Committee meeting is to discuss risks of these drugs, their benefits, and discuss the risk/benefit in adult and pediatric patients with asthma.

As you can see on the agenda, Dr. Robert Lemanske, professor of pediatrics at the University of Wisconsin, will speak first, giving an overview of asthma and current asthma treatments. We are very fortunate that Dr. Lemanske, an expert in

asthma, particularly pediatric asthma, has agreed to speak at this meeting.

I thank Dr. Lemanske on behalf of the FDA.

After Dr. Lemanske, we'll have representatives presenting from the FDA for the representations by sponsors of these products. We will reconvene tomorrow with brief presentations by the FDA, open public hearing, and discussion by the Committee.

Dear members of the Committee, as you hear the presentation, I request that you keep in mind the questions that you will discuss and vote on tomorrow.

There are a total of 10 questions. I will show the questions in 10 subsequent slides. I will not read all the questions, because there are some common themes in some of these questions, and also, they're available in print at this meeting.

As you can see, questions 1 through 4 are related. These questions are by active

ingredients and by age groups. Questions 1 through 4 are not for voting.

Questions 5 through 8 are also related. These questions are by individual, long-acting beta agonist bronchodilator-containing drug products, and also by age group. Questions 5 through 8 are voting questions.

Here is question 1, and I will read this question for you. Discuss the benefit of using salmeterol for the treatment of asthma in patients not adequately controlled on other asthma-controller medications; e.g., low to medium dose inhaled corticosteroids, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies in each of the following age groups: In adults equal to 18 years of age or older, in adolescents 12 to 17 years of age, in children 4 to 11 years of age.

Question 2 is related to Question 1. This is also a benefit question,

but the active moiety in this question is formoterol. The lower age for children is five years, to match the lower age of approval of single-ingredient formoterol-containing products.

Question 3 is related to the previous two questions, with the exception that the question is on risks, and the active moiety in this question is salmeterol.

Question 4 is related to Question 3. This is also a risk question, but the active moiety in this question is formoterol. The lower age for children is five years, to match the lower age of approval of single-ingredient formoterol-containing products.

Here is Question 5, and this is a different theme, and I'll read this question. Do the benefits of Serevent -- salmeterol xinafoate -- outweigh its risk for the maintenance treatment of asthma in patients not adequately controlled on other asthma-

controller medications; e.g., low to medium dose inhaled corticosteroids? All host disease severity clearly warrants initiation of treatment with two maintenance therapies in the following age groups: In adults 18 years of age and older -- this is a voting question; in adolescents to 17 years of age -- again, a voting question; in children 4 to 11 years of age -- again, a voting question.

Question 6 is related to Question 5, where the drug product subject of this question is Foradil. The lower age for children is five years, to match the lower age of approval of single-ingredient formeterol-containing product.

Question 7 is related to Question 5 and 6, where the drug product subject of this question is Advair.

Question 8 is related to Question 5 through 7, where the drug product subject of this question is Symbicort. The lower age

for children is 12 years, to match the lower age of approval of single-ingredient formeterol-containing product. Of note, Advair and Symbicort are combination products containing a long-acting beta agonist and an inhaled corticosteroid.

Question 9 and Question 10 are different, and I'll read these for you. Question 9: Based on your discussion, are there further labeling changes or risk mitigation strategies for individual LABA products or the class as a whole that would be advisable?

Question 10: What further studies, if any, would clarify important unanswered questions of safety and efficacy for individual LABA products or the class as a whole?

We look forward to an interesting meeting. I thank you again, the Committee members, for your time, effort, and commitment to this important public health

service.

I now turn the podium over to Dr. Henry Francis, deputy director, Office of Surveillance and Epidemiology, for him to make some brief opening remarks.

Dr. Francis, please.

MR. FRANCIS: Thank you, Badrul. Chairpersons, distinguished members of the Committee, and guests, the Office of Surveillance and Epidemiology wants to welcome all of you and give a couple of simple messages.

First, from the office level, we have not made a final conclusion on this very complex subject, which is dealing with a very important public health issue. We look forward to the insights, advice, and recommendations from the Committee, and look forward to working with our colleagues and FDA in making an informed decision on the things that we have to do.

Have a good morning, and we look forward to a very successful meeting.

DR. SWENSON: All right. At this juncture then, Dr. Lemanske will give us an introductory lecture here on asthma and its control.

DR. LEMANSKE: Well, thank you very much. I greatly appreciate the opportunity to address this incredible audience. I've never seen so many bright people in one room before. And it's not just because it's Christmas. It's because obviously, there's a lot of people with a lot of talents.

With the time that I have, I would like to address some clinical studies that I have been part of for the last 15 years that have been generated by two NHLBI-funded networks: The Asthma Clinical Research Network and the Childhood Asthma Research and Education Network.

I'm going to focus on studies that we have dealt with beta agonists, both short-acting and long-acting beta agonists, to sort of give you a historical perspective

of what the field was thinking in the last 10 to 20 years; what studies we put together to try and address what we consider to be important questions; and then the answers that we got to the questions, and how these answers generated some more questions, and where we need to go in the future.

Before I go over some of these trials, I thought it would be important for me to just give you a little bit of a background on some of the things that we have done also with the EPR-3 group to -- which relies on some of the data that has been generated by these networks to give treatment recommendations to the community.

Can I advance this from here? Oh, it's this one. Sorry.

So first of all, to set the stage, when I was training, we were taught that asthma was primarily a bronchospastic condition of lungs. Then in the 1990s, with the advent of bronchial biopsies in asthmatic

patients, we began to recognize that it was truly an inflammatory condition. Some of the questions that we still need to answer are, first, when does this inflammatory process start, particularly in the pediatric population? If we can figure the answer to that, can we prevent it from occurring? If we can't, can it be reversed? And finally, is it possible that certain of the therapies that we use to treat asthma could actually make the inflammatory process worse?

As far as the guidelines are concerned, this inflammatory process was the major focus for the first National Asthma Education and Prevention Program in 1991. In 1997, based on two studies -- one in the adult population and one in children -- we began to realize the importance of early recognition and diagnosis of asthma and appropriate treatment intervention in order to conserve lung function over time.

In 2002, we didn't revamp the whole

guidelines, but we focused on five important questions, and hopefully answered them. And this then led to the current document which was released in 2007.

Now, the new concepts in this current document are on this slide. First, the recommendations that we made are now made using three age ranges, not two. And for the purposes of this Committee, I think this grouping will be very convenient: 0 to 4, 5 to 11, and greater than 12 years of age.

We also advanced the concept of not only asthma severity, but much more detail in terms of asthma control, and evaluated both severity and control using two domains: Impairment and risk.

Now, severity of asthma is really the intrinsic intensity of the disease process, and is most easily and directly measured in patients not receiving long-term therapy. It basically guides clinical decisions during the initial evaluation and

prior to the start of controller therapy.

The other concept, control, is the degree to which asthma-related symptoms, functional impairment, and the risk of untoward events are minimized and the goals of therapy are met. Control really guides clinical decisions to either maintain or adjust therapy once the therapy is initiated.

And finally, a concept which many different clinical research groups have been interested in is the concept of responsiveness. Why do some patients respond better to certain types of medications while others do not? Is it related to certain phenotypic characteristics of the patient -- gender, for example, race -- or is it related to certain genetic characteristics or the patient's genotype?

Both severity and control include the domains of current impairment and future risk. And I think Dr. Stoloff in his presentation this afternoon will go into this

in much detail. The importance of impairment is it's basically a cross-sectional evaluation of the patient at any point in time, and it looks at the frequency and intensity of symptoms and functional limitations reflected by evaluations of pulmonary function and quality of life.

The risk domain is a more longitudinal look at the patient in terms of the frequency and severity of asthma exacerbations; progressive decline in lung function, which is somewhat difficult for us to assess, but we need to think about it; or the risk of adverse effects from various medications; and in children, of course, inhaled corticosteroids and their effect on growth.

Now, it's quite possible that therapy with a certain medication may do a wonderful job in controlling impairment, but not do a very good job in controlling risk. So when we look at clinical trial data, I

think it's important for us to understand what outcomes are being evaluated, and what drugs effect impairment risk or potentially both.

The primary goal of asthma therapy is to enable a patient to achieve and maintain control over their asthma to eliminate impairments, including symptoms, functional limitations, poor quality of life, and other manifestations of asthma.

This is impairment, and then reduce future risks of exacerbations, emergency department use, and hospitalizations. The treatment goals, it's important to recognize, are identical for all levels of asthma severity.

With that as a background, I'd now like to review with you some of the trials that have been generated by the Asthma Clinical Research Network and also the Child Asthma Research and Education Network. And it's important for you to understand that

these trials that I'm going to show you have been funded by the National Heart, Lung, and Blood Institute and not by the pharmaceutical industry.

Therefore, we feel that we have been very dispassionate, if you will, in terms of designing these trials, to hopefully answer questions that we felt were important in terms of filling in on some of the evidence that we thought was lacking, so we could better make recommendations for asthma treatment in national and international guidelines.

Let's look first at short-acting beta agonists. I'm sure many of you remember in the early 1990s, there was debate as to whether or not taking a short-acting beta agonist on a regular basis was bad or good. And there was a -- when I would go to scientific meetings, there was heated discussions about this.

So the Asthma Clinical Research

Network felt that this is an area that we should try to address. And all of our trials have acronyms, so you'll have to bear with me on this.

And the first trial was called the Beta Agonist Study, or the BAGS trial. And the question we wanted to answer here: Is treatment with regularly scheduled albuterol safe? We took a group of mild asthmatics, treated them with two puffs four times a day of albuterol or matching placebo, and then took them off for a five-week period to see if there were differences during treatment, and when we took the treatment away, if the albuterol-treated group got worse because albuterol was doing something bad to their lungs.

The answer we got from our trial was it was neutral. This therapy wasn't harmful nor was it beneficial. And we published these results in the New England Journal of Medicine in 1996.

At the time we were working on this trial, Steve Liggett and his colleagues began to uncover the importance of beta adrenergic polymorphism, receptor polymorphisms. And we asked the question, is it possible that there may be a subgroup of patients based on their genotype that might actually do better with beta agonist therapy or potentially do worse? And so we did a retrospective ancillary study.

And the question we wanted to ask here is do beta receptor polymorphisms influence the response to chronic treatment with beta agonists? And lo and behold, what we uncovered was that patients with the Arg/Arg genotype at codon 16 may be at increased risk of loss of asthma control. And let me show you the data on which this was based.

The major outcome in this trial was a.m. peak flow. The yellow bar here, this is looking at the weeks of the study. This is

16 weeks of treatment followed by 5 weeks in the run-out period.

And you can see the homozygote Arg/Arg, when they were treated with placebo, did fine. The opposite genotype, the Gly/Gly, when they were being treated with regularly scheduled albuterol, they also did fine. But the Arg/Arg genotype, which represents about 16 percent of the Caucasian population and about 25 percent of the African-American population, when they were given regularly scheduled albuterol, their peak flows went down. And when we took them off, they went down considerably further. This strongly suggested to us that there may be a genotype-attributable effect with chronic beta agonist therapy that was important for us to try to learn more about.

Because this was a retrospective study, and retrospective studies can be hypothesis-generating but really don't do much for the evidence base, we decided to

design a prospective study which we called BARGE. And the question we wanted to answer here is does this B16 loci influence asthma outcome measures other than peak flow?

And what -- as far as we know, this was the first asthma clinical trial in which patients were randomized by genotype. And what we found and published in Lancet in 2004 was, yes, the subjects with the Arg/Arg genotype had better control when regularly scheduled albuterol was stopped and subjects with the Gly/Gly genotype had improved control with regular use.

Now, there's much more data to this trial than I have time to discuss, but this confirmed in our minds that at least for short-acting beta agonists, there may indeed be a genotype-attributable effect that we needed obviously to learn more about.

With that as a background, the long-acting beta agonists came on the marketplace as we were designing BAGS and

thinking about other trials that would be important for us to be able to do. And we focused on long-acting beta agonists by designing two companion trials: One called SOCS, and the other called SLIC. The patients who were enrolled in these trials were treated with a medium dose of inhaled corticosteroids for six weeks. At the end of that six-week time period, if they were well-controlled, they went into SOCS. And if they were not well-controlled, they went into SLIC. Let me cover SOCS first.

The question we wanted to answer in SOCS: In patients with mild persistent asthma, who are well-controlled on inhaled corticosteroids, can salmeterol replace the inhaled corticosteroid and be used as monotherapy? There were clearly patients who were coming into our clinics and saying, Doc, you started me on this new medicine, salmeterol. It makes me feel really good, and do I have to keep taking these inhaled

corticosteroids on a daily basis? And what we found is once they were entered into SOCS, they continued their inhaled corticosteroid, they went off their steroid and went on monotherapy with salmeterol, or they went on to placebo. And what we found and published in JAMA was that, no, salmeterol monotherapy would increase the risk of loss of asthma control and actually increase the risk of asthma exacerbations. So this really confirmed what many of us thought, that salmeterol should not be used as monotherapy.

What about combination therapy? In the mid-1990s, two groups published some very, very surprising data. Andrew Greening from United Kingdom, and the late Ann Woolcock from Australia asked the question, in adult patients who are not doing well on low doses of inhaled corticosteroid, which is the next best treatment step to pursue: Giving them more steroid, thinking that this was an inflammatory condition of the lung,

and that would be helpful or giving adjunctive therapy in the form of a long-acting beta agonist? And lo and behold, what both groups were able to demonstrate is that adding the long-acting beta agonist was actually significantly better than giving more steroid for a number of different outcomes.

Then came the Facet Study, published by our European colleagues, in which they took a group of patients on budesonide, 200 micrograms per day. They took another group and they quadrupled the dose of the steroid. And then they did one other intervention where they kept the steroid dose the same, the low dose the same, added the long-acting beta agonist formoterol, or took the high dose and added the long-acting beta agonist as well.

And I think you can see here when they looked at severe exacerbation per patient year, that as you added a long-acting

beta agonist, you got improvement, a reduction in exacerbation. If you gave more steroid, you also got improvement in terms of exacerbation rates. And if you did both, you got the greatest effect.

So the data from Greening and Woolcock, along with the Facet Study, suggested that the addition of a long-acting beta agonist could not only influence impairment significantly, but also potentially the risk domain as well.

This then led us to SLIC. And remember, the patients going into SLIC were those who were not well-controlled on a low dose of -- or, I'm sorry, a medium dose of inhaled corticosteroid. And we felt that what the patients were going to do is if we put them on a long-acting beta agonist based on the data from Greening and Woolcock, if they were uncontrolled and then they became controlled, or their control was improved by the addition of the long-acting beta agonist,

the patients would then come back to our clinic and they would say, Doc, I'm so much better now that you added this long-acting beta agonist. Can I reduce the dose of my steroid?

And if the answer to that question was yes, we thought they would come back again and ask us, can I eliminate the steroid altogether?

And what we found and published in JAMA in 2001 is we could reduce the dose by about 50 percent with impunity, demonstrating that LABAs have the potential of being inhaled corticosteroid-sparing. But when we eliminated the drug altogether or the steroid altogether, the treatment failure rate went up significantly. So like we found in SOCS, monotherapy with the long-acting beta agonists, at least salmeterol, was not a good idea, but it did offer the potential of steroid reduction in patients on higher doses of inhaled steroid.

Well, you're probably asking, he told me about this Arg/Arg genotype stuff with short-acting beta agonists. What about the long-acting beta agonists? Well, we looked at a retrospective analysis of our SOCS and SLIC data. And remember, when we do this, this is hypothesis-generating.

And the questions we wanted to ask -- or answer: Are the adverse effects of chronic albuterol treatment in patients with the Arg/Arg genotype at this loci also demonstrable with the long-acting beta agonist salmeterol? And if so, does concomitant treatment with an inhaled corticosteroid alter these effects?

And what we found and we published in the Blue Journal in 2006 was that similar effects were seen with salmeterol in the Arg/Arg patients, and also the effect was not prevented by concomitant inhaled corticosteroid treatment. So this led us then to thinking about designing another

trial, prospective trial, to try and look very specifically at genotype-attributable effects, with the addition of a long-acting beta agonist with an inhaled steroid backbone, if you will.

So this is the stud, LARGE. And I have to tell you that this data was presented at the AAAAI (?) meetings and the ATS meetings, so it has been in the public forum. But the manuscript is currently in preparation. It has not been peer reviewed. So I've been asked by my NIH colleagues that you please look at this data, but don't quote it until we have a chance to get it in press.

The question we want to answer in LARGE: Are there genotype-attributable adverse effects on control due beta receptor polymorphisms in patients receiving LABAs in combination with inhaled corticosteroid? And what we found, to our surprise, was the answer to this question was no. Addition of salmeterol to inhaled corticosteroids for 18

weeks produced similar improvements in airway caliber in both Arg/Arg and Gly/Gly genotype groups, and exacerbation rates were also similar.

There have been a number of other groups within industry who have also looked at this particular question regarding beta receptor polymorphisms and long-acting beta agonists. And I don't have time to quote all of them, but this is some work published by Gene (?) Bleecker, who looked at a salmeterol study, and his results were that the response to therapy was not dependent on B16 genotype or haplotype. And the response to salmeterol does not vary between adrenergic genotypes after chronic dosing with an inhaled corticosteroid.

So the majority of the evidence at this point would suggest that the addition of a long-acting beta agonist, if it has adverse consequences, we are having a very, very difficult time attributing this to the

patient's genotype in terms of the beta receptor polymorphisms that we have looked at thus far.

So why did we see these differences with SABAs, or short-acting beta agonists, and we can't see them with long-acting beta agonists? There may be a number of possibilities.

First, genotype-specific differences only occur with short-acting beta agonists, but not with long-acting beta agonists when used with inhaled corticosteroids.

Second, higher doses of inhaled corticosteroids could possibly blunt a genotype-specific effect of the therapy.

Third, higher doses of inhaled corticosteroids could delay a genotype-specific effect of salmeterol.

And finally, genotype-specific effects may be more prominent in subpopulations that were under-represented in

our LARGE study.

What about combination therapy in children? Some of the work that led to some of the current approval of this class of drugs in this age group was some work first by Dr. Russell and colleagues, who looked at 4 to 16-year aged children who were currently taking inhaled corticosteroids, whose peak flow was less than or equal to 90 percent predicted, and had diurnal variation at peak flow of greater than 15 percent.

So these kids were taking inhaled corticosteroids, still had some abnormalities in pulmonary function that the group felt was noteworthy and deserving of something else.

And so what they did is they gave half the group salmeterol powder and the other half placebo, and they treated them for 12 weeks.

Now, this is a summary of what they found. The addition of salmeterol powder significantly improved morning peak flow,

reduced asthma symptoms, and reduced daytime rescue albuterol use. Now, this is a common theme that we see with long-acting beta agonists. They're very good at addressing the impairment domain.

Evening peak flow of nighttime asthma symptoms and nighttime rescue albuterol use followed a similar pattern, but were not significant after the first four weeks. This has also been seen in other studies in which the difference between LABAs and placebo seems to be most noteworthy within the first four to eight weeks. And then whether it's due to placebo effect or the children are taking their medicine more on a regularly scheduled basis, the inhaled corticosteroid monotherapy group tends to catch up.

The overall incidence of adverse events was similar in both groups. However, headaches were more common in the salmeterol group.

What about the addition of salmeterol versus doubling the dose of beclomethasone in children with asthma? This is some work published by our Dutch colleagues, Dr. Verberne et al., in the Blue Journal in 1998, in which they looked at 177 children, ages 6 to 16 years, with mild to moderate asthma: Pulmonary function 55 to 90 percent predicted, and using low to medium doses of inhaled steroids for at least three months.

These kids had demonstrable reversibility with bronchodilator and methacholine hyper-responsiveness. And they were then put into a six-week run-in period at a constant dose of inhaled steroid, and then treated for an entire year with the addition of a placebo to this inhaled steroid background. This inhaled steroid background plus additional steroids. So this gave him 800 micrograms per day of inhaled corticosteroid. And finally, the low dose

was continued and salmeterol was added twice daily.

And there was a lot of data generated from this trial, and I don't have time to summarize it all, but when they looked at pulmonary function for the entire 54 weeks, there was really no difference between the three treatments. Importantly, when they looked at side effects, this bottom line here, this is the change in height from baseline and this is going down about .3 sonometers (?).

It appears as if the higher dose of the inhaled corticosteroid significantly reduced growth velocity compared to the other treatment groups.

And I think this is an important thing to keep in mind, that when we look at patients who are not well-controlled on low doses of inhaled corticosteroid, what is better to give them more steroid, particularly in the pediatric population, or

add a long-acting beta agonist? This data would suggest that adding a long-acting beta agonist may actually be the safer way to go in terms of producing adverse effects.

The problem with that thinking, though, is that there really was no difference between these two treatment groups, suggesting -- or begging the question: What greater amount of efficacy does adding a long-acting beta agonist do in children to a backbone of inhaled corticosteroids, and in children who are enrolled in a clinical trial and probably taking their medicine on a regular basis?

The CARE Network has also done some work with beta agonists that I'd like to briefly review with you. And again, the data that I'm going to present to you is not from our group alone, but from a group of wonderful colleagues at National Jewish Medical and Research Center, University of California, San Diego, Washington University

at St. Louis, and Fernando Martinez in the audience here from the University of Arizona.

The Data Coordinating Center is located at Penn State University. And again, the information that I'm going to share with you has been funded by the National Institutes of Health.

A number of years ago, when we were trying to make our recommendations for EPR-3 in terms of step 2 care for children, we did not have a lot of comparative -- in fact, we had no comparative studies in which an inhaled corticosteroid was compared to montelukast or compared to combination therapy, all of which were in the marketplace.

And we needed to learn more about what is the best choice of therapy for the treatment of mild persistent asthma in children. Three choices: Inhaled corticosteroid monotherapy, combination therapy with LABA plus an inhaled steroid, or

monotherapy with montelukast.

The way the trial was designed, there were three parallel groups. One group got fluticasone, 100 micrograms in the morning, 100 micrograms in the evening. A second group got -- we wanted to see if the long-acting beta agonist salmeterol could potentially be steroid-sparing.

We treated the kids with 100 micrograms of fluticasone in the morning, also salmeterol, and salmeterol at night. The final group got a leukotriene receptor antagonist at night. And so these were the three groups: Monotherapy ICS; packed combination therapy because the steroid was not given twice a day -- we couldn't because of the formulations available to us at the time -- and finally, a leukotriene receptor antagonist group.

The primary outcome of packed was asthma control days during the 12-month treatment period. And using self-reported

diary data, an asthma control day was defined as a day without albuterol use, it was permitted pre-exercise; the use of non-study asthma medications; daytime or nighttime asthma symptoms; unscheduled health care provider visits for asthma; and school absenteeism for asthma.

Now, we generated a lot of data impact, and I don't have time to go over it all with you, but this is a summary slide looking at a number of different outcomes: Asthma control days, of course, was the primary outcome; asthma control questionnaire; asthma treatment outcomes; time to prednisone burst (?); first prednisone burst; time to treatment failure; number of treatment failures.

And then looking more at impairment or pulmonary function outcomes: a.m. and p.m. peak flow; FEV1 and FEV1/FEC ratios; exhaled nitric oxide, which we think is a biomarker for airway inflammation; PC-20, which is a

reflection of airway responsiveness, a major physiologic characteristic of asthma; and maximum bronchodilator response.

Now, this first column, on a statistically significant basis, fluticasone was favored over montelukast for every single outcome we evaluated. The outcomes favoring fluticasone over combination primarily were in the pulmonary function domain, including exhaled nitric oxide and PC-20. Also, in terms of the different outcomes that favored combination over montelukast, asthma control days were better compared to montelukast.

And a number of other pulmonary function outcomes were better on combination than montelukast. Based on the packed data, we felt very confident when we were putting the stepwise approach for managing asthma in children 5 to 11 years of age, that clearly in the majority of patients, the preferred step two therapy should be low dose of inhaled corticosteroids as opposed to

combination, or as opposed to leukotriene receptor antagonists.

We have also now begun to design trials that are looking at the questions of adjusting therapy based on asthma control. In the children who are not well-controlled, what is the best way to step them up?

Secondly, in the children who are doing well, the parents are coming to us and they say, Doc, my kids have been on this therapy for years, and is it possible for me to be able to take them off? And if I can take -- and if you can take them off, can you do it safely? And what are my options?

So the two trials we're doing right now are, one, looking at the importance or the question of stepping up, and the other the question of stepping down. The step up protocol is called BATGER. And just to give you a little background, there is one principal investigator that's responsible for putting together a trial. And I think -- if

you know that the University of Wisconsin mascot is the Bucky BATGER and I'm from the University of Wisconsin, you can imagine who put this trial together. I fought long and hard with Penn State University because they were not really too happy about this.

So I told them, look, you guys, if you can think of a trial with an acronym of Nittany Lions, go for it. We still don't have that trial. So let me tell you what BATGER is. BATGER is an acronym which stands for "best add-on therapy giving effective responses." And the question we're attempting to answer here -- and all the kids are enrolled in BATGER; we should finish this trial next spring -- is as follows: In patients receiving daily low-dose inhaled corticosteroid treatment who are not well-controlled, what are the next best treatment options?

And the trial is a very unique study design. It's a three-way crossover in

which the children have to demonstrate a lack of control on a low dose or 1X ICS therapy. They're then in a randomized sequence given one of three treatments. And I'm going to depict for you in yellow what one particular subject might undergo through the trial.

First, they're doubling the dose of inhaled corticosteroids to see if giving more steroid is better.

Second, they then cross into receiving the same dose, but now LABA is added to see if that would be a better therapy for them.

And finally, the dose of inhaled steroids is kept the same at this low dose and a leukotriene receptor antagonist is added.

Now, obviously, the kids aren't going to be random -- in a very random sequence here. They're not all going to get this order. And each of the treatment periods is for 16 weeks.

Now, the trial has a very interesting design in terms of statistical analysis, in that we are looking at the tendency for a child to have a differential response. That is, they do better with one therapy versus another. And we have a priori defined three outcomes in which we're going to gauge or evaluate this differential response.

First, in the risk domain, exacerbations. And we're going to say that a differential response occurs when the total amount of prednisone prescribed to control asthma symptoms is at least 180 milligrams less on one treatment than on either of the other two treatments.

The reason we did this is because in our previous trials, exacerbations were really a dichotomous variable in which it either occurred or didn't occur. And many of our kids in our trials get prolonged courses of prednisone, which means that their

exacerbations are different because they're lasting longer and perhaps more severe. So by doing it in this way, we're going to be able to evaluate a continuous as opposed to a dichotomous variable.

FEV1 we're defining as like a differential response is occurring when the FEV1 changes at least five percent higher on one treatment than on the other two.

And finally, asthma control days, another impairment domain. Characteristics we're defining as occurring when the number of annualized asthma control days achieved is at least 31 days more on one treatment than on either of the other two treatments.

Now, at the end of the trial, we're going to, hopefully, have a group of kids who are going to be put in different silos (?), if you will. A group that's going to do better with more steroid, a group that's going to do better with the same dose of steroid adding a long-acting beta agonist,

and a group that's going to do better on 1X ICS and the addition of montelukast.

If children demonstrate this preferential response to one treatment, they will then be evaluated using secondary outcomes to determine if there are phenotypic and/or genotypic characteristics that are associated with this positive response. The goal of BATGER is obviously to help us decide up front, which is better therapy, to individualize the therapy for our asthmatic children.

So in summary, what I've gone through so far is in terms of the ACRN and CARE input into the guidelines, we started with BAGS trying to see if chronic beta agonist therapy was good or bad, at least with short-acting beta agonists. And we found that the answer to that question was at least in the general population, it wasn't harmful, nor was it beneficial.

But when we did the retrospective

analysis, it was hypothesis-generating, suggesting that there may be a specific beta receptor polymorphism genotype that may confer increased risks. We, therefore, designed a prospective study, BARGE, and found out that that may well be the case, at least for short-acting beta agonists in the context of no concomitant inhaled corticosteroid administration.

We then designed SOCS. We're trying to establish whether or not at step two CARE people could come off their inhaled corticosteroids and just treat themselves with the long-acting beta agonist salmeterol. And we clearly found that that was not a good idea.

SLIC was very helpful in moving from step two to step three. The people who were not well-controlled on inhaled steroids, we demonstrated that we could clearly replicate the findings of Woolcock and Greening, that they got better when we added

the long-acting beta agonist. But we went further than their trials in that we were able to demonstrate that we could reduce the dose of steroids by at least 50 percent in the majority of patients. But when we tried to take the steroids away completely, the treatment failure rate was significantly increased.

LARGE, to our surprise, when we did a prospective study to look at long-acting beta agonists with the inhaled corticosteroid being administered at the same time, we were not able to demonstrate that there was a genotype-attributable effect. And our industry colleagues in their retrospective look at their data sets have not been demonstrate this as well.

Pat, we looked at step two. I think I -- I hope I convinced you the data strongly suggests that inhaled corticosteroid monotherapy is clearly the treatment of choice for the majority of children at this

juncture.

BATGER, we're in the process of doing. And this will, hopefully, give us some very, very needed information as to what we do between step 2 and step 3 in this 5 to 11 population. So finally, I'd like to end with -- I'm sure this is a topic that you might not want me to say anything about and this is off-label. I guess I have to say that.

But the potential for beta agonists and inhaled corticosteroids are both maintenance and reliever therapy, our colleagues from Europe and Canada have done a lot of work with this, and I believe that the drug is approved, the combination therapy is approved for this approach in a variety of different countries.

Now, I don't have time to go over all this data with you, but this is some work that was summarized by Paul O'Byrne (?) in the Blue Journal in 2005 from the state study

in which patients, both children and adults, were treated with four times the dose of budesonide plus a short-acting beta agonist as a rescue. The combination of budesonide and the long-acting beta agonist formeterol plus the short-acting beta agonist does the rescue.

And the maintenance and the lever group who were treated with budesonide, formeterol as maintenance therapy, but when they had symptoms they also used this combination as a reliever instead of a short-acting beta agonist.

And the importance of this is that when they're using this beta agonist for symptoms, they're not only getting a bronchodilator. They're getting some more steroid. And lo and behold, what they found was the time to first exacerbation. The total number of exacerbations were significantly reduced in the group that was receiving combination therapy both for

maintenance and reliever.

This begs the question in my mind: If combination therapy or LABA had something to do with increasing exacerbation rates -- and I know you're going to be discussing this -- this data would suggest, well, that may not be the case in all patient populations. That in certain groups used in a certain way, this combination -- maintenance and reliever -- may have some significant benefit.

Now, let me be a little more controversial for you. Is it necessary for reliever medication in this context to be a long-acting beta agonist? Is it possible that we could design an inhaler that would have albuterol in it plus an inhaled steroid, so when the patient was -- when they needed some symptom relief, they would be getting a short-acting beta agonist, but they would also be getting an increased dose of inhaled steroid.

So this is some work that was published by Dr. Poppy (?) et al., in the New England Journal of Medicine in which they looked at four treatment groups. All of these patients had mild asthma; important to keep that in mind. They were treated for six months. The primary outcome variable was a.m. peak flow. And you can see here the four treatment groups.

There was a scheduled and there was an as-needed. Group A received placebo. And when they needed relief, they were given not only albuterol, but also a dose of beclomethasone, the inhaled steroid.

A second group got placebo scheduled, but they only got albuterol for relief.

A third group got steroid maintenance every day and they got albuterol-only rescue. And the third group got both the inhaled steroid and the short-acting beta agonist daily for

maintenance, but they got albuterol only for rescue.

And if you look at the data, Group A, which is not getting daily therapy -- remember these patients are mild -- but they are getting albuterol plus the steroid when they need it. In terms of a.m. peak flow, the major outcome, and exacerbations, Group A was equal to Group C, was equal to Group D, all of the groups that are getting some form of steroid, either daily or intermittently. And they did much better than the patients who are not receiving inhaled steroids at all.

The cumulative dose of inhaled corticosteroids was actually lower in Group A compared to that that was received in Group C or Group D. This data is very intriguing and begs the question, again, is this benefit that we see with maintenance and relief therapy, is it related to the additional of LABA, or is it related to the fact that

patients are getting more inhaled corticosteroids when they're having symptoms?

So with that in mind, the final study I'm going to show you is also a CARE study. The title of this is TREXA, "treating children to prevent exacerbations of asthma." And as I just showed in this adult population who had mild asthma, they could potentially get by with just intermittent therapy with the inhaled steroid, plus a short-acting beta agonist for relief.

So the question we're trying to answer in TREXA: In patients receiving daily low dose inhaled corticosteroid treatment, who are well-controlled, can inhaled corticosteroid doses be reduced? And if possible, what is the best strategy for doing so?

The design of TREXA is a run-in period in which the children have to demonstrate control on low dose of inhaled corticosteroid. And they are then randomized

into 1 of 4 treatment groups for a total of 44 weeks. Group A continues to receive the inhaled corticosteroid twice a day, but gets inhaled corticosteroid and albuterol now, the short-acting beta agonist, for relief. Group B continues to receive the inhaled corticosteroid on a daily basis, but now gets placebo inhaled steroid and albuterol for rescue.

Group C receives now no maintenance therapy except placebo. We're obviously now stepping down their maintenance therapy, but they're receiving combination therapy, if you will, with ICS and albuterol as a reliever. And Group C is getting, again, a step down from the inhaled steroid to getting placebo for maintenance. And now their reliever therapy is placebo-inhaled corticosteroid plus albuterol.

This trial is currently about two-thirds enrolled. And the major outcome measure that we are looking at in TREXA is

asthma exacerbations. The combination of BATGER trying to give us more data in terms of how we step children up and the -- along with TREXA in terms of how we can best step kids down, if we can do this at all in children who are controlled, will be extremely helpful information for us in terms of putting together future treatment recommendations in this age group.

So in conclusion, I'd like to leave you with a final -- my final thoughts. From the data that I have been privileged to be part of, I'll have to say that I could not recommend long-acting beta agonists to be used as monotherapy.

Second, combination therapy significantly improves asthma control in both the current impairment and future risk domains.

Third, our responses to therapy based on beta adrenergic receptor genotype different with short-acting beta agonists

than with long-acting beta agonists. This is really not a conclusion, but a question that I think we need to think about answering.

Fourth, another question. Did children respond differently to long-acting beta agonists? And here, I think the question should be not in terms of adverse outcomes, but from a therapeutic standpoint. Do they perform the same as adults? And I showed you some data to suggest that that might not be the case. Not that they're harming the kids, but they're not exactly doing a lot more than monotherapy with inhaled steroids. And BATGER should very much help us address this question.

And finally, I left you with something to think about in terms of the concept of using combination therapy, both for maintenance and reliever, and whether or not this combination in terms of reliever needs to be a long-acting beta agonist or whether or not it can be replaced with a

short-acting beta agonist as long as the patient is getting additional inhaled steroids.

And finally, I would like to thank all of my colleagues in the Asthma Clinical Research Network and the CARE Network. This has been a tremendous opportunity for me. It's been one of the highlights of my career to work with such an incredible group of people, such a dedicated group of scholars.

And finally, the data that I showed you is obviously generated by some very hardworking coordinators at all of our centers.

And I don't want to forget the patients who have participated in our trials and many other trials that have helped us learn a lot about asthma.

And with that, I'd like to thank you all for your attention and it's been a great privilege to be here.

Thank you.

DR. SWENSON: Dr. Lemanske, thank you for that fantastic review. We're just a little bit ahead of time, so I think we should just proceed with Dr. Seymour's presentation from the FDA. And then after her talk, I think we'll have time for questions.

DR. SEYMOUR: Good morning. My name is Sally Seymour, and I'm the deputy director for safety in the Division of Pulmonary and Allergy Products. And we're here today to discuss the risk/benefit assessment of long-acting beta agonists for the treatment of asthma.

In order to have a vigorous discussion today, I think it's important to understand the background and regulatory history of these products. And that is the focus of my presentation.

Here's an outline of my presentation. I'm going to spend the majority of my time on the regulatory history of these products, specifically focusing on

two areas: the basis of approval of these products; and then a chronological walk through the important milestones in the regulatory history, including some safety studies, advisory committees, communications issued by the Agency, and the labeling history for these products.

Towards the end, I'm going to spend a few moments on the current labeling so that everyone is clear on the language regarding the risks of these products that's in the current labels. And I'll close with a brief summary.

As you've heard, there are two inhaled long-acting beta agonists -- salmeterol xinafoate and formoterol fumarate. Salmeterol is approved as Serevent Diskus, which is a dry powder inhaler, or DPI. Salmeterol also used to be marketed as Serevent Inhalation Aerosol, which is a meter dose inhaler, or MDI, but this product is no longer currently marketed

due to the phase-out of the propellant chlorofluorocarbons.

There are two combination products containing salmeterol and the corticosteroid fluticasone propionate. These are Advair Diskus, which is a dry powder inhaler, and Advair HFA inhalation aerosol, which is a meter dose inhaler.

Formoterol fumarate is marketed as a dry powder inhaler, Foradil Aerolizer. There is also another dry powder inhaler marketed -- I'm sorry -- that's approved but not currently marketed, and it's Foradil Certihaler. In addition, there is a combination product formoterol, and the corticosteroid budesonide Symbicort inhalation aerosol, and this is a meter dose inhaler.

I do want to mention that there are two other long-acting beta agonist products marketed: Perforomist Inhalation Solution and Brovana Inhalation Solution. Perforomist is

formoterol and Brovana is aformoterol, the R-enantiomer of formoterol. But these products are only approved for COPD, and they are not the focus of discussion today.

So now that you have an idea of the products we're discussing, I'm going to walk through the regulatory history. This slide shows the approval dates of the long-acting beta agonist products for asthma in patients 12 years of age and older, for asthma in patients less than 12 years of age, for exercise-induced bronchospasm, or EIB, and for chronic obstructive pulmonary disease, or COPD. And as you can see, these products date back to the mid-1990s.

Several products are also approved for COPD and exercise-induced bronchospasm. And this is important to note, because one of the issues for discussion today is withdrawal of the asthma indication from these products. However, if the asthma indication is removed, there would be still available several

products on the market containing these long-acting beta agonists.

I'd also like to take this opportunity on this slide to make the following point. Inhalation products are drug device combinations that act locally in the lungs, and each product is considered unique and is required to have a complete development program to support approval.

It's a nice segue to my next slide. What is the basis of approval for these products? I'm going to start in the adolescents and adult patients 12 years of age and older.

LABAs are bronchodilators, which means that they dilate the airways, and these products have a well-established clinical development program. Typically, a Phase II program includes a dose ranging study to inform dose selection and to evaluate the pharmacodynamic effects on safety variables such as glucose, potassium, and heart rate.

The Phase III program consists of at least two clinical trials in patients 12 years of age and older. An inclusion of adolescents down to 12 years of age is acceptable since the pathophysiology of asthma in response to bronchodilators is expected to be similar in adults and adolescents.

The duration of these trials is typically 12 weeks or longer, and the primary efficacy variable is the forced expiratory volume in one second, or FEV1. And I'm going to discuss that more in a moment.

There are supporting efficacy variables, including peak expiratory flow, rescue medication use, symptom scores, and nocturnal awakenings, which are included. But these trials are not powered for these secondary variables.

In addition to the safety and efficacy of trials, a long-term safety trial is required. This trial is typically one year in duration for a new product. And

although the purpose of this trial is safety, efficacy is also usually assessed.

And this is a very abbreviated outline of the clinical development program. I can assure you there are many other studies conducted throughout these products' development.

So what about the basis of approval in pediatric patients -- patients less than 12 years of age? Prior to considering a pediatric program, the efficacy and safety in patients 12 years of age and older must be evaluated to ensure it's appropriate to study the pediatric population.

And because the pathophysiology of asthma in response to bronchodilators is expected to be similar in patients in this age group, the pediatric program is not as extensive as the adult program. Nevertheless, we expect clinical trials to establish appropriate dosing with safety and efficacy measurements in pediatric patients.

A dose ranging study to inform dose selection is expected, as well as safety and efficacy trials in asthma patients less than 12 years of age. The number and duration of these trials depends on the novelty of the drug substance and product, but efficacy and safety are assessed in these trials. In addition, the efficacy assessment in pediatric patients is supported by the efficacy data in adults and adolescents.

In addition to the development program, the Agency can request additional studies for pediatric data under the Best Pharmaceuticals for Children Act. When we do this, this is called a written request, and the Agency's pediatric group provides input on these requests in the design of these studies.

Based upon this process, a written request was issued for salmeterol for children less than four years of age, and for formoterol for children less than five years

of age. Additional studies in children older than four or five years of age were not requested.

There are several additional important points to make regarding the basis of approval of these products. First, I need to mention the combination products. They have a development program that must establish the contribution of each component, and because of this, these programs are more complex. But keep in mind that the safety and efficacy of each component has been established, and the Division views the combination products as products of convenience.

Next, long-acting beta agonists are bronchodilators, and the primary basis of approval is FEV1. All the other endpoints are supportive, but these programs were not powered for these secondary efficacy variables. The development program I describe is really not unique, as the basis

of approval of long-acting beta agonist products is really similar to all other asthma medications, including inhaled corticosteroids, with the primary endpoint of FEV1 and similar supportive secondary endpoints.

And one may argue how these endpoints translate into benefits for the patients, but these efficacy variables are important, and are the same variables used to measure asthma control severity as outlined in the Asthma Guidelines such as the NHLBI, an AEPP that Dr. Lemanske described.

So the long-acting beta agonist development programs do include endpoints that are important to patients, including FEV1. And I'd like to spend a little time discussing this particular efficacy variable. Some of you may recognize this type of figure, which is a flow/volume curve during maximal exhalation as part of a pulmonary function test.

FEV1 is the volume of air exhaled in the first second of forced expiration. On the X axis, you have the volume, and on the Y axis you have the flow. And at the beginning of forced exhalation -- this is the flow curve -- until there is no longer any flow of maximal exhalation. And the forced expiratory volume in one second is the volume exhaled in one second.

This is a measurement of air flow that's useful for obstructive airway diseases such as asthma and COPD. And this measurement of air flow is a direct clinically meaningful endpoint. And for bronchodilator drugs, this is really not a surrogate endpoint. For pulmonary disease such as asthma with symptoms of wheezing, beta agonists relax the airway's smooth muscle and dilate the airways to relieve the cardinal symptoms of asthma that are from airflow obstruction.

And you can see, this particular

figure has two curves: one pre-bronchodilator and one post-bronchodilator. Administration of a bronchodilator is a method used to evaluate airway reversibility. And as you can see in the figure, there is an increase in FEV1 following bronchodilator administration.

An FEV1 increase of greater than 12 percent and 200 milliliters suggests a significant bronchodilation, but lack of this increase does not preclude a clinical response to bronchodilator therapy. A response to bronchodilator provides evidence of reversibility, and is one of the criteria used to establish a diagnosis of asthma. So clinical trails in asthma patients usually include a response to bronchodilators as an inclusion criterion for the diagnosis of asthma.

Finally, for spirometry, there are standards from professional organizations for measurement of FEV1, and we consider the FEV1

a reproducible, reliable, well-established clinically meaningful endpoint in clinical trials for bronchodilators. In addition, FEV1 is used to grade severity of impairment for obstructive pulmonary diseases such as asthma and COPD.

In the NAEPP Guidelines, FEV1 is a component of asthma severity, along with symptoms, nighttime awakenings, rescue medication use, interference with normal activity and exacerbations.

As Dr. Lemanske mentioned, there are two concepts within the NAEPP Guidelines -- the concept of asthma severity and asthma control. And FEV1 is used to help classify patients in both of these concepts.

So now that I've given you kind of an overview of the development programs for these products, I'd like to provide some data regarding the efficacy of these products. Over the next few slides, I'm going to show you some data from the development programs

for these products. The data comes from the product labels or the FDA review of the clinical studies conducted to sort approval.

These are by no means complete efficacy data. For LABAs, there are many additional studies conducted not only by the sponsors but by other sources such as the NIH, and Dr. Lemanske showed you many of these studies. And these studies have further established the efficacy of these drugs, and the NAEPP has reviewed these published studies along with the NDA studies to form the basis of their recommendations.

The first data I will show you is for Serevent Diskus, and the results of two 12-week pivotal trials in patients 12 years of age and older with asthma are shown. The primary efficacy variable was FEV1, and the change of a placebo was a 20 percent increase in percent predicted FEV1 at 12 hours. Keep in mind that this is at the end of the dosing interval. And the results for secondary

endpoints were supportive of efficacy, even though these trials were not powered for these endpoints.

And I'd just like to highlight a couple of the secondary endpoints. Note that there is a change -- a decrease in rescue inhalation use of 1.8 puffs per day. Patients take rescue medication when they have symptoms, so this suggests that symptoms are decreased. And this is consistent with the other endpoints of percent days without symptoms and nights without awakening, which also indicates that symptoms are improved.

And these results show that Serevent Diskus is an effective bronchodilator in the secondary efficacy variables, showing more days and nights without symptoms, and a decrease in rescue medication use support the benefit of this drug.

For Foradil Aerolizer, the results are shown from one of the 12-week pivotal

trials. In this slide, the FEV1 is expressed in liters, and at the end of the dosing interval, which was 12 hours. And at the end of the dosing interval, there's a 300 milliliter difference compared to placebo, with a peak difference of 400 milliliters. The FDA review also noted a statistical difference in terms of peak expiratory flow and rescue inhalation use compared to placebo.

Symptom scores improved and the percent of nights patients required rescue medication use also was less in the Foradil Aerolizer group compared to the placebo.

These data show that Foradil Aerolizer is an effective bronchodilator. The secondary endpoints such as rescue medication use and fewer nights awakened support the benefit of this drug.

And these are figures from the Serevent Diskus and Foradil Aerolizer product labels which show the post-dose serial FEV1

measurement on the last treatment day, week 12, in adult and adolescent patients with asthma. On the X axis is hours, and on the Y axis on the left is percent predicted and on the right is FEV1 in liters. But the message is the same.

You can see that the placebo group, shown here and here, really have no change in the FEV1 over the 12-hour dosing interval. The long-acting beta agonist Serevent Diskus and the two different doses of Foradil Aerolizer show an increase in FEV1 that is sustained throughout the 12-hour dosing interval.

In both of these trials, albuterol was also included and administered four times daily. And these figures also show the curves for albuterol inhalation aerosol. And you can see that compared to albuterol, the long-acting beta agonists have a sustained bronchodilator effect compared to those products.

Moving on to the pediatric population. And here are some results from the Serevent Diskus.

The results for one pivotal 12-week trial are shown. The 12-hour data shows an increase in percent predicted of 3.3 percent compared to placebo. The FDA review also noted a decrease in rescue medication use of 0.5 inhalations per day, as well as an improvement in symptoms and more nights without awakenings in the salmeterol group compared to placebo.

This, taken with the robust adult data in the other clinical trials in the development programs, these data show that Serevent Diskus is an effective bronchodilator in children.

For Foradil Aerolizer, the results from a one-year study are shown in which efficacy was assessed at three months. There was a 150 milliliter improvement of FEV1 area under the curve compared to placebo, and an

improvement in peak expiratory flow as well. Many of the other secondary variables, including rescue medication use and symptom scores, showed improvement. And taken with the robust adult data and the other trials in the development program, these data show that Foradil Aerolizer is an effective bronchodilator in children.

Now on to the combination products. The first combination product approved was Advair Diskus. Data from one of several pivotal 12-week and efficacy and safety trials is shown. And I'd like to make several points from this slide. This type of factorial design is typical of a combination program so that we can assess the contribution of each component and we can look at several different comparisons. But the focus today are the long-acting beta agonists.

So first, I want to point out that compared to placebo, Advair Diskus shows an

improvement in all of the endpoints: FEV1, peak flow rate, percent rescue-free days, days without symptoms, and awakening-free nights. And then also the Asthma Quality of Life Questionnaire, which I will mention in a moment.

Looking at the salmeterol treatment group showed an improvement in FEV1, percent rescue-free days, and percent days without symptoms compared to placebo. But another way to look at the contribution of salmeterol is to look at the difference between Advair Diskus and fluticasone. The combination product shows an improvement in all of the endpoints compared to fluticasone. And this shows the contribution of salmeterol to the combination product.

This slide also introduces a new endpoint, the Asthma Quality of Life Questionnaire, or AQLQ, which measures the impact of asthma on patients' perception of health. This is a Juniper questionnaire with

32 items representing four domains: activity limitation, emotion, symptoms, and exposure to environmental stimuli. Questions are scored on a seven-point scale, where one is maximum impairment and seven is no impairment. So an increase in the score is a good thing.

The minimum important difference is thought to be 0.5. And you can see that Advair Diskus improved more than the minimum important difference even when compared to placebo. And based upon the known efficacy of fluticasone and the known efficacy of salmeterol, the data submitted in the clinical program established the efficacy of Advair Diskus in patients 12 years of age and older.

In the pediatric population for Advair Diskus, patients less than 12 years of age, this slide slows data from a 12-week clinical trial with Advair Diskus. And as I discussed in the overview of the clinical

development programs, the pediatric programs are not as extensive because of the following: The efficacy and safety of salmeterol and fluticasone have been established in adults and adolescents as well as children, and the efficacy of Advair in adults and adolescents has been established.

In this program, the trial included Advair Diskus and fluticasone. And you can see that there's improvement in all the endpoints compared to fluticasone, which shows that salmeterol contributes to the efficacy of Advair Diskus. And taken with the robust adult data and the other trials in the development program, the known efficacy of salmeterol and fluticasone, these data support the efficacy of Advair Diskus in children.

The last product I'm going to show you the data for is the Symbicort Inhalation Aerosol. This slide shows the results from one of two 12-week clinical trials taken from

the FDA review for this product.

You can see that this program is quite complex, and there's a couple things I'd like to point out about this program. In addition to the factorial design including each of the components, a fifth arm, with budesonide and formoterol administered in free combination or in separate devices, was also included.

The next thing I'd like to note is the formoterol product used in this program is the Oxis Turbohaler formoterol product. And this is not approved in the United States but is approved in the European Union. And the use of the Oxis Turbohaler product as a comparator in this program is acceptable, because the sponsor performed a study which bridged the Oxis Turbohaler to the formoterol and Symbicort. And I mention this because I think this will come up later in the discussion today.

This program also included

predefined criteria for asthma exacerbations. And the data shown here is the percent of patients withdrawn from predefined asthma exacerbations. Actually going to the data on the slide, there's a lot of information but I only want to highlight a few points.

Compared to placebo, you can see that the Symbicort Inhalation Aerosol group showed an improvement in all the endpoints, including the Asthma Quality of Life Questionnaire. But it did not reach the MIB of 0.5.

Two, compared to placebo, the formoterol group showed an improvement in most of the efficacy variables, particularly post-dose FEV1, percent of rescue-free days, and percent of awakening-free nights. And you can see that compared to placebo, all the treatment groups, and especially the combination, decreased the percent of patients withdrawn due to the predefined asthma events.

And finally, what I want to point out is that the results for the Symbicort versus the free combination treatment groups are fairly similar, which emphasizes the point that the combination products are products of convenience, as there are similar results when a long-acting beta agonist and inhaled corticosteroids are administered in the same device or in separate devices.

I've discussed a lot of different endpoints. And one endpoint to look at across programs is the AQLQ. This endpoint is typically performed and evaluated in the same manner. But I want to remind you that this is cross-study comparison, so keep that in mind. But I have some data here showing the results of the AQLQ from several different programs in adult and adolescent patients with asthma.

I've already shown you the results for Advair Diskus and Symbicort, and I did note the data for the Advair Diskus program

crossed the minimum important difference of 0.5.

The results from montelukast or Singulair, which is a leukotriene receptor antagonist, is from a one-week clinical trial, and shows a small improvement of the AQLQ but does not reach the minimum important difference. Similar results are seen from another product, omalizumab, which is a monoclonal antibody against IgE, used for severe asthma. The point of this slide is that both long-acting beta agonist combination products show a greater improvement in the AQLQ compared to some other asthma medications.

So now that I've outlined the basis of approval for the LABA products, let me draw your attention to the current indication. These products are indicated for the maintenance treatment of asthma and prevention of bronchospasm in patients with reversible obstructive airway disease,

including patients with symptoms of nocturnal asthma. They should only be prescribed for patients not adequately controlled on other asthma controller medications, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

These drugs are intended for maintenance therapy and not as monotherapy. And I'm going to get into more details on the labeled use of these products later in my presentation.

But now I'm going to begin a chronological walk through the regulatory history of these products that spans over a decade. Bear with me as I kind of move back and forth between different drugs, but I think the chronological process is the best way to present this data.

Serevent Inhalation Aerosol was approved in February 1994, and this was the first long-acting beta agonist approved and was a meter dose inhaler.

There was a Pulmonary Allergy Drug Advisory Committee held prior to the approval of Serevent in February 1993, and the results of the Serevent nationwide surveillance study were considered during the approval process. And I'm going to briefly touch on this study.

The SNS study was a randomized double-blind active controlled parallel group 16-week trial in the United Kingdom, and the population were 25,000 patients 12 years of age and older with asthma who were randomized in a two-to-one fashion to salmeterol twice daily or salbutamol 200 micrograms four times daily. Salbutamol is a short-acting beta agonist, known as albuterol in the United States.

This was not a placebo controlled study, but was an active controlled study in which both arms were treated regularly with a scheduled beta agonist. The outcome measures were serious adverse events and reasons for withdrawals. This table displays the key

findings in the SNS study and remember that the randomization was two-to-one.

I'd like you to note the following: There was a numerical increase in the respiratory- and asthma-related deaths in the salmeterol, group with a relative risk of three. There was no difference in the respiratory-related and asthma-related hospitalizations or serious events, but there was a difference in respiratory- and asthma-related withdrawals between treatment groups, and that was statistically significant, favoring the salmeterol group.

These results were known and discussed during the 1993 Pulmonary Allergy Drug Advisory Committee regarding Serevent Inhalation Aerosol.

Just to spend a moment on this meeting, the Serevent Inhalation Aerosol NDA was the topic of discussion. Here are some comments in voting from the summary minutes. The Committee felt that the dose and dosing

interval was supported, and that safety was adequately demonstrated, but a few caveats and concerns, as would be expected with any drug in this particular class. The Committee noted that the pediatric data was not sufficient, and recommended additional studies.

There was a unanimous recommendation to approve salmeterol for chronic asthma in EIB in patients 12 years and older, and a unanimous recommendation to not approve salmeterol for chronic asthma in patients less than 12 years of age. Based upon the data submitted by the sponsor, and consistent with the recommendations of the Advisory Committee, Serevent Inhalation Aerosol was approved in 1994 for patients 12 years of age and older.

Shortly after approval, reports of life-threatening respiratory events and fatalities with salmeterol were reported. Some of these reports suggested that there

were possible inappropriate uses of salmeterol such as as a rescue medication.

To address these events, the label was revised in January 1995, and new warnings were added to the label -- warnings that serious acute respiratory events including fatalities have been recorded with salmeterol; salmeterol is not for acute symptoms; is not a substitute for inhaled corticosteroids; and should not be initiated in worsening or acutely deteriorating asthma; and that patients should have a short-acting beta agonist for acute symptoms.

Following discussions with the FDA, GSK developed a large simple trial to assess the risk of asthma-related death and serious asthma exacerbations with salmeterol. This trial is called the Salmeterol Multicenter Asthma Research Trial, or SMART. SMART was a multicenter randomized double-blind placebo-controlled trial of 28 weeks duration.

The sample size was initially planned to be 30,000, but then was increased to 60,000 in 1999 because of fewer numbers of events than expected. Subjects were 12 years of age, with a clinical diagnosis of asthma, and were currently taking prescription asthma medication. Subjects were randomized to salmeterol 50 micrograms twice daily or placebo twice daily 28 for weeks, in addition to usual asthma care.

Ideally, the endpoints for SMART would have been asthma-related deaths and serious asthma exacerbations. Based upon historical data, the number of events was expected to be low. Thus, the primary endpoint of the study was brought into the combined respiratory-related deaths or respiratory-related life-threatening experiences, which meant intubation or mechanical ventilation. SMART was initiated in June 1996.

Now we're going to jump forward a

few years. Advair Diskus was approved in 2000, and prior to approval, there was another Advisory Committee. This was held in November 1999 to discuss the new drug application for this product. At this meeting, there was unanimous consensus that the benefits of Advair outweighed the risks.

The following year, in 2001, formoterol was approved as the Foradil Aerolizer. This is a single-dose dry powder inhaler. One very important point is that the higher dose of formoterol, 24 micrograms, was not approved due to safety concerns of serious asthma exacerbations. In addition, a Phase IV commitment was requested to further evaluate the safety of these products.

The following year, the data safety monitoring board for SMART noted an increase in asthma events with salmeterol, particularly in African-Americans. And they also noted that enrollment was slow. And they recommended if the study could not be

completed in a timely fashion, that the study be terminated and the company disseminate the findings.

SMART was terminated in January 2003, and a summary of the interim analysis was submitted to the data at that time. FDA released a communication to the public about the interim findings of SMART, and later that year, a box warning was added to the Serevent and Advair labels regarding a small but significant risk increase in asthma-related deaths, and that the risk may be greater in African-Americans compared to Caucasians.

As I mentioned, this box warning was applied to both the Serevent and Advair labels. This is important to note because the Agency made the decision to apply the box warning to Advair, because Advair contained salmeterol, and there was no convincing data that inhaled corticosteroids mitigate the risk of long-acting beta agonists.

When the box warning was placed on

these products, FDA released another communication that year to discuss the labeling changes. And this was the second communication issued in 2003 alerting the public about the risks of these products.

Switching gears a bit, recall that with the approval of the Foradil Aerolizer product in 2001, there was a Phase IV commitment for a safety study, and Novartis submitted the results of this study in August 2004. In that same year, GSK also submitted some updated results for SMART. Based upon the FDA review in September 2004, the box warnings and warnings for these products were revised again, addressing the additional findings for SMART, including appropriate datasets and statistical analyses.

Because the Agency had the updated results of SMART in the Phase IV study with Foradil Aerolizer, we brought this information to the Pulmonary-Allergy Drug Advisory Committee in July 2005 to

specifically discuss the results of these safety studies. At the time of that meeting, the labeling for the long-acting beta agonists included a box warning on Serevent Diskus and Advair, but there were no medication guides and there was no box warning on Foradil.

On the next few slides, I'll show you the key results that were discussed at that meeting. Here are some results from SMART. Recall that this was a large safety trial in 26,000 patients, and the results are shown for the primary endpoint, the combined respiratory deaths or respiratory-related life-threatening experiences.

And you can see the relative risks for the total population is 1.4, and that African-Americans had a higher relative risk, appearing to be a particular risk for this endpoint.

A key secondary endpoint was asthma-related deaths, with a relative risk

of 4.37 for the total population. This is a similar finding to the results of the SNS study.

Here are the key results for the Phase IV study with Foradil Aerolizer. And this was a randomized blinded placebo controlled 16-week trial in 2,300 patients with asthma 12 years of age and older. Note that the size was significantly smaller than the SMART trial. This trial also included the higher dose of formoterol, 24 micrograms twice daily, that was not approved.

The results show that the rate of events were too low to draw firm conclusions, but the data trended towards an increase in serious asthma exacerbations in the formoterol groups compared to placebo.

After reviewing the SMART results and the results of the Foradil Aerolizer Phase IV study, the Preliminary Allergy Drug Advisory Committee was posed the following question: Based on currently available

information, do you agree that salmeterol should continue to be marketed in the U.S.? And there was a unanimous recommendation to keep salmeterol on the market.

A similar question regarding formoterol: Based on currently available information, do you agree that formoterol should continue to be marketed in the U.S.? And again, there was unanimous consensus to recommend keeping formoterol on the market.

And finally, based on currently available information, should the label of the formoterol-containing product include warnings similar to those in the salmeterol label? And there was nearly a unanimous consensus to recommend class labeling regarding the risks of these products.

Some of the additional comments from the 2005 Pulmonary-Allergy Drug Advisory Committee included the following: Recommendations to modify the box warning; to discourage monotherapy; and encourage

co-administration with an inhaled corticosteroid; to provide a medication guide and direct patient information; and to maintain a box warning on all the salmeterol-contained products.

Following the July 2005 Advisory Committee meeting, the FDA issued a Public Health Advisory. In this Public Health Advisory, FDA requested that the manufacturers of these products update product labels with new warnings for all the LABA products, including the fact that long-acting beta agonists should only be used as additional therapy in patients who have not adequately responded to other asthma controller medications. FDA also requested medication guides for each of these products.

At the same time, we issued health care professional sheets regarding these products. And the Public Health Advisory and health care professional sheets are tools FDA can use to communicate important safety

information to the public and health care providers. These actions are consistent with the recommendations from the 2005 Advisory Committee.

Because we've requested a medication guide, I wanted to make sure that you were familiar with this. A medication guide is FDA-required labeling that is necessary for patients' safe and effective use of a drug. Normally, patient labeling is optional, but per the regulations, a medication guide can be required for one of the following: If the product labeling could help prevent serious adverse event; or if the drug product has serious risks of which patient should be made aware of because the information concerning the risk could affect patient's decision to use or to continue to use the product; or that the drug product is important to health, and patient adherence to direction is crucial to the drug's effectiveness.

It is somewhat of a high hurdle to require a medication guide, and the majority of drugs do not have this. But for the long-acting beta agonists, a medication guide was required so that patients are aware of the risks of the medications.

Following the FDA's request for updated labeling and medication guides, all the labels for the long-acting beta agonist products, including Foradil Aerolizer, were updated in 2006. In the same year, Symbicort Inhalation Aerosol was also approved. The combination product would be budesonide and formoterol. Importantly, the product label included the class labeling, including a box warning and medication guide.

In the same year, pediatric exclusivity was granted for salmeterol. And this is important because discussion of products granted pediatric exclusivity are required at a Pediatric Advisory Committee. And that brings us to the Pediatric Advisory

Committee held in November 2007.

At this meeting, salmeterol was one of many products discussed. Typically for these meetings, the Office of Surveillance and Epidemiology performs a review of the post-marketing safety data. Because of the safety profile of salmeterol, there was an expanded discussion of this product, and concern was raised regarding the risk/benefit assessment in pediatric patients. The FDA committed to discuss this issue at a future Advisory Committee meeting, and that, of course, is the meeting we're having today.

To be complete, I wanted to show you the questions discussed at the 2007 Pediatric Advisory Committee. There were no voting questions to the Committee, but a very long statement followed by a request for discussion. And I will not read this introductory statement; it is included in the briefing package in the Pediatric Advisory Committee summary minutes.

But I will paraphrase as follows: The Office of Surveillance and Epidemiology provided an analysis of available observational studies and a subgroup analysis of the pediatric population in clinical trials. FDA committed to bring this issue to a future Advisory Committee meeting.

The Committee was asked to discuss the following: Whether the current labeling and medication guide adequately communicate the potential risks in children, and whether the labeling adequately addresses the increase in pediatric hospitalizations; or whether it's clear that salmeterol should only be used as additional therapy for patients not adequately controlled on other asthma medications; and whether the labeling is clear that there is no clear evidence that the inhaled corticosteroids mitigate the risk of asthma-related deaths.

This slide shows some of the Committee responses from the summary minutes.

There were some members who discussed the possibility of removal of salmeterol from the market, but the Committee agreed more extensive discussion was needed. The Committee requested that FDA report back after additional review of the data, and some expressed a sense of urgency from a public health perspective. Some recommended the FDA update the labeling to identify pediatric risks, including hospitalizations. The Committee generally agreed with the FDA's recommendation to continue this assessment of the risks of long-acting beta agonists, and to seek advice from a future Advisory Committee.

Following the Pediatric Advisory Committee, FDA requested that manufacturers of these products provide data from the controlled clinical trials to further evaluate the safety of the long-acting beta agonists when treating asthma. In March of 2008, FDA updated its website, confirming

plans for a future Advisory Committee for this topic. Since that time, the sponsors have submitted the data FDA requested, which was used with the meta-analysis in the FDA briefing package.

And that brings us to today -- the joint meeting held to discuss the benefit/risk assessment of long-acting beta agonists for the treatment of asthma in adult and pediatric patients.

Recall that the discussion at the Pediatric Advisory Committee was regarding salmeterol use in pediatric patients, but the Agency decided that the discussion should be broadened to include all LABA products in adults as well, because the majority of the safety data with these products is in adults and adolescents. The Agency has made a decision to label salmeterol and formoterol similarly with class labeling; thus, the discussion today is for both adult and pediatric patients with asthma and for both

salmeterol and formoterol.

So now we're up-to-date on the regulatory history. And I'm going to end my presentation with the current labeling so that everyone is clear on the language in the labels.

The product labels for the long-acting beta agonist products have information regarding the risks in multiple sections of the product label, including those listed on this slide. The Agency thought it was important to repeat the message regarding the risks and appropriate use throughout the label. Over the next few slides, I wanted to highlight some specific sections of the label. And I'll begin with the box warning.

First, the box warning in all the products is regarding asthma-related death. The data regarding asthma-related deaths was from SMART.

There were other endpoints in

SMART, including respiratory-related deaths, respiratory-related life-threatening experiences, and hospitalizations. However, the Agency did not want to label the LABAs -- the Agency decided to label the LABAs for asthma-related deaths, as this was the most important endpoint, and we did not want the message to be diluted with discussion of all the other endpoints in SMART. And although the asthma-related death data is with salmeterol, the Agency has labeled formoterol with the same box warning. It contains the same language.

Second, although not explicitly stated, the box warning applies to all age groups. Despite the fact that there's no asthma deaths seen in the pediatric population, the Agency takes the conservative approach and assumes that the risk of asthma-related deaths applies to all ages.

Next, the box warning addresses the appropriate use of LABAs as an additional

therapy to a controller medication. This information was included not because inhaled corticosteroids mitigate the risk, but because patients with intermittent or mild asthma are not appropriate for long-acting beta agonist therapy. And this language allows for practitioners to add salmeterol or formoterol to a variety of different controller medications.

And finally, the box warning contains information from SMART. This slide shows the current box warning for Serevent Diskus. And I'm not going to read it to you. These are in the briefing package. But the box warning describes the risk of asthma-related death, appropriate use because of this risk, and it does in the salmeterol product labels include some data from SMART.

This slide shows some of the figures from the clinical trials section where SMART is discussed in the Serevent Diskus product label. The label includes the

data regarding asthma-related deaths. Even though this was not the primary endpoint, as I mentioned earlier, the Agency felt this was a most important endpoint. And in addition to the relative risk, the data was also expressed as the excess incidents. In per 10,000 patients treated for 28 weeks, there were 8 additional asthma-related deaths in patients treated with salmeterol in SMART.

The label also includes cumulative incidence figures for asthma-related deaths. So the SMART data is described in detail in the product labels, and these types of figures and tables provide prominence in the label in this information.

This slide shows the current box warning for Foradil Aerolizer, with information regarding asthma-related death, appropriate use because of this risk, and a reference to SMART. Again, I won't read it because it's in your briefing package.

The Foradil Aerolizer does not

contain the same figure table from SMART, but contains the result of the safety and efficacy studies in the Phase IV safety study with Foradil Aerolizer. And the results for serious exacerbations are displayed in the adverse reaction sections. These are three tables from the product label. You can see that these tables provide some prominence of the safety information.

This is a repeat of an earlier slide, because even though I'm only showing you parts of the label, the warning regarding the asthma-related death and appropriate use is throughout many sections of the label. Plus, I wanted to remind you that there's a medication guide which has the information, which is the required patient labeling.

And for the combination products, the warning and appropriate use information is very similar and is included in these sections of the product label, so I'm not going to show you details.

But that brings us up-to-date on the current labeling.

And I'm going to close my presentation with a brief summary. The long-acting beta agonists and the safety of these products have a long regulatory history, and this figure displays many of the key milestones. Each colored line represents a different product, and diamonds represent approval for different indications.

Each long-acting beta agonist product was approved first for asthma in adult and pediatric patients greater than 12 years of age and older. As you can see, Serevent Inhalation Aerosol was the first one marketed, and as I mentioned, is no longer marketed due to the phase-out of the propellant chlorofluorocarbons.

Other LABA products have been approved for other indications during this time period. The Foradil Certihaler is an approved product that has not been marketed.

This figure also shows, with the red arrows, the Advisory Committees that have been held regarding these products. The 1993 Pulmonary-Allergy Drug Advisory Committee, dedicated to the discussion of the Serevent NDA; the 1999 Pulmonary-Allergy Drug Advisory Committee, dedicated to the discussion of the Advair Diskus NDA; the 2005 Pulmonary-Allergy Drug Advisory Committee, dedicated to the discussion of the safety of these products, including SMART and the Phase IV Foradil Aerolizer study.

And the Pediatric Advisory Committee, in which the one year post-exclusivity of salmeterol was discussed. And of course, we can add another red arrow for this meeting we're having today.

I also want to explain this figure. In the blue boxes are significant changes to the product label throughout this time, beginning, of course, following the approval of Serevent Diskus in 1995, the additional

warnings to the label regarding these products.

And then following the SMART study ending in 2003, box warnings were added to the labels and were revised again based upon updated results in 2005, I believe. And then following the Pulmonary-Allergy Drug Advisory Committee meeting in 2005, medication guides were added to these products, as well as class labeling was extended to the formoterol products. And I believe this timeline shows the Agency's active participation in addressing the risk of these products.

During my presentation today, I described the basis of approval of the long-acting beta agonists and the benefits of long-acting beta agonists. And I believe Dr. Lemanske also touched on this in his presentation.

Long-acting beta agonists are bronchodilators, approved based upon the measurement of air flow, FEV1. FEV1 is a

clinically meaningful endpoint and has been used as the basis of approval of virtually all asthma medications. There were additional efficacy measures that supported approval, such as rescue medication use, peak expiratory flow, asthma symptoms, and nocturnal awakenings.

The risks of LABA are known. There is a box warning regarding asthma-related deaths, serious asthma exacerbations, and the box warning regarding asthma-related death applies to all ages, and applies to salmeterol- and formoterol-containing products. It also provides appropriate use information, but these products should only be used as additional therapy in patients not adequately controlled on other asthma controller medications.

Today's discussion is a continuation of the benefit/risk assessment of these products for the treatment of

asthma.

Thank you.

DR. SWENSON: Thank you, Dr. Seymour.

At this juncture then, we have time for questions both to Dr. Lemanske and to Dr. Seymour. And I would ask if any members of the several committees, if they would simply put on their mic, we'll see the red light and we'll try to take questions in order.

So it's now open for questions.

MR. HENNESSY: Sean Hennessy. This is a question for Dr. Seymour. I'm wondering what the most plausible biological mechanism is for the apparent increased risk in asthma-related events and deaths associated with long-acting beta agonists. Has there been any discussion of biological mechanisms?

DR. SEYMOUR: I don't think we know the answer to that for sure. And I think Dr. Lemanske touched a little bit on some of the pharmacogenomics. And I think that the data is

not there to support the pharmacogenomics -- are the cause of the difference in asthma-related death with these products.

One theory is that these products make symptoms -- make patients feel better, and that maybe they mask an increase in inflammation that's going on, and that the patients build up to a catastrophic event. But I think the bottom line is that we really don't know the mechanism for this.

DR. SWENSON: Dr. Jones.

DR. LEMANSKE: If I could make one other comment. I think the other thing you have to consider here is the design of the trials on which this data is based. I think I hammered home the point that salmeterol should not be used as monotherapy. And the trial, at least in the SMART study, the patients were given the medication and they could be using any other medication that they wanted to but it wasn't monitored. So it's quite possible that many of these people -- because you feel better when you

take long-acting beta agonists and other medicines -- and they were getting this for free, and other medicines, they'd have to pay for -- that it's possible that they stopped their other medications and continued their long-acting beta agonists.

Now, this is pure speculation. We have no data to say that's simply the case. But I will tell you from a clinical standpoint that it's harder to prescribe -- to get somebody to take a steroid because when they take it, they don't feel any different acutely. It's much easier to use any form of a beta agonist because they're getting symptom relief, and it's very reinforcing in terms of what that inhaler can or cannot do.

DR. SWENSON: Dr. Jones?

DR. JONES: This is for Dr. Lemanske. Could you talk a little bit about the biology of inhaled corticosteroids and beta agonists, and how they might biologically interact?

DR. LEMANSKE: Well, it's been hypothesized and there is some in vitro data to demonstrate this -- that corticosteroids will increase the numbers of receptors for beta agonists and perhaps have something to do with their function as well in a good way.

And the other piece is the other direction, and that is that beta agonists may actually facilitate steroid metabolism, or its effect in terms of its biologic effects. So, it looks like there's an interaction going both ways. Positive interaction.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Can you hear me now? Okay. For Dr. Seymour, on the heels of our PADAC meeting in 2005, we took a number of actions that you described -- the FDA did -- in terms of medical guidelines, revised box warnings, the health care professional materials. What, if anything, do we know about the effectiveness of that in terms of modifying practice?

DR. SEYMOUR: I don't know that I can answer the effectiveness of those different changes in labeling in terms of modifying practices. It's possible that some of the pharmaceutical companies may be able to address that because they can track their prescription sales and see how their prescription sales are compared with inhaled corticosteroids. And they may be able to provide that information.

DR. NEWMAN: Thank you. I'll ask it again later then.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: Two very good presentations. On one end of the spectrum, on the benefit side, you have clear, objective evidence that FEV1 improves, which is what beta agonists should be doing. On the other end of the spectrum, the risk side, you have clear, objective evidence from asthma deaths, asthma hospitalizations, and intubations. Somewhere between is this idea of severe exacerbations. The question for I guess both of you is how

precise is this definition? I'm sure that severe exacerbation includes but is obviously not limited to hospitalization. So in these various studies that you describe so nicely, how specific and reproducible was the definition of severe exacerbation?

DR. LEMANSKE: That's a very, very good question, and that's what we struggle with in interpreting the literature. Exacerbations were hopefully defined a priori in any study design. And the definition will differ from study to study. We're currently right now taking all our trial data and getting DNA from all the patients. And we're going to look at genotyping and looking at exacerbations as an outcome, control as an outcome, et cetera, et cetera. And we're defining an exacerbation as an episode of asthma that requires Systemic corticosteroids, whether it's oral, or intravenously, or intramuscularly.

But if you look at some of the trial data, some of the stuff that I showed

you this morning with maintenance and reliever in the stay study, they had three definitions of exacerbations. Peak flow definition. They had increasing inhaled corticosteroids as a definition. And they also had oral steroids as a definition. So it really, really depends on how the exacerbations are defined. And then you, as a clinician, whether you feel that what they're telling you is clinically relevant or not.

DR. WOLFE: Just a follow-up question to Dr. Seymour, which is on your slide 12, which is Regulatory History of Serevent Diskus Efficacy Data, there was no difference -- I mean, there was a difference in things such as FEV1, obviously, but the last line is on page 6. Asthmatic exacerbations -- there was really no difference between the placebo and Serevent. So whatever -- again, the definition was there, it did not show any difference.

And this is really sort of why I'm

asking this question. I think your answer, I'm sure, is accurate that it varies all over the lot. And some of the criteria you just described would be exacerbation, but not necessarily severe exacerbation.

So when you start looking at this measure of the benefit, it seems far mushier, obviously, than either FEV1 on one end or asthma deaths, asthma hospitalizations, and the other end. That was the only point.

DR. SEYMOUR: I think that's a good point, and your observation on that slide is correct. I concur with Dr. Lemanske that there really is no standardized definition for asthma exacerbation. And they're going to vary from study to study. And that is one of the issues with comparing these cross-studies.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: Thank you. The box warning is rather intimidating, I think, when you read it. And I'm kind of wondering, given the high percentage of illiterate people we have

in the U.S., if you took into account illiteracy when you developed the box warning and maybe the patient information -- and wondering if you took into account again how a patient could make a good informed decision on whether or not to use the product based on the box warning and the information that's available to them.

DR. SEYMOUR: Right. So the box warning that I showed you is from the patient -- the product label, which is intended for health care providers. And I hope that this is at a level that they can understand.

But the medication guide and all the patient labeling do go through our patient labeling experts within the FDA. And they evaluate the literacy level for the language in the medication guide. And I did not show you the medication guide language, but it is adjusted to -- for patients, this message. But this is a message that I think is very difficult to write for patients, but we did feel it was important to have a

medication guide so at least they were aware that there were some risks with these medications, and that they need to talk with their doctor to make sure that this product is appropriate for them.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: For Dr. Lemanske. I'm thinking ahead toward risk management alternatives.

Could you give us a state-of-the-art of genetic testing? Outside of the research arena, how practical and accessible are tests that would allow us to distinguish between hyper-risk among patients?

DR. LEMANSKE: Well, to just answer your question very quickly, we're not there yet. But we're working on it. The NIH is putting together a Genome-wide Association Study with all of the trials that the ACRN has done, CARE has done, CAMP -- the Childhood Asthma Management Program -- and that's in process.

We've defined our different phenotypes, and we're now beginning to do genome-wide screening to see if we can learn more about asthma genes, or genes that are responsible for response to therapy.

I think it's important to point out that the data that I showed you with beta adrenergic receptor polymorphisms is not the reason why there's a black box label in the product insert; okay? The two are disconnected. It's possible that there may be something to do with a person's genotype that may confer increased risk, but we haven't really established exactly what that is at this point.

So to go one step further in terms of risk management, there are companies now who are making tests that you can look at. Beta adrenergic receptor polymorphisms at disposition 16 looking for the R RH (?) genotype. And clinicians are using this in different areas, but we have no data to

support that that is going to be helpful in terms of management or assessing risk in the future. So we have to be very careful with that.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: Just a point of confirmation or clarification regarding the SMART trial. Is it correct that when patients were recruited initially, they were essentially handed seven containers of Serevent and then the rest was 28 weeks over phone? And then also related to that, I understand that over the course of the trial, the way the patients were recruited into the study somewhat changed, and it became more of a physician referral basis to get patients into the study. Did that affect how the medications were given in bulk and educated for use with the patients over that time course?

DR. SEYMOUR: So I'll respond to this question, and if I respond incorrectly, I'm sure GSK will let me know.

So I believe it is correct that at the beginning of the trial, patients were handed the medication for the entire 28-week treatment period, and they were contacted by telephone every four weeks. You have to remember that this is a huge trial. It's a simple safety trial, so this is -- in 30,000 patients, this was a way that the trial could be conducted. And so it's certainly not ideal trial process, I think, for the study to get done.

There was a change in how patients were recruited. I can't remember the exact year cutoff, but I believe that the same thing happened after they changed the recruitment. They were still given all the medications at the beginning and then contacted every four weeks.

I would like to use this opportunity to reiterate something Dr. Lemanske said, and to remind everybody that both the SNS and SMART study were done

in the 1990s. And this was before all the guidelines had really become standard of care with the use of inhaled corticosteroids.

So I think, you know, the timing of these studies and what patients were receiving at that time probably had some impact on the outcomes of these studies. And if they were done today -- which they wouldn't be done today; you wouldn't give salmeterol as monotherapy -- but there might be different outcomes because patients would be on inhaled corticosteroids.

DR. SWENSON: Dr. Goldstein?

DR. LEMANSKE: I think if I could just make one more comment. I think what's been very hard for us clinically is to try and determine once and for all if these adverse effects that we're seeing rarely are related to the drug itself, or whether it's related to the fact that the patients are not taking something else that they need for their asthma, like inhaled corticosteroids. And that's a very, very

important point that you probably all recognize from how we've gone over the data. I think I've shown you a number of studies that clearly, salmeterol should not be used as monotherapy. And in the SMART study, there was really no way of being able to monitor that.

DR. SWENSON: Dr. Goldstein?

DR. GOLDSTEIN: Question for Dr. Lemanske. And I'm going to limit my question to the pediatric population. In your estimate, what is the percentage of pediatric patients that are receiving long-acting beta agonists? The follow-up is that if -- in anticipation of discussion later on -- if these were removed from the market, what burden would that place on the population? And then a follow-up question is, we've looked at data from prospective studies and prospective data gathering on deaths related to these medications.

As a pediatric intensivist, I took care of these children when they were in the

ICU after they had failed whatever treatment they were on. Death was a very rare occurrence. Has anybody looked retrospectively and done an analysis on pediatric deaths in terms of what types of variables were associated with mortality?

DR. LEMANSKE: In answer to your second part, the numbers of deaths are so small that it's really hard to come up with a common pathway that these patients are following to get to that unfortunate end.

With regards to the percentage of patients, I'm sure that my colleagues -- our colleagues from GSK and Novartis, et cetera, have data on what the uses in the pediatric population. In my own practice, I would say -- now, remember, I'm at a university-based practice so I'm seeing kids with more severe disease -- but I'm prescribing it for about 25 to 50 percent of my asthmatic children. That said, I've shown you data that clearly children respond very

well to monotherapy with inhaled corticosteroids.

And many, many, many, many children do not need combination therapy. It's this step up from step II to step III, where they're not being controlled on low dose inhaled corticosteroids, and we as clinicians have to make the decision should I push the steroid dose or should I give them something else? And that's what BATGER is trying to address. What is the best way to approach those kids? We know that as soon as we get over a dose of 200 micrograms of fluticasone a day, you increase the risk of growth suppression in the kids. So that seems to be a cut point where we want to stay underneath if we can.

Now, obviously, that doesn't happen in all kids, but it's a cut point where you have to start thinking about other options.

DR. GOLDSTEIN: The follow-up to my other question -- I know there were three in

there -- if long-acting beta agonists were lost as part of your pharmacologic armamentarium, what burden would that pose for your patient population?

DR. LEMANSKE: I think right now, in terms of how I use these drugs clinically, if they're not being controlled on low dose inhaled corticosteroid, my next step would be to add LABA as opposed to adding montelukast. So it would be a burden for me because I wouldn't have that option anymore. I'd have to choose something else, like give more steroid. And maybe that would be the best option. And again, we'll learn from BATGER which kids that would be the best option for.

As soon as you start limiting choices -- the thing about asthma that's most important and I didn't even say this is it's so individualized. Every patient with asthma is unique, I think. And what works for Johnny is not going to work for Jane.

And the challenge we have as

clinicians is to try to find which form of therapy is going to work best for that patient. And if we limit our options, our ability to do that gets more and more limited.

DR. SWENSON: At this point, our schedule calls for a break, so we'll have to hold on those questions. I hope they'll come up at another point in the meeting. And we'll reconvene at 11:00.

(Recess)

SPEAKER: Panel members, please select your menu and pass it on over to me, or actually our staff will be around to collect it.

Thank you.

DR. SWENSON: And now, Andy Mosholder from the FDA will give us a presentation on the background on the safety issues of LABAs.

DR. MOSHOLDER: Can someone put my slides up, please?

I'm Andy Mosholder from the Division of Epidemiology in the Office of

Surveillance and Epidemiology at FDA. Pleased to be talking with you this morning. I'll be giving some background on these safety issues. Some of this, we will have heard already earlier this morning, and also for those of you who were participants in last year's Pediatric Advisory Committee meeting on Serevent, some of this will also be familiar.

I want to start by acknowledging the many collaborators who assisted me in preparing this. It clearly was a team effort both within FDA and some people from outside who were kind enough to supply information.

This is just an outline of the topics I'll be covering. First, I'll look at the history and some of the postmarking surveillance data for long-acting beta agonists; a brief discussion of some of the observational pharmacoepidemiology studies that have been done to look at safety issues with these compounds.

We'll be looking at data from large safety trials of salmeterol, some of which we've already discussed this morning. And I'll be giving an overview of some of the clinical trial meta-analyses that have been done. We'll talk some about the current use of LABAs in the United States, and there's already been some interest expressed in looking at that, so hopefully that will address some of those issues. And then finally some concluding remarks.

So first let's look at postmarketing surveillance data for the LABAs. And I want to start with a historical note. As has been alluded to previously, even before the era of the long-acting beta agonists, there were concerns regarding beta agonists used in the treatment of asthma.

I should add, too, that nothing that I'll be discussing today applies to use of these products in COPD. That's a different subject. So this discussion is

limited to asthma.

But at any rate, in the 1960s, there was an epidemic of asthma deaths in countries -- in younger patients in countries which had marketed a high dose isoproterenol inhaler. And then similarly in the early '90s in New Zealand, specifically, again among younger patients, there was an epidemic of asthma mortality which was linked to use of a short-acting beta agonist, formoterol. And when it was removed from the market, asthma deaths declined. So even before the long-acting beta agonists, there were concerns about safety of this type of compound.

So let's look now at postmarketing surveillance data with the long-acting compounds. These are cases that have been reported to FDA's spontaneous reporting database, which is the Adverse Event Reporting System, or AERS. And these are spontaneous cases reported by either

consumers or health care professionals involving use of one of the LABA products for which the cause of death -- these are all fatal events, and the cause of death appeared to have been plausibly related to asthma.

We see here in the early '90s -- actually, there was a peak coinciding with the initial marketing of salmeterol with Serevent, and this raised some concerns. And there was a qualitative nature to some of these reports, such that they seemed to be describing overwhelming asthma attacks such as descriptions of the patients found dead clutching their inhalers and things of that nature. So there were concerns then.

And then there is a decline. And then in recent years, some increase in reports. Specifically -- I should add that these are classified by age group. And then specifically in 2008 -- this is a partial year total -- since our discussion last year at the Pediatric Advisory Committee reports

of asthma deaths with these compounds, we accrued a total of five additional cases here all in children under 12 years of age.

So what conclusions can we draw from the postmarketing surveillance data? Well, despite the fact that there have been these reports, it's actually very difficult to assess causality from these types of data. And the reason is that we have confounding by indication. And by that, I mean that the events of interest being reported, which are serious or fatal asthma exacerbations, are actually related to the condition or which the drug is being prescribed.

Furthermore, it's not possible to estimate an incidence from spontaneous reporting data, as I'm sure many of you realize, because we have an unknown degree of under-reporting. We never assume that we would receive all reports of all cases that are occurring in the population. So because of these limitations, we have to turn to more

systematic data sources.

So that brings us next to observational pharmacoepidemiology studies of LABA safety. And there have been a number that have been performed. I'm just going to touch on this. We can go into it further if there's interest, of course. But there have been a number of studies conducted in recent years. I've listed seven of the more salient ones here on this slide, and there are probably others. But rather than go into the results of each one individually, for now, I'll just make some summary observations.

Basically, despite having the advantage of large sample sizes, the problems with these type of data include the following: First, the findings have been inconsistent regarding the association or lack thereof with serious asthma outcomes. These studies have tended to have limited data relative to the pediatric population. There has been difficulty obtaining adequate

statistical power for outcomes of interest.

In fact, there was one study by GSK that had to be abandoned because of lack of statistical power. And also, there's great difficulty methodologically accounting for differences in the types of patients getting the different types of drugs. In other words, because these aren't randomized data, the patient's treatment is tailored to their condition.

And that is very hard to account for in the analysis. So on balance, we would view these of less inferential value than controlled clinical trial data.

So let's turn next to the controlled clinical trials. Dr. Seymour has already discussed two of these with you. We have the two large randomized safety trials with salmeterol -- SNS and SMART. And I'll be recapitulating some of the findings with those. For formoterol, we have no such comparable studies.

And then I want to introduce the concept of the meta-analyses, which is a technique that's often used to enhance sample size and statistical power by combining data from different randomized trials into a single analysis. And we'll be talking about that throughout the day.

Before we look at the results from these trials, there's a couple of concepts I wanted to mention. And these are the risk difference and the number needed to harm, which are related, as I'll describe. Basically, they're trying to ask the question -- exposing how many patients will produce one excess adverse event or adverse reaction to the drug?

And they're related in that the number needed to harm is actually the inverse of the risk difference. And let me walk you through this example.

Suppose one does a study and this particular side effect has an instance of

5 percent on drug and 3 percent on placebo within that study.

The risk difference is going to be .05 minus .03, which is a difference of .02. So that's the risk difference. Or you can say that that's equivalent to two excess events for every 100 study subjects who received the drug -- over the risk in placebo.

Now, the number needed to harm is calculated as the reciprocal of that. So it's 1 over .02, or 50. And what that means is that for every 50 patients administered the drug in the study, there was one excess event over what would have occurred on placebo.

So with those concepts in mind, let's take a look at the data from the salmeterol large safety trials. First, this is the Serevent Nationwide Surveillance, the so-called SNS study that was published in 1993. Just to reiterate, it was a randomized

16-week double-blind trial done in the U.K. The purpose was to assess safety, and there was no single a priori primary outcome designated. The treatment groups were salmeterol 50 micrograms twice a day, albuterol 14 micrograms four times a day, and the randomization ratio is two-to-one. So when one looks at the results, one has to keep that in mind.

The population was mostly adults, although 6 percent were adolescents and were considered to have mild asthma. Data on concomitant ICS use, which is of course a critical issue, unfortunately was not collected during the trial. In order to obtain complete data on patients who dropped out, the investigators had to follow up dropouts at the end of the study period to ascertain whether they were still alive or dead.

And so now let's look at the results. Here, we see that there were close

to 17,000 patients received salmeterol and just over 8,000 albuterol. If first we look at asthma-related withdrawals, we see actually that the relative risk is .8, which that means it's favoring salmeterol. But then if we look at asthma-related deaths we have 12 versus 2, and with the two-to-one randomization, that works out to a relative risk of 3. And the p-value associated with that of marginal statistical significance .105.

And for all cause death, we see a numerical imbalance again favoring albuterol, which did not reach statistical significance.

Let's look next at the SMART trial, which -- as you've heard, this was a U.S. trial. Actually, 28 weeks in length, so a bit longer than SNS. And here, the randomized treatment arms were salmeterol 42 micrograms twice a day, and placebo in a one-to-one randomization ratio in this case. Twelve percent of subjects were adolescents;

the remainder being adults. And again, data on concomitant ICS use was not collected during the trial. In order to be complete, the National Death Index was used to complete data on vital status for the participants, including the ones who had dropped out of the trial. This study was actually terminated early and did not meet its targeted enrollment.

And so we'll look at the results. Again, you saw this previously, but just to review, there were roughly 13,000 in each treatment arm. The primary outcome that had been a priori designated was a combination of respiratory-related death or life-threatening experience. And this was a numerical imbalance favoring placebo. It did not reach statistical significance. However, asthma deaths, 13 versus 3, giving a relative risk of 4.4, with a confidence interval that excluded one -- that translates to a number needed to harm of about 1,300. Meaning that

for every 1,300 patients who received salmeterol in the trial, there was one excess asthma death over what would have occurred on placebo.

The other point here, with a relative risk of this size, it means that in actuality, one would attribute the majority of the asthma deaths in the trial to the action of salmeterol. There was another outcome respiratory-related death which is a somewhat larger category, as you see. Again, this was increased -- it was more than doubled with salmeterol statistically significant. And the number needed to harm for this definition of about 1,000. And for all cause death, again, a numerical imbalance favoring placebo, which did not reach statistical significance.

Now, I wanted to put the results from the two studies side by side to make a few points here.

I've labeled them LABA and no LABA

just for consistency with the later meta-analyses. Now, it's true that in SNS, the patients had randomized albuterol on a scheduled basis. In SMART, they were able to use it as a reliever medication, so it's not too much of a stretch to compare these two trials. And we see, first of all, if one look at withdrawals for lack of efficacy and asthma-related withdrawals, we see that actually, the relative risk favors salmeterol. So the more ordinary types of symptoms, as we've heard, are being -- are responding to the salmeterol.

But then as one goes up the hierarchy we, see sort of the opposite pattern. If you look next to asthma hospitalizations, in SNS, it was a neutral effect and slightly increased -- 1.2 or 20 percent higher with salmeterol in the SMART trial. And then if one looks at even more severe outcomes, either intubations or asthma deaths, we see even higher relative

risks. So this I think illustrates the paradoxical nature of the phenomenon here, which is that the more ordinary routine symptoms are being controlled, but at a price of greatly increased asthma mortality and life-threatening events.

And then the other point to make as we look later on at data from the meta-analysis, it's important to note I think that for asthma hospitalizations, which sort of make up the majority of events in the meta-analysis Dr. Levenson will present, actually these trials, were close to being neutral between treatment arms.

So when one lacks data on more severe outcomes because of sample size or whatever, I would argue that it's difficult to draw too much reassurance from the finding of neutrality on asthma hospitalizations, because it's not necessarily predictive of what will be the case for asthma deaths.

This is taken from the labels. I

think we've seen this already this morning, but just to make the point, this is a cumulative incidence plot for asthma deaths. And this is the total sample at the top. And this is the African-American subgroup at the bottom. And this is to make the point that it appears the African-American subpopulation out of the total sample was actually showing a greater risk of asthma-related deaths relative to placebo.

So what can we conclude from these trials? Here, I quote an editorial from the European Respiratory Journal: "In view of the results of the two studies, both of the highest evidence class, the existence of salmeterol-related excess mortality has to be assumed with near certainty." And actually, the Cochrane Review Group was able to quantify that.

They calculated a combined odds ration of combining the two trials for asthma mortality and the result was 3.7, with a

p-value of .0074. So putting some statistical probability testing on this finding, that's consistent between the two trials.

And the next, I hope Dr. Martinez doesn't mind that I quote him here, but as he wrote in the New England Journal, "One death was attributable to salmeterol for every 700 patient years of treatment in SMART, a result strikingly similar to that in the United Kingdom study." Unfortunately, the limitations of the trials preclude definitive conclusions regarding the potential for inhaled corticosteroids to limit or prevent these adverse outcomes.

A point here -- an excess death rate of 1 per 700 patients per year is not going to be obvious to prescribers, particularly if the milder symptoms are responding at the same time. So that illustrates part of the difficulty with this -- handling these kinds of risks.

To change gears now, look at formoterol. As I mentioned, we have no such comparable large safety trials with formoterol, but there was a pattern of serious asthma events noted in the clinical trials pre-approval, and in fact, it resulted in the highest dose not being approved. I'll show you those data. This is simply pooled data from three of the key pivotal trials, and showing sort of the progression.

Here, we have placebo .4 percent; albuterol .7 percent. And then formoterol 12 micrograms twice a day, 2 percent had serious asthma events, and at 24 micrograms twice a day, 4.5 percent. And that number actually included one asthma death and two patients who required intubation.

One can imagine if one had scaled up a large trial with formoterol, one would probably have seen many such events. And also, one could argue that the dose relatedness of these phenomenon lends weight

to there being a causal relationship to formoterol.

Let's change gears now and start to talk about some of the meta-analyses that have been done. As I said, this is a technique to improve the sample size and statistical power. And sort of the seminal meta-analysis was by Saul Peter and Associates, (?) published in 2006. So this was not available at the time of the 2005 Advisory Committee meeting. And the purpose was to assess the risk for severe asthma exacerbations with either of the compounds.

They looked at 19 placebo-controlled trials at least three months in duration with close to 34,000 subjects all told, and six of the trials were pediatric. They calculated PO odds ratios and confidence intervals for outcomes. They did describe in the paper outcomes on asthma deaths, but that's dominated by the SMART trial. So I didn't display that here but it

is in the paper.

But what this analysis did is it extended the finding from asthma mortality to asthma hospitalizations, for which there is an odds ratio of 2.6, statistically significant, and also exacerbations requiring intubation for which there was an odds ratio of 1.8, again, statistically significant.

And then next, this will be familiar to those who participated in the Pediatric Advisory Committee last year on salmeterol. This was a subgroup of pediatric data that Dr. Saul Peter was kind enough to supply, and actually added data from the SMART trial which we obtained pursuant to last year's Advisory Committee for the adolescent patients in SMART.

And one caveat I should mention, some of these data include the unapproved high dose of formoterol, in this trial at least. But basically when one looks at the overall estimated odds ratio for asthma

hospitalizations, they were close to tripled over placebo with one of the two compounds.

So just a small digression. We've talked about this already this morning a bit, but the question came up of, given this sort of paradoxical finding where the most severe outcomes are increased even when sort of the immediate symptoms may be reduced, what are some possible explanations?

As we heard, one is masking a progression of the underlying asthma by the symptomatic relief provided by the bronchodilation, as Dr. Seymour mentioned. The second one is the genetic variant of the beta adrenergic receptor, and Dr. Lemanske already spoke to that. The evidence is mixed on that, but that's one of the hypotheses.

And then third would be desensitization or down-regulation of the beta adrenergic receptors. There is some experimental evidence of tolerance, at least in exercise-induced asthma.

I don't claim to be an expert in these types of physiologic and pharmacologic phenomenon, but this is just to introduce that there are some plausible hypotheses to explain the pattern seen in the data.

So we want to turn next to look at how LABAs are being used currently in the United States.

First, I present here the 10-year prescription trends. This is from the STI Vector I National Database. And you see here this is salmeterol, the mono product. And in red here is the combination product Advair with fluticasone. You can see that in recent years, that has come to dominate the market. And then salmeterol and the formoterol-containing compounds making up a much lower proportion.

And something over 18 million prescriptions annually for these products, most of which being the Advair product.

This is, again, from STI a

different database, the Total Patient Tracker. And the previous slide was numbers of prescriptions. This is to show the numbers of patients. And we wanted to make this as current as possible, so we went up to the year ending September 2008. And we see that for Advair, there's about 5.5 million patients receiving it, and then smaller numbers of the remaining product. So altogether, about 6 million patients receiving the long-acting beta agonists per year.

And we also wanted to look at age distribution of the use. This shows for each of the four marketed products, just breaking down the age by 0 to 16 and 17 and over. And we see that -- I guess roughly speaking, something like 10 percent or less in each case are going to pediatric patients; the remainder going to older patients. And it varies, as you see, somewhat by specific product.

And then finally, we're interested, of course, in what the diagnoses associated with their use is. As I said, the other main -- as I said, this discussion is limited to asthma, but of course, these products are indicated for COPD as well. So this is data taken from a physician survey known as the Physician Drug and Diagnosis Audit. And we see that for the four products, something perhaps between 50 and 70 percent are being prescribed for asthma.

Now, unfortunately, I don't have this subgroup by age because this survey isn't that granular, but roughly speaking, something over half of the products going for use in asthma. So if one takes the earlier figure of approximately 6 million patients and takes about half of that, we would estimate that there would be 3 million patients receiving LABAs for asthma in the U.S. annually. And from the public health perspective, that of course means we have to

be extremely careful with judging the risks of these products, because with an exposure of 3 million per year, any risks are going to be magnified in the population accordingly.

Then there's the interest, of course, in the single entity products, which are a minority of the use, but we wanted to see if we could discern how many patients receiving those were also receiving an inhaled corticosteroid. And we have a database that recently became available to us where we are able to look at that. It's from a managed care organization -- a set of managed care organizations, I should say -- selecting patients who had been enrolled for at least a year and who did not have COPD. We have access to information on diagnoses as well. So limiting it to asthma.

We looked at prescriptions for single ingredient LABAs over a three-year period. The sample was close to 12,000 patients receiving single entity LABAs for

asthma, and we found that almost half had never received a concurrent prescription for an inhaled corticosteroid.

Now, it's true that the majority of these actually were single prescriptions for LABA monoproducts, but still, I have to say we were a bit surprised at this because it was contrary to what's stated in the guidelines, as we've heard. And the source, I should mention -- this is IMS Health Plan claims database.

So finally, we wanted to look at what data we have to address the important issue of whether concomitant ICS protects against the catastrophic asthma events with these drugs. There have been a couple of clinical trial meta-analyses completed recently that have tried to address this.

First, Bateman and Associates published earlier this year, and that was looking at salmeterol with ICS versus ICS without salmeterol. They found an odds ratio

of asthma hospitalizations of 1.1, not statistically significant.

For more severe events, however, there was only one asthma death and one asthma intubation in their dataset. Both happened to be with salmeterol. And then there also was another meta-analysis published just in September by Jaske and Associates. And this looked at actually both compounds, formoterol and salmeterol, with ICS. There, they found actually asthma hospitalizations reduced, although it did not reach statistical significance. However, for more severe events, all five deaths and intubations were occurring in patients who received the LABAs.

So although there's not much of an indication of a problem with asthma hospitalizations from these two meta-analyses, we have sort of the uncomfortable fact that all the deaths and intubations were occurring in the patients

who received LABAs.

So for data on asthma mortality, we have to turn again to the two large salmeterol trials -- SNS and SMART. And the problem, as has been mentioned, the data on concomitant ICS use was not collected during either trial. What we do have is ICS use at entry into the study, and we can look at how the data are subgrouped according to that.

Now, down at the bottom, this is the SMART trial. This is taken from the publication, and you see salmeterol with baseline ICS and placebo with baseline ICS on the left, and without ICS at baseline on the right. And then at the top is the SNS trial.

This is data recently available that the Cochrane Review Group obtained and published earlier this year. And there was -- some data was missing, so it's not data on the complete sample in the trial. Again, you can see how it's subgrouped according to whether presence or absence of

baseline ICS. And just sort of to the naked eye, you can sense that there's a greater imbalance in the group without baseline ICS.

And the Cochrane Group was able to do some calculations which Dr. Cates was kind enough to provide me. Basically, if you look down here, the group without ICS use at baseline, we have a P odds ratio for asthma mortality of 6.4, statistically significant. Actually, the lower band well away from 1.

So with ICS use at baseline, we have a much more imprecise estimate. Odds ratio of 1.5, with a confidence interval of .5 to 4.1. Additionally, they did a test just comparing these two groups. It had marginal statistical significance of .06. So I would emphasize that that's only to say that it seems probable that this group is worse than this group. It's not to say that this group has the risk and this group does not have the risk. And in fact, if one were to accept the odds ratio of 1.5 and were

willing to extrapolate that to the situation of using salmeterol with fluticasone as per Advair, one would still feel that the 3 million or so asthma patients receiving the drugs with ICS would have a 50 percent increased risk in asthma mortality.

So just to wrap up then, we looked first at the post-marketing surveillance data for which we have reports of asthma deaths with LABAs, but as I explained, this is of limited inferential value in terms of causation. We touched on some of the observational safety studies that have been done, but because of methodological issues with non-randomized data, these are of limited inferential value.

We talked about the large randomized safety trials with salmeterol, which showed an increase in asthma mortality. With formoterol, we're lacking comparable trials, but there was definitely an imbalance of serious asthma events seen even

premarketing. And we looked at some of the clinical trial meta-analyses that have been done, which, as I said, was to improve sample size especially for the pediatric age group. And then finally, use of LABAs with concomitant ICS is currently very widespread, but evidence that the ICS nullifies the LABA-related risks is lacking.

And I'll stop there. Thank you.

(Applause.)

DR. SWENSON: Thank you.

Dr. Levenson now will take up the story further here, with a bit more analysis of these meta-analyses.

DR. LEVENSON: Hello. I'm Mark Levenson. I'm a statistical safety reviewer in the Quantitative Safety and Pharmacoepidemiology Group in the Office of Biostatistics in CDER. Today, I'm going to be talking about a FDA-conducted meta-analysis on long-acting beta agonists and serious asthma-related events.

Here is the outline for my talk.

First, I'm going to present the goals and objectives of the meta-analysis, then describe the methods used in the meta-analysis, including beta sources, endpoints, conclusion criteria, comparisons in subgroups, the statistical methods that we used.

Then I'll present the results, starting with trial and patient summaries, event summaries, the meta-analysis results, results for subgroups. Then I'll talk about the limitations of the meta-analysis and compare it to other meta-analyses. And finally, I'll present some concluding statements.

The goal of this meta-analysis that we conducted was to provide risk information for a risk/benefit assessment of LABAs. The benefits in this risk/benefit assessment were to come from action packages of approved drugs. So this has an important consequences in what drugs and doses we use in the

meta-analyses. Because we're going to balance the risk against approved drugs, only drugs and doses approved in the United States were considered in this meta-analysis.

Here are the four LABAs that are in the meta-analysis. These are the LABAs approved for the treatment of asthma in the United States. You've already heard a lot about them, but I'll emphasize a few points here. Advair and Serevent are salmeterol-containing -- the LABA is salmeterol, and Foradil and Symbicort, the LABA is formoterol. Advair and Symbicort are combination products. Advair has ICS gluticasone, and Symbicort has the ICS budesonide.

I should say throughout my presentation when I refer to Advair or Symbicort, I mean the combination product in a single inhaler, not the two constituent products that may be delivered in separate inhalers.

You also notice and you also heard that the age which these drugs are approved for differs.

Advair and Serevent are approved from age 4 and up, and Foradil is approved from age 5 and up. Symbicort is approved from age 12 and up.

The first objective of the meta-analysis was to examine if LABAs are associated with increased risk of the following serious events: Asthma-related death, asthma-related intubation, and asthma-related hospitalization. The second objective was to examine the risk by various subgroups, including inhaled corticosteroid use and demographics, particularly age, sex, and race.

Now, I move on to the methods that were used in the meta-analysis. The data sources -- FDA requested patient-level and trial-level data on LABAs from sponsors of LABAs. Only trials where the study

indication was asthma was requested. And only parallel placebo and/or active controlled trials with or without ICS were requested. Actually, first period of crossover trials was also requested.

The sponsors were instructed to identify and adjudicate serious asthma events, including the events I mentioned on the last slide: the asthma death, intubation, and hospitalization.

We defined these endpoints -- again, asthma-related death -- asthma-related death or intubation. Because of the way the data was collected by one of the sponsors, we couldn't consider intubation separately from death. We had asthma-related hospitalization and an asthma-composite endpoint that we defined as the death, intubation, or hospitalization. And only events which occurred during the protocol-blinded treatment period were included in the analysis.

For the first comparison, the primary comparison, we compared LABA treatment versus no LABA treatment. Here, no LABA includes ICS, short-acting beta agonists, other non-LABA treatments, placebo, or combinations of the above treatments. As subsets of that primary analysis, we looked at two additional comparisons. The first is LABA with randomized defined ICS versus randomized defined ICS. In this comparison, the specific ICS and the dose must be the same in both comparison arms within a trial. And the final comparison is basically the complement to that, the LABA without randomized ICS versus no LABA.

Here are the inclusion criteria for the analysis on the trial level. Again, we only considered study indications of asthma, and randomized blinded parallel trials or the first period of a crossover trial. The trials -- this is an important inclusion criteria -- the trial must have had both a

LABA and a no LABA arm, which we refer to as an internal control. Without trials with internal controls, different background rates across trial may distort the overall findings of the meta-analysis. So this is an important criteria in our meta-analysis.

The LABA arm may have had additional therapy if the non-LABA arm has the same therapy, including dosing. The nominal blinded treatment duration had to be at least seven days. There had to be at least 20 subjects in both the LABA and no LABA arms, and subject level data had to be available.

Now, on the subject level, the inclusion criteria was the assigned dose for a subject had to be approved for the treatment of asthma. The delivery device was not part of the criteria. And the age of the subject had to be in the approved age range for the drug.

Here are the subgroups we

considered for demographics. We considered four age groups. We considered the gender and race of the subject and the location of the subject's site, whether it was in the United States or not in the United States. We considered baseline ICS use, and whether the nominal trial duration was less than 12 weeks of blinded treatment or greater than equal to 12 weeks of blinded treatment.

The primary analysis method was a Manzel-Handel (?) risk difference. This is a stratified method. It maintains within trial control. It uses trials with no events and is a fixed-effect method in that it assumes the common risk difference across trials. The details of this were the uni-analysis was the subject and the primary display was the risk difference and 95 percent confidence interval.

We performed several sensitivity analyses, including the influence of certain trials. First, the exclusion of SMART.

SMART was part of the primary analysis. We also examined the inclusion of SNS. SNS was not part of the primary analysis because subject-level data was not available. We considered the statistical properties of the primary method using the exact method for an odds ratio, and we examined trial heterogeneity with a generalized linear mix model with a random treatment effect.

Now I move on to the results. First, trial and patient summaries. There were 110 trials that met the inclusion criteria. Roughly 61,000 subjects. Those subjects were roughly divided between LABA and the no LABA groups. Serevent accounted for 72 percent of the overall subjects. Advair accounted for 22 percent. Foradil and Symbicort each supplied relatively few subjects for the meta-analysis. Foradil 3,765 and Symbicort 1,270, which represents only 2 percent. The nominal trial duration -- the mean was 172 days. The

medium was 196 days. It ranged from 7 days to 476 days, and 50 percent of the subjects were between 84 and 196 days.

The majority of the subjects, 77 percent, the age was between 18 and 64. Six percent were between age 4 and 11, which represents 35 -- 115 subjects; 11 percent between 12 and 17; and 7 percent greater than or equal to 65. The median age was 37 and the range was from 4 to 100. The majority of the subjects' race were White Caucasian at 72 percent; 4 percent were Asian; 11 percent were Black or African-American; and 14 percent were other/unknown.

Looking at other demographics, 50 percent of the subjects were female; 69 percent of the subjects had U.S. sites; and 94 percent of the subjects were in trials with a nominal treatment duration of at least 12 weeks. For other baseline characteristics, 20 percent of the subjects were in trials that required ICS at baseline;

50 percent of the subjects reported that they used ICS as baseline.

In terms of the actual treatment duration, not the nominal treatment duration, the mean was 154 days, and there was little difference between the no LABA and the LABA group. Likewise, the medium was 169 days, and there was little difference in treatment duration between the comparison groups.

Here are some selective summaries by drugs. These summaries are chosen to display differences among the drugs. Other characteristics were generally the same. Serevent had a large or medium treatment duration of 193 days versus Advair, Foradil, and Symbicort. Serevent also had a higher percentage of subjects from U.S. sites, 84 percent versus 27, 48, and 38.

Both Serevent and Foradil had lower percentages of subjects in trials that required ICS at baseline. Ten percent for Serevent, and 16 for Foradil, versus 49 for

Advair and 100 percent for Symbicort.

Now I'll talk about some descriptive summaries of the four endpoints that we defined. There were 20 asthma-related deaths -- 16 in the LABA group, 4 in the no LABA group; 71 deaths or intubations -- 44 in the LABA group, 27 in the no LABA group; 666 hospitalizations -- 369 in the LABA group and 299 in the no LABA group.

As you recall, as I noted earlier, the asthma composite is made up of the death, intubation, and hospitalization endpoint. And you can see that the hospitalization is driving the asthma composite endpoint here. Also note that the percentages of subjects where each of these events in the LABA group is higher than the corresponding percentage in the no LABA group for each of these events.

Now I'm going to look at these event summaries for the four individual

drugs. First, Advair. There were no deaths or intubations in Advair trials. There were 21 hospitalizations in the LABA group, and 20 in the no LABA group. For Serevent, Serevent is responsible for all the deaths and intubations in the meta-analysis, and the percentages in the LABA group for all the events are higher than the no LABA group.

Again, Foradil had no deaths or intubations. There were 18 asthma hospitalizations in the LABA group and 14 in the no LABA group. For Symbicort, again, there was no deaths or intubations. There were six hospitalizations in the LABA group and one in the no LABA group.

Now the results of the meta-analysis. These are the four asthma endpoints -- asthma death, intubation, hospitalization, composite. I'm displaying risk difference estimates. A risk difference greater than zero implies that the LABAs are associated with a greater rate of events

relative to the no LABA group.

You can see from the estimates for all four asthma endpoints, the risk differences are greater than zero, implying that the LABAs are associated with an increased rate of events relative to the no LABA group. Also, when you look at the 95 percent confidence intervals, none of them contain zero. So the null value of a no association is not contained in the confidence intervals. They're all greater than zero on the lower side.

This is a forest plot which I'm going to show several of, so let me go through the first one slowly. For the remainder of the presentation, I'm going to be concentrating on the asthma composite endpoints, and I'm going to be showing the asthma composite here by the four drugs.

The square plot symbol represents the risk difference estimate, and the line that extends beyond it is the confidence

interval, also displayed numerically over here.

Here is the overall result across all the drugs. For three of the four drugs -- Serevent, Foradil, and Symbicort -- the risk difference estimate was greater than zero. For Serevent, the confidence interval did not contain zero. And Advair, the risk difference was slightly negative. Based on a post hoc analysis, differences between these four drugs was not statistically significant, and that's that p-value .307.

Now, it's a forest plot, but now broken down by the comparison groups. The first comparison group is LABA without randomized ICS versus no LABA.

The second comparison group is LABA with randomized ICS versus randomized ICS. In both cases, the risk difference estimate was greater than zero. For the LABA without randomized ICS, the confidence interval did

not contain the value of zero. Again, a post hoc analysis showed that the difference between these two comparisons was not statistically significant. And that's that p-value .339.

We examined whether the increased association of events occurred -- at what time period did that occur -- early in the trial, late in the trial. And here, we looked at that two ways. One through a life table approach and one through a Kaplan-Meyer approach. First I'll show the life table estimate. Here, you have four periods of time starting from randomization or starting from initiation of treatment. Roughly four periods of 90 days from 0 to 89, 90 to 179, up to a year. The last one is slightly longer -- six days longer -- to include the remaining events that were observed.

For each of these periods -- well, for three of these four periods, the hazard of the asthma composites endpoint was higher

in the LABA group than the no LABA group. Here, .11 versus .08. So for three of the time periods -- the first, second, and fourth -- the hazard was higher in the LABA group than the no LABA group.

You could look at this in terms of a Kaplan-Meyer incident curve. The top curve is the LABA group. The bottom curve is the no LABA group.

And it's over a period of about a year. And you can see throughout the year the two curves are generally spreading apart, so the increased rate of events in the LABA group seem to occur throughout a year, which is what we have data on.

Some sensitivity analyses. This is the asthma composite by drug risk difference estimates, but excluding SMART. Now, SMART was a Serevent trial, so excluding SMART only affects the Serevent estimates. Excluding SMART actually increased the risk difference estimate for Serevent and increased the risk

difference estimate overall. SMART actually had a lower differential rate of hospitalization than the other Serevent trials.

Other sensitivity analyses, including the exact odds ratio which examines statistical properties, and the generalized linear mix model, which examined trial heterogeneity, did not show any deviations from the overall result.

Now I'll talk about subgroups. First, age subgroups. Again, here's a forest plot. The different rows represent the four age subgroups -- 4 to 11, 12 to 17, 18 to 64, and 65 and up. What you can see by this forest plot is that there's a clear trend that the lower age groups are at higher relative risk compared to the older age groups. There's a clear trend here.

And again, a post hoc analysis actually did demonstrate that there is a linear effect in this effect across age

groups. And the p-value there was .081.

I'm going to look at this effect by the four individual drugs. It was actually seen in three of the four drugs. First, Advair. It was not seen in Advair. In fact, Advair had the reverse situation, where the oldest age group, 65 and up, had the largest risk difference estimate.

For Serevent, the trend is very similar to the overall results, which is not surprising, because Serevent makes up a large majority of the data. For Foradil, although the dataset is quite a bit smaller and the estimates quite a bit more variable, I think the trend is relatively clear, with the youngest subjects at higher risk -- higher relative risk compared to the older subjects.

Symbicort, because it's not approved for age 4 to 11, there's no subjects in this first age group. The 65 and up did have subjects, but there were no events, so we couldn't calculate a confidence interval,

but the estimate falls on zero. And for the limited amount of data available for Symbicort, the age trend might exist as well.

Here's the asthma composite by race subgroups. The Black African-American subgroup had the highest risk difference estimate. This was seen in SMART, and SMART represents a significant amount of the subjects in this meta-analysis, so perhaps it's not surprising. This next plot shows the results without SMART -- excluding SMART. And although the estimate for the Black African-American subgroup is lower than with SMART, it's still the highest among the racial subgroups considered.

Here is the asthma composite by gender subgroups. The female subgroup had a somewhat larger risk difference estimate than the male subgroup. What's interesting about this is this was seen in each of the four drugs -- this difference between genders. For other subgroups, there were no noticeable

differences among subgroups based on location, nominal treatment, duration, and baseline ICS use.

I'll now discuss the limitations of this meta-analysis, and some comparison with other meta-analyses. First of all, the trials using this meta-analyses were not generally designed for the present purposes. The endpoints that we're analyzing were not systematically collected. The events were identified and adjudicated post hoc. Information on subjects in trials are limited in the meta-analysis.

We did not collect information on dropout, so it's possible a differential dropout rate might explain some differences. However, as I showed you earlier, the treatment durations between the LABA and the no LABA group were very similar, so we don't expect there's a large difference there.

We collected information on concomitant ICS use, whether it was used or

not, but we weren't available -- information on the amount of ICS use or the specifics of the ICS use was not available.

The SMART results were known prior to the design of this meta-analysis, so it's not surprising a lot of the results we see in SMART are confirmed -- are seen in this meta-analysis. However, the sensitivity analyses that excluded SMART did not show any major deviations without SMART. And again, there were many comparisons performed on this meta-analysis, so there's exploratory and multiple testing issues.

Now I'm going to discuss three other meta-analyses, mainly not to summarize these meta-analyses, but to compare how they compare to the FDA meta-analyses so you can understand the similarities and differences.

In parentheses are the drug that the meta-analyses considered. There's a correction to the slides that you were distributed. In those slides, I had Advair

under Bateman, but it's really salmeterol plus ICS. Both the Advair combination product and separate products -- separate inhalers.

So the Bateman considers salmeterol plus ICS. Saul Peter discussed salmeterol and formoterol, and Sears (?) was based on formoterol. First I'm going to discuss the Bateman meta-analysis. Again, the drugs under evaluation were salmeterol plus ICS. The comparison was salmeterol plus ICS versus ICS. This comparison does not include SMART since SMART was a placebo-controlled trial. So SMART is not in the Bateman analysis.

The ICS did not have to be the same drug or dose within a trial in this comparison. Salmeterol had to be an approved dose, but I don't know about the ICS. And the results for asthma hospitalization, the risk difference was .2, with a confidence interval from -.1 to 2.3 per 1,000 subjects. When you compare that to the FDA

meta-analysis for asthma hospitalization, only Advair, which is slightly more narrow, the risk difference was -.15 minus 2 to 1.7. The confidence intervals were actually very qualitatively similar. So there's actually a good agreement between the Bateman and the FDA meta-analysis, at least when it comes to Advair.

Now, the Saul Peter meta-analysis. They considered the drug formoterol and salmeterol. The comparison was LABA versus placebo. This would include SMART. Non-approved dosages were included.

The results for asthma hospitalization of LABA versus placebo in terms of an odds ratio was 2.6, with a confidence interval from 1.6 to 4.3. I don't believe SMART is actually included in this outcome.

And this compares -- it's relatively similar to the comparable FDA results for asthma hospitalization of the

LABA versus no LABA, which is 1.3, with a confidence interval from 1.1 to 1.5. It's slightly lower here, but it's actually relatively qualitatively similar.

Finally, the Sears meta-analysis -- this is based on the AstraZeneca safety data -- considered the drug formoterol. The comparison was formoterol with and without ICS versus ICS and other no LABA treatments. All this was pulled together, where with and without ICS was combined. Trials may not have had a non-LABA control, and non-approved dosages were included in the Sears analysis.

Let me -- since the Sears analysis differs so much in terms of number of subjects than the FDA analysis, I'm going to explain how you get from roughly 60,000 subjects in the Sears analysis to the 1,270 for the FDA analysis of Symbicort. First of all, we did not compare trials -- specific trials -- so the details are not known. I

just know that 34,000 subjects were submitted to the FDA based on our inclusion criteria.

Thirty thousand of the Sears analysis probably came from trials with only LABA arms -- no non-LABA comparisons. In the Sears paper, these are described chiefly as Symbicort versus Symbicort trials.

So that brings us mainly down to the 34,000 that were submitted to FDA. From those 34,000, 31,000 were removed because they were unapproved dose or product. So that brings us down almost all the way now. 256 subjects had no comparison in the comparisons that we defined. 807 subjects had an age less than 12, so they're not approved for the drug and were excluded based on the FDA inclusion criteria. And 362 subjects had to be removed because of data limitation in how we asked for the data. They came from a single trial and there were no events in that trial.

Finally, the conclusions. Overall,

there was an effect of LABAs on each of the asthma-related endpoints -- asthma-related death, asthma-related death or intubation, asthma-related hospitalization, and asthma composite, which is made up of the death, intubation, and hospitalization.

For the asthma composites endpoint, the risk difference was 2.8, with a confidence interval from 1.1 to 4.5 per 1,000 subjects. Three of the four drugs had adverse signals, but the sample size varied substantially among the drugs.

Differences among the drugs were not statistically demonstrated. And observed differences may be related to trial or subject differences.

LABA with defined ICS appears to have less adverse effect; however, the difference was not statistically demonstrated.

The effect was dominated by Advair, which supplied most of the data for this

comparison. There is an apparent age effect with the youngest at greatest risk. And I talked about the limitations of the meta-analysis, including the ascertainment of events, the limitations on information available, and its exploratory nature.

And finally, there was an agreement or at least resolution among the three meta-analyses that I discussed.

Thank you.

DR. SWENSON: Thank you, Dr. Levenson. It's now 12:15, and so we're right on schedule. I know there's more questions and they'll just have to be retained, and we'll have chances later today and tomorrow.

So we'll meet back again at 1:15. And just a reminder to the Committee members that discussions of the subject matter at hand should not occur during lunch. It should be within this forum.

(Whereupon, at approximately 12:15 p.m., a luncheon recess was

taken.)

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

(1:15 p.m.)

DR. SWENSON: We'll resume, but slightly departing from the schedule, because there's still a number of questions that have been percolating. We'll spend about the next 10 minutes with questions directed to our last two speakers. So if you'll identify yourselves, then we'll go ahead and get started.

I think I see Dr. Goldstein there.

We'll start with you.

DR. GOLDSTEIN: Is Dr. Levenson back? Is Dr. Levenson back yet?

DR. SWENSON: I don't know. Dr. Levenson? He's coming.

DR. GOLDSTEIN: Thank you. I have two quick questions. One is that in the meta-analysis study design, was the study design done prospectively? In other words, were the inclusion and exclusion criteria and the statistical analysis plan, et cetera, proscribed prior to requesting data from the various

companies?

And then my second question was that you mentioned an effect both in age, gender, and race. Was that a composite effect as well? In other words, if you were a 4-year-old black female, was that analyzed to see if that was the ultimate risk?

DR. LEVENSON: The first question about the prespecified plan, the data requests were initially made in March, which specified some inclusion criteria. The final statistical analysis plan was not done more until the June time frame, before we actually got the data. So the request was out there before the analysis plan was finalized -- but before we got the data, the plan was finalized. There were some deviations from the plan that are noted in the briefing package. We weren't able to look at everything we wanted to look at because of limitations in data.

You know, there were a lot of missing values for certain variables. We

wanted to look more at baseline asthma control.

The second question about perhaps an interactive effect between the risk factors, no, we did not look at that. We didn't look at interactions between the demographic variables.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: In your presentation, you showed a slide on the median duration of the treatment. And it was interesting that the median duration for Advair was barely more than half of the median duration for Serevent. And then on the Kaplan-Meyer curve, you show very nicely that as a function of time out there, the risk gets progressively more. It looks like it may be about twice as much at a couple hundred days than it is at 100 days.

So the question is, was it possible to do any kind of analysis with Advair since one explanation could be that since the median duration of treatment was shorter,

that that in and of itself independent of the drug could have made it look better?

DR. LEVENSON: Yes. I actually did do these curves by drugs, but I do not have them available. But you're right. The observation that some of this data towards the longer time points may be more dominated by Serevent is probably a correct observation. I do not have the information handy, and I don't recall the results.

DR. WOLFE: If you could maybe send it. I'd like to see it.

DR. LEVENSON: I should be able to get those to you.

DR. WOLFE: It's certainly a confounder based on your Kaplan-Meyer analysis.

The time.

DR. LEVENSON: Yes.

DR. WOLFE: Thank you.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I have a question for Dr. Mosholder but I don't see him in the room.

Is he here?

SPEAKER: No, he --

DR. HENNESSY: Okay. When he comes back, I have a question for him.

DR. SWENSON: Dr. Newman is next.

DR. NEWMAN: Yes, I had one for Dr. Mosholder as well, but I do have a follow-on question for Dr. Levenson. In terms of -- I know you had written in what we received that you did not have access to the baseline control data and the baseline severity data. I'm wondering if you can just elaborate on how that -- how you consider that in terms of limitations of the work that you're presented. And I'm also curious why you wouldn't have that information, because I would think that information exists.

DR. LEVENSON: We had some of that information, but when we do these meta-analyses, we have to come up with a somewhat unified data request that will cover hundreds of trials. So it's hard to find characteristics that are

uniformly collected across all these trials. So we tried to collect some, but it turned out there were a lot of missing information.

In terms of baseline asthma control, I can only comment on what I read. It could be -- I mean, the editorial on SMART could be a factor why results differ across different trials. And I think that does make SMART unique in that it's different. It's real world. It may be more relevant or less relevant, but it's unique. So the baseline asthma control is something I think that would be of interest, and is a limitation that we did not have more information on it and were able to analyze it.

DR. SWENSON: I see Dr. Mosholder is back up. I think we had -- Dr. Hennessy, did you have a question for him?

DR. HENNESSY: I do. Dr. Mosholder, on your slide -- 33 I think it is -- you show that only 11 percent of long-acting beta use is consistently together with an inhaled

corticosteroid, but your slide 27 appears to show that of all the long-acting beta agonist use, the vast majority of it is the combination product Advair. And I'm wondering how those two things can both be true.

DR. MOSHOLDER: Yes, the data from the managed care organization was looking at the question of single entity LABA products, mainly Serevent and Foradil, and how many were co-prescribed -- or how many patients got concomitant prescriptions for an ICS as a separate device. So I think that's -- does that answer your --

DR. HENNESSY: Sure. So if I'm interpreting correctly, the very low lines at the bottom of the single agent use, relatively little of that is in combination with an inhaled corticosteroid, but if you look at all the long-acting beta use, it looks like the majority of it is in combination with an inhaled corticosteroid and the combination product.

Is that right?

DR. MOSHOLDER: Yes, by virtue of the fact that the inhaler itself is a combination; therefore, of the total universe of LABA use, most is coming with an inhaled corticosteroid. But if one drills down on use of the single entity inhalers, we found only about half were being prescribed with a concomitant separate ICS inhaler.

DR. HENNESSY: Thank you.

DR. SWENSON: We have time for just a few more.

Dr. Zito?

DR. ZITO: Yes, I have a question for Dr. Mosholder. I appreciate your presentation around the limitations of observational research studies. But at the same time, I would wonder that we are not taking full advantage of community-based information on practice patterns, for the reason that trial data often do not generalize to the populations that we are seeking to bring to treatment. And if we are to do a reasonable job of benefit to risk

assessment for future use, I would think that we would like to take advantage of the racial ethnic information that's available in the Medicaid population, which represents 40 percent of the children now -- the pediatric population -- if we include the S-CHIP kids, for example.

And in addition, that we are now able methodologically to look across time so that we can see the length of duration of the use of monotherapy versus the combination, which is a big question here. And then finally, that we could begin to think about looking at subgroups of kids who have other problems that would suggest that they are using -- that will tell us that they're using medications that increase the risk burden for severe adverse events.

DR. MOSHOLDER: Well, I guess by way of reply, I'd just say when I looked at the observational studies, I was really focusing on their value in determining the risk of -- the

intrinsic risk of the product. And because of the methodological issues, for example, it appeared that LABAs were going to a somewhat different patient population in practice than comparative drugs. And it was very hard in the studies to account for that.

One way that people have attempted to adjust, say, for asthma severity is to look at asthma hospitalization. Well, the problem is, as we've seen, if asthma hospitalization is itself associated with LABA use, then the jargon is you're adjusting for something that's in the causal pathway, and that you'll get maybe a bias.

So because of all those limitations, just for the purpose of looking at the intrinsic risk of the products relative to comparative groups, that was the nature of the limitations.

DR. SWENSON: We have Dr. Martinez next.

DR. MARTINEZ: Thanks. This is a

question for Dr. Levenson based on Dr. Mosholder's presentation. In his slide 17, he proposed to us some interesting interpretation of both SMART and SNS, which is that the effects seen for asthma death and intubation is much stronger than the effects seen for asthma hospitalizations. If I understood correctly what he was implying was that perhaps there's something specific about the individuals who die of asthma or need to be intubated. In other words, have very severe attacks with respect to those who have less severe manifestations.

And I think also what he was trying to imply was that if the explanation that has been given for this effect, which is that individuals were taking separate canisters of these two medicines, stopped taking the inhaled corticosteroids when they're taking the canister that they feel is effective for their disease, which in this case would be LABAs, then why would the effect be only seen

for asthma deaths and not for asthma hospitalizations? You would also see an increase in asthma hospitalizations. So in that respect, my question for Dr. Levenson is, did you see the same trend when you analyzed the data as a whole? In other words, for the effect to be stronger with asthma deaths and intubations than when they were with hospitalizations? And therefore, if that is true, would the compound outcome that you have selected underestimated some of the most severe effects?

DR. LEVENSON: In terms of the risk difference, the largest effect was seen in hospitalization. But that, of course, in terms of odds ratio, the story may be different. And I don't have that information available now. I can get you that.

DR. MARTINEZ: Because also, the number of events is much larger.

DR. LEVENSON: Right. Yes. So I'll have to look at some notes to see what the trend

is in terms of like a relative measure.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I just wanted to just sort of quantify this. My sort of brief calculations of this that the number needed to harm for patients taking the combination of -- you know, taking both an ICS and a LABA is -- the number needed to harm is about 4,000. Is that right? That's what I think your estimate was.

SPEAKER: Yes.

DR. SCHOENFELD: But that's per year. And the other estimate seemed like about the same. Am I close there? Or did I--

DR. LEMANSKE: Which presentation are you referring to?

DR. SCHOENFELD: Well, both presentations. Your -- the first presentation, I think that was the number. It was .25 and then you would multiply -- it would be roughly 1 in 4,000. In your presentation, you had several estimates but -- and you have to multiply by two

because most of the patients only were treated a half a year. So it would be something like 1 in 4,000. Maybe you didn't calculate that.

DR. LEMANSKE: I didn't calculate number needed to harm in my analysis.

DR. SCHOENFELD: Am I right in the first presentation, that that would be about 1 in 4,000 for people taking concomitant ICS?

DR. LEMANSKE: People taking -- oh, actually, I don't think I did the number needed to harm for that. That was the odds ratio of 1.5. I didn't derive the number needed to harm from that odds ratio. I think you're talking about whether the conquering group combined the two trials.

DR. SCHOENFELD: I'm just trying to get a notion of what the risk estimate is for that subgroup.

DR. LEMANSKE: If you take the 1.5 point estimate, it's 50 percent increase, which you want to derive the number needed to harm from that, but I haven't done that.

DR. SWENSON: Well, I regret to say that we have to keep on schedule here. I apologize for the number of questions I know are out there. But we'll move on now.

Dr. McMahon from the FDA will speak.

DR. McMAHON: Good afternoon. I would like to thank the Committee for their participation and input on this important public health matter: the benefits and risks of long-acting beta-2 agonists for the asthma indication.

My name is Ann McMahon, and I will be giving an overview of benefit/risk issues before the Committee on the subject of LABAs from a perspective in CDER's Office of Surveillance and Epidemiology. I am the acting director of the Division of Pharmacovigilance II and have been working on post-marketing surveillance at the FDA since 2002. I'm a pediatrician.

My purpose in this brief

presentation is to discuss the risks of long-acting beta-2 agonists for the asthma indication; to discuss the benefits of LABA use for the asthma indication; and to pose questions of benefit versus risk.

I will start by giving a brief background of LABAs for asthma indication, followed by a presentation of the highlights of the FDA meta-analysis aimed at summarizing the risks. Then the pivotal studies reviewed by the FDA in drug approval will be discussed, highlighting documented benefits of the drugs.

Thereafter, there will be a discussion of weighing the risk and benefits of LABA use for the asthma indication as a whole and in population subsets. This will be followed by conclusions, recommendations, and a brief presentation of the questions for the Advisory Committee, although those will be in your packet and won't be read at this presentation.

This slide briefly outlines the approved long-acting beta-2 agonists for the asthma indication in the United States. This information was reviewed by Dr. Seymour this morning, and I will refer you to her slides.

I think that's probably my Blackberry. Try not to forget it; okay?

The Serevent Nationwide Surveillance study, or SNS from the United Kingdom, and the Serevent Multicenter Asthma Research Trial, or SMART from the United States, both were randomized controlled trials and were discussed at some length this morning.

This slide simply is a reminder of some of the key outcomes. Notice in the column farthest to the right, in both trials, there was an elevated relative risk in the three to four range of deaths from asthma in salmeterol-treated patients as compared to controls.

OSE reviewed a number of

meta-analyses, summarizing a variety of outcomes with LABA use for the asthma indication. We notice that only a subset of those trials designated a mean or median trial duration, and all of those had a trial duration of at least three months. Those three are shown in this table.

There are many others shown in the similar table in the OSE review which you have in your background package. Two of the three in this table included children and adults and compared formoterol and/or salmeterol to placebo and/or salbutamol. Those are the first two, by Kates and Saul Peter as primary authors. The third by Bateman et al. compared Advair or Salmeterol plus ICS with ICS.

Note that where available in the righthand column, the odds ratio of asthma exacerbation was higher, though not statistically significantly so, in children than in the overall population. Also, the

odds ratio for asthma exacerbation with Advair overlapped one, as we've been hearing about this morning, but the upper end of the confidence interval approached two. Therefore, this subset of meta-analyses underlined the risk of salmeterol and formoterol as single agents, and bring out the following questions. Are children at higher risk than adults for severe asthma-related events with LABA use? And two, what role, if any, in risk mitigation is played by inhaled corticosteroids?

I will now review brief highlights of the FDA meta-analysis of the data related to risks of LABA use, performed and presented by Dr. Mark Levenson this morning -- presented this morning, that is.

As was outlined by Dr. Levenson, the meta-analysis of data submitted by sponsors was performed by the FDA. There were approximately 60,000 patients included in the meta-analysis, and approximately half

of those received a LABA. The majority of the patients received Serevent; many of them from the SMART study. Most of the patients included were adults, though there were approximately 10,000 children and adolescents, and approximately 4,000 older individuals included.

The risk difference, as you heard in Dr. Levenson's talk, is essentially the attributable risk, and was measured by the incidence of the adverse event in the group that received a LABA minus the incidence of the adverse event in the comparison group. A risk difference of zero, shown by the dotted line in the middle -- a risk difference of zero, indicated by the dotted line in the middle, shows risk neutrality.

Overall, combining data for all the drugs, the youngest patients showed the highest risk difference, and this risk difference decreased with increasing age. In fact, the FDA meta-analysis showed a

significant age trend in the endpoint of asthma composite index, which included, as Dr. Levenson said, asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations, but was driven by asthma-related hospitalizations. It showed a significant age trend in the asthma composite index, with a p-value of 0.018, which was mostly driven, as I said, by asthma hospitalization.

This slide shows the risk differences for the asthma composite index for the drugs that include salmeterol as their active LABA component. In this case, Advair, which has an inhaled corticosteroid as the other active ingredient, has a risk difference which was essentially zero. This differs from Serevent, which was significantly elevated -- had a significantly elevated risk difference. Note also that the pediatric data for Serevent do show an elevated risk difference compared to the data

in older individuals; whereas for Advair in a small subset of 400 or so individuals over 65 years of age, there was actually an increase in the risk difference.

This slide shows the two drugs with formoterol LABA component. Note that there are no data for children less than 12 years of age for Symbicort in this analysis. On the other hand, there were less than 500 children and adolescents in the meta-analysis that received Foradil. Notice that overall, there was an elevated risk difference for patients receiving both Foradil and Symbicort, although the confidence intervals did not -- the confidence intervals both did overlap zero.

I will now briefly review some highlights of the efficacy endpoints in pivotal trials of U.S.-approved LABAs for the asthma indication. I will talk separately about each of the four main LABAs approved for the asthma indication, and will divide my

comments into those related to pediatric versus adult data. This slide is busy and is meant for reference. It is a sample of data from the pivotal trials highlighting the efficacy of Serevent. Notice that there was a significant increase in peak expiratory flow rate, and the secondary endpoints show some clinical improvement with Serevent compared to albuterol, depending on baseline and other details.

Notice that, for example, 0.6 less puffs of rescue medication per day might or might not have a large clinical impact. Note that in these studies, the percent of asthma exacerbations were no different in the Serevent versus albuterol group.

Again, this table has many figures and is for your reference, but please note that although the spirometry measures were significantly improved for Serevent compared to placebo in 4- to 11-year-old children, the secondary endpoints in children show little

difference in the treatment group compared to placebo. Note that during two weeks post-treatment, there was a 10 percent net increase in asthma exacerbations in the Serevent group compared to placebo.

In summary, in patients over 11 years of age comparing salmeterol with albuterol, the primary spirometric endpoints were met. The change in percent nights with no symptoms and change in percent days with no symptoms favored salmeterol by 10 to 20 percent, but all other symptoms measured in secondary endpoints showed little difference between salmeterol and albuterol, or favored albuterol in the case of change in percent with asthma exacerbations.

In children 4- to 11-years of age receiving salmeterol compared to placebo, the primary spirometric endpoints were met, and there was little difference in the asthma symptoms score, but other secondary endpoints measured showed slightly less asthma

symptomatology in salmeterol-treated patients.

So on to Advair. This slide again is busy and is meant for reference. It is a sample of data from a pivotal trial highlighting the efficacy of Advair Diskus in individuals over 11 years of age. Notice that there was a significant increase in FEV1, and the secondary endpoints show some clinical improvement with Advair compared to fluticasone, depending on baseline and other details. However, 4 percent more awakening-free nights most likely does not have a large clinical impact from a baseline of 90 percent.

These are summary points regarding Advair efficacy. In individuals greater than 11 years of age comparing Advair and fluticasone, all three primary experimetric endpoints were met. Notably, the change in 12-hour under the curve FEV1 was higher at one week than at 12 weeks. Notably, for the

secondary endpoints, both change in percent symptom-free days and change in percent days without rescue medication showed approximately 20 percent increase, which, depending on baseline and other clinical parameters, may have a large or less large impact. In children, there were clinical data on Advair collected for children that were presented by Dr. Seymour this morning, and data for approval in children were extrapolated from adults.

This is another slide to give you a sense of the clinical data in some of the pivotal trials for -- in this case, for formoterol compared to albuterol. The FEV1 endpoint was met, but the secondary endpoints do not appear to correlate with the FEV1 endpoint and extent of improvement.

This is an example of a pivotal trial of a LABA -- in this case Foradil -- that was performed -- the trial performed in children 5- to 12-years of age.

Here, Foradil is compared to albuterol, and showed spirometric significant improvement in subjects receiving Foradil compared to albuterol. This slide shows that in light of the baseline data presented, most if not all of the secondary outcome measures amount to arguably minimal clinical improvement in children.

Review of the pivotal trials for the Foradil products in patients greater than 12 years of age showed that the two FEV1 endpoints were met, and FEV1 was significantly greater in patients receiving Foradil compared to albuterol. The secondary endpoints of percent nights awakened and percent nights using rescue medication were both lower in Foradil-treated patients than albuterol-treated patients, though the decrease was less than 20 percent.

In all other secondary endpoints, there was a small difference in the Foradil recipients compared to albuterol. In

children 5 to 12 years of age, the two primary spirometric endpoints again were met, and none of the secondary endpoints, however, showed large difference in the Foradil compared to the albuterol group or placebo.

Another busy slide again for reference, this time showing an example of data from a pivotal trial for Symbicort in individuals over 11 years of age. Here, comparing Symbicort with Budesonide. Notice again that this LABA is an effective bronchodilator. But given the baseline values, the improvements in the various secondary endpoints are likely not to be very clinically significant.

For example, a difference of 10 percent or a total of 40 percent rescue medication-free days compared to a baseline of 30 percent may or may not be terribly clinically significant.

Here, I will summarize the pivotal trials comparing Symbicort and Budesonide.

In patients greater than 11 years of age, the primary spirometric endpoints were met. There was very little, if any, difference between Symbicort and Budesonide in the secondary endpoints, including change in percent nocturnal awakening, but there was some improvement over Budesonide in change in percent rescue-free days, a net of 10 percent increase, and change in percent with exacerbations, a decrease of 14 percent. There was no data reviewed on individuals less than 12 years of age.

This slide summarizes overall comments from efficacy endpoints for pivotal trials of U.S.-approved LABAs for asthma. Some measure of forced expiratory volume 1, or FEV1, was the primary endpoint in all of the U.S. studies. In all of the studies reviewed, there was a statistically significant increase in some spirometric measure compared to either placebo or albuterol or an individual component product.

Some degree of response to a short-acting beta agonist was required for enrollment. That's a parenthetical comment. And in adults, the largest clinical differences between LABA and comparator were approximately 1.5 -- sometimes a little more, sometimes a little less -- of rescue medicine per day, or 15 to 20 percent more symptom-free days in the LABA versus comparator group.

Although the pediatric studies met the spirometric endpoints, there was little improvement over comparator in the secondary endpoints for children less than 12 years of age. Adolescents were not assessed separately; thus, an analysis of this group of patients with respect to LABA benefits is not possible here.

So some considerations for risk versus benefit. The first comment to be made is spirometric endpoints were consistently met in the LABA pivotal trials. Data

reviewed did not suggest large benefits on secondary endpoints, especially in children less than 12 years of age. Efficacy trials not powered to study were not powered, as has been mentioned this morning, to study more quality of life endpoints. And it was difficult to assess age-specific benefits because the numbers were small in the pediatric and elderly populations, although I haven't mentioned elderly much.

With respect to risk, the age of the recipient may have had a large impact on the risk/benefit ratio. Specifically, there was a trend of decreasing age -- decreasing risk with increasing age -- that was present overall in the FDA meta-analysis. Data reviewed do not suggest large secondary benefits, especially in children less than 12 years of age. Additionally, drawing distinctions between LABA drugs was not possible, at least in part due to small sample sizes.

So our conclusions based on these observations are that these data substantiate and quantify an increased risk overall in serious asthma-related events with the use of LABAs compared with non-LABA therapy for asthma. Children appear to be at greater risk of the adverse effects of LABAs than adults. LABAs have a consistent effect of improving spirometric outcomes. And data reviewed do not suggest large secondary benefits, especially in children less than 12 years of age.

Correlation of spirometric endpoints with clinical benefits was not clear.

The LABA Safety Review Team within the Office of Surveillance and Epidemiology shared most conclusions and recommendations, and agreed that there is a signal for asthma-associated morbidity and mortality in adults; that that signal is largely from the SMART and SNS studies, which as you know were

performed using a single entity LABA salmeterol.

It is unclear what role inhaled corticosteroids play in mitigating LABA-associated risk; that there is an age effect, such that the risk of age-attributable asthma-associated hospitalization anyway is increased in children; and the extent of increased risk of LABA use for other demographic subsets among adults is less clear.

Therefore, the team unanimously recommends withdrawing the asthma indication from LABAs for individuals less than 18 years of age, and removing the asthma indication contraindicating the use of single entity LABAs Serevent and Foradil for all ages.

There was a point of disagreement among OSE reviewers on recommendations, which was whether to recommend removing the asthma indication for Advair and Symbicort for adults.

I'd like to thank the individuals who have helped with this presentation and analysis. As I mentioned, I will not read through the questions, but they are in your handouts for your reference and we'll be talking about them tomorrow.

That concludes my comments.

DR. SWENSON: Thank you, Dr. McMahon. Next, Dr. David Graham will continue this discussion.

DR. GRAHAM: Good afternoon. I'm David Graham with the Office of Surveillance and Epidemiology, and during the next half hour or so, I would like to talk about public health considerations in weighing benefits and risks, and particularly as it pertains to LABAs.

This is important because FDA is a public health agency. We are part of the Public Health Service. Decisions that FDA makes are at a population level. They are to be directed at the entire population and not at the level of the individual patient. And

so that's why it's necessary to now move from the level of clinical trials and individual patients up to a little higher altitude, where we're going to look at the population and what is it we're doing with benefits and risks.

This is a rough outline of the talk. What I'd like to talk about first is that in the approval process and in the assessment of safety post-marketing, that there is an asymmetric handling of benefit and risk, and that that needs to be considered when weighing population effects. I also will discuss how the uncertainty created by low power to exclude high levels of asthma mortality risk with the non-Serevent LABAs is critically important to the consideration of this committee.

I'll use Foradil pivotal trials as an example to illustrate the pitfalls of low statistical power. I'll then summarize the evidence addressing the presence or absence

of important clinical benefits with LABAs, and then contrast the decision-making paradigms in controlled trials at the population level in the public health arena.

We'll then move to focus on Advair, its health benefits and its mortality risks. Why? Well, as you saw from Dr. Mosholder's presentation earlier, Advair dominates the market -- the LABA market now. It has the largest population exposure.

It has the most data to work with. I'll show that the problems of asymmetric power exist, and raise the question for consideration by this committee, which is, is the absence of proof proof of absence? Is the absence of proof of harm -- the definitive proof of harm -- proof that there isn't harm? And what kind of decision should be made as the basis of that?

The current drug approval paradigm, and the way safety is handled and efficacy is handled post-marketing, is that pivotal

trials are powered to show efficacy. There's a prespecified value of what qualifies a success. There's a null hypothesis that states the drug doesn't work. It's something that can be tested and rejected. We set the Type I error, which is the probability of finding a difference if there isn't one -- given that there isn't one -- at 5 percent. And we do that to minimize false positives.

This is sometimes referred to as the regulator's risk, because the regulator doesn't want to falsely approve a drug that doesn't work. And that's maximally protective of the public, because there's an opportunity cost if we approve a drug that doesn't work and there's another drug out there that does and I happen to take the drug that doesn't work. Well, you can see the opportunity cost.

Now, there's also a prespecified Type II error, the beta, which is the

probability of failing to find a difference given there is one. The purpose of this is to minimize false negatives. And this is sometimes referred to as the company's risk, because the company wants to be sure to find an effect if there is one, because that'll be the basis for approval. So typically, the power to find the clinical effect they're looking for is in the range of 80 to 90 percent.

Now, statistical tests are then used to reject the null hypothesis, either p-values or the lower bound of the confidence interval, excluding the null. And that's illustrated in this slide, where here we have a p-value that's below .05. The confidence interval does not include the null effect level. The null hypothesis is rejected, efficacy is demonstrated, and FDA-approved. If the confidence interval or the p-value don't show significance, the null hypothesis is not rejected. So then the conclusion

really is the drug doesn't have efficacy, at least operationally, because the drug isn't approved.

Now, under the current, paradigm we have asymmetric handling of safety and efficacy. The pivotal trials, as I'm sure you know, are not powered to demonstrate safety or exclude harm. Well, let's examine that in a little more detail. There's no prespecified value for safety, so what is a safe drug? What qualifies as success to show that I have a safe drug? What level of serious harm is acceptable in exchange for the prespecified value of efficacy? And do the pivotal trials exclude this prespecified level of risk -- of acceptable harm, if you will. Well, the studies aren't designed to do that, and so those things aren't tested. The null hypothesis is the drug is safe rather than the drug is harmful. Why is there an a priori presumption of safety? I think -- I don't have an answer for that, but

it is an inherent bias in the way the drug approval process works.

Now, a question I would ask is why aren't drugs presumed a priori to carry some specified level of unacceptable risk which I can then test? And if I can reject that level of unacceptable risk, then at least I sort of have capped the level of risk that I'm dealing with, and I can say as far as we're able to say, the benefits that we know about exclude the risks that might exist because we capped the risk. We know it's no greater than a particular level. But that's not done. It hasn't been done with these drugs; it hasn't been done with any drug that FDA has ever approved.

Now, further, when we come to the post-marketing setting and we're talking about harm, FDA has insisted on a standard of definitive proof in order to reject its presumption of safety. This was the standard that was used in the past recently with

Avandia and Actos. And as I'll show you in a minute, it was also the standard used in the original approval of SNS -- of Serevent in light of the SNS study.

Now, in looking at safety, there's no attention to the Type II error to minimize false negative conclusions of safety. As we showed before, the typical beta to show harm is very high, which means that the power in a typical clinical trial to even cap the risk at a particular level is below 50 percent; whereas the power to show the effect they want is 80, or 90, or 95 percent.

So again, then there is a focus on p-values and the confidence intervals and we get the same situation. It's the same slide, but now, it's applied to safety rather than efficacy. And in this situation here, we're looking at a harmful effect. And if the p-value is less than .05 and the confidence interval doesn't include the null effect, we will say that we have definitive proof of

harm and the risk is real. If, on the other hand the p-value is greater than .05 and that confidence interval happens to go down below the null effect level, the null hypothesis of safety isn't rejected.

Harm hasn't been proven definitively, and so then the risk operationally isn't real because the drug continues more or less to be used the way it was before.

So we end up then with a situation that's a little bit difficult to deal with. We have a double standard. And at the time of approval, but especially post-marketing, it becomes more important to address this in a realistic way, especially where we know that one of the drugs we're talking about is beyond doubt lethal to some patients -- that it carries an increased mortality risk. And in a population level as I'll show you in a few minutes, that could be quite substantial.

So this slide summarizes then when

we compare efficacy and safety, are we evidence-based or is the deck really stacked in favor of the drug and against finding harm? We have the a priori presumption that the drug doesn't work and it can be tested; an a priori presumption that the drug is safe and that can't be tested. You go down here to the randomized trials, and you'll find out that where we're talking about the probabilities of false positive and false negative conclusion, that they're the opposite.

I now want to focus your attention on the SNS study, which as Dr. Seymour told us earlier, was available to FDA at the time that Serevent was approved. This is from the original BJM article. I've blown it up here. Relative risk of 3. The p-value was.1. This is what the confidence interval was on that: .7 to 28. FDA looked at the p-value and said it's not statistically significant. And so if you look at the label when Serevent

was approved, there's no mention whatsoever of asthma mortality.

They didn't look at a potential for a 28-fold increase in asthma mortality, which these data are consistent with. And what I would argue is that for an evidence-based rational benefit/risk weighing, one has to have a benefit that you know about that would exceed the risks that you can be certain about. In this situation, we can't be certain that the risks are not as high as 28.

So a few more things about SNS and SMART. They've been talked about by several speakers before. One point I think that hasn't been mentioned was that although inhaled corticosteroid therapy wasn't monitored during the studies, it was captured at the start of the study. And in the SNS trial, about 70 percent of patients were taking inhaled corticosteroids at the time of randomization. In the SMART study, I think it was about 30 or 40 percent.

What I want people to see in this slide is that although these studies were done 10 years apart, opposite ends of the Atlantic Ocean, that they found almost identical attributable risks. About 17 per 10,000 per year -- and this is for asthma mortality -- with a combined relative risk of about 4, with an upper bound of about 13.

Now, if you take that attributable risk, you can use the drug use data that we have and you can estimate what the number of asthma deaths could be based on that attributable risk in the population.

Dr. Mosholder earlier showed us the prescription use of Serevent and Advair and all the other LABAs. And so for the years 1994 to 2004, if we just focus on Serevent, where we have the SMS and the SMART data, there's over 5,000 deaths that are likely to have occurred in the United States as a result of that. That would account for about 10 percent of all asthma deaths during that

11-year period.

Now, if that same risk applies to all LABAs used in that time period, then we're talking about 9,000 total deaths. Now, for the period 2005 to 2007, the last three years where we have data on drug use, the Serevent number of deaths that are attributable to it are low. But as you saw in the drug use data, the use of Serevent as a single entity product has fallen quite dramatically, but it's been replaced by the use of Advair, which is three times as high as what the highest use of Serevent ever was. And so if that same level of risk applies to Advair, for example, then in three years, we have half as many deaths as occurred in 11 years with all the other LABAs. So from a public health perspective, this is an important point to deal with and to be cognizant of.

Now, I said I would go to Foradil to show what is the blind side -- the blind

spots that result from low statistical power. This summarizes all the studies that were in the pivotal trials for the approval of Foradil in adults and children.

And what you can see is that the number of patients, the number combined, the number of cases here -- now, this is serious asthma exacerbations -- the number of person years -- look at that. Two hundred person years of use for a drug that we expect to be used potentially by hundreds of thousands of children. That's a small amount of data for a large population exposure.

The attributable risk that we get is 66 events per 10,000. But look at the confidence interval on that risk. It could be as high as 570, which means the attributable risk could be -- the number needed to harm could be as high as 17 per year. What that means is treating 17 people per year to produce one extra serious asthma exacerbation. The data in the entire pivotal

trial -- the entire program that FDA bases assumption on couldn't exclude a number needed to harm of 17. And yet the decision was made that the benefits exceed the risks.

So now within the Foradil NDA for the dose that's marketed, there was no asthma mortality. At an internal meeting two years ago, this was pointed out by other colleagues in the Office of New Drugs, that the fact that there were no deaths was proof that the drug was safe.

Well, I want to describe to you how in such a small database of 235 person years, zero cases of death really is not reassuring at all. We have the inability to exclude a mortality rate as high as 1 per 6 per 100 per year.

So that isn't anything. Now, how does Foradil -- the approval of Foradil compare to what we know about Serevent salmeterol? Well, for incidence, the upper bound for salmeterol could be 34 per 10,000

per year. Because of the small database for Foradil, it could be as high as 160. Going down here to number needed to harm, it's about -- the upper bound is about 370. Here, it could be as low as 70. So we could see that there's really a lot that we don't know about the drug. And for us to presume that it's safe or to even conclude that it's safe really I think is premature because there's no actual evidence to conclude that the drug is safe. There's absence of evidence.

Okay, now what I'd like to do is look at the single entity products -- the single ingredient products and then the combination products, and summarize a couple of measures abstracted from the action packages. Some of this information was presented by Dr. Seymour earlier, and some of it was presented by Dr. McMahon.

When Dr. Seymour presented these data, she presented them in comparison -- the active drug in comparison to placebo. What I

will be presenting here is, wherever possible, to the active therapy that was also included in that treatment, because a natural question would be if LABAs are -- if that indication is removed from these drugs for any of the age groups or all of them, well, what's the consequence of that? And so this is the only place where we really have head-to-head information.

Dr. Lemanske gave a really excellent presentation this morning, but one thing I'd like to point out to people there is that in none of the studies was there actually a comparison with the LABAs and say scheduled albuterol were there in the same trial. You've got all these LABA studies and various combinations of do I add steroid? Do I not add steroid? I've got these albuterol steroids with the TREXA study at the end where he's going to do all these different combinations of albuterol and steroids. But there isn't one where they're together. And

so this is the only place where we have that information.

So now it's indisputable that the LABAs are bronchodilators. And so we don't dispute that.

What we do dispute is whether that bronchodilation translates into meaningful clinical benefits that justify the mortality risk that we believe these drugs confer at a population level. So now this takes all four pivotal trials for Serevent for the two formulations -- the one that's not marketed anymore and the one that is because of the inhalant -- looking at asthma quality of life, asthma score, and rescue medication use. And you can see for the Serevent studies, at that point maybe asthma quality of life wasn't being used, but asthma score was. And we had these minor differences. In the medical officer's review for these drugs changes in the asthma score of up to like about .4 going down were characterized as

being small. So we're not talking about here -- this would be a small at best to really not much of anything.

For asthma rescue therapy, one place in one of the reviews the medical officer said .6 rescue therapies a day change isn't clinically meaningful. I couldn't find a statement about what does 1.7 mean. Now, if we look at Foradil, where we have asthma quality of life, which is a validated instrument and where as previously described you need to have a change of .5 or more to have an effect that's actually clinically meaningful -- that actually means you've done something that the patient actually is experiencing what they would call a clinical benefit. You see, for Foradil these just don't -- they don't make it. They don't make the .5. The asthma scores were minimal. Here, they were just cited by the medical officer as not being different.

I'd like to point out that in one

of -- in this 2303, where there were 80 patients exposed to Foradil, one of them was hospitalized with life-threatening exacerbation required intubation. So it's an anecdote in a way, but the fact is that in a study as small as this, you had this happen. And remember, when these clinical trials are done, you're not selecting patients who are sort of at the worst end. You don't expect this. You don't expect patients to require intubation in clinical trials.

Now, if we look at the combination products, Advair and Symbicort, the set-up of the slide is the same. And you can see that it doesn't -- neither Advair nor Symbicort make the asthma quality of life. Now, this is comparing the combination products to inhaled corticosteroid alone. Now, for Symbicort, there's no change in rescue therapy; no change in asthma score. For Advair, the data were presented as 18 percent increase in symptom-free days here,

22 percent increase in rescue-free days here. And the question is well, what does that mean?

In this slide, what I've tried to do is show like the correlation between asthma quality of life, asthma score, rescue use, and then what do these things actually mean. And you can look across asthma quality of life. None of them are meaningful from the clinical perspective, so they're all pretty much the same. The asthma scores here, we don't have them for Advair but they're not meaningful there. And the rescue use isn't important.

If we look here, these are the numbers from the previous slide. But look over here for one of the Symbicort studies. 19 percent rescue-free days. That's pretty much the same as 21 or 22.

11 percent symptom-free days. Well, that's not very far different from 18 or 16 percent. So the question in my mind

then is what do these things mean that isn't being captured here? Because this is a validated instrument and it examines like four different axes that relate to asthma control, sense of well-being, functioning, environmental stimuli, need for rescue control, sleep disturbances at night. It captures a whole array of symptomatology, and it puts it down in a single value that we can look at.

Now we'll look at children. The evidence in children -- from these data, it doesn't look like the LABAs do a whole lot in adults. They do even less in children. I think Dr. Lemanske pointed that out as well in one of his slides, where he pointed up and he says it really raises a question why you'd add a LABA to the ICS in the first place. Look for Foradil first. I mean, these are microscopic. And Advair, those don't make any difference. These don't make any difference. There's no evidence of an actual

clinical benefit to the children who were getting these drugs. But we have the mortality effects that we have to talk about as well.

Now, what's the level of certainty about asthma mortality risk in combination products? And at this point, what I'd like to mention is that the questions that you'll have tomorrow, you're asked to vote separately on children up to the age of -- I guess it's 11 or 12; and then adolescents, which are like 12 to 17; and then older than that. And the reason why our office thought it was important to carve out the adolescents is because in the clinical trials that we've talked about up until now, the adolescents are lumped together with adults. But if you look back at Dr. Levenson's slides where he summarizes the ends in these studies, you'll see that the number of adolescents across all of the LABAs is pretty small.

And I'd just like to give an

illustration of one study that formed part of the basis of approval for Foradil for adults and adolescents. It was a study. It had one adolescent. One adolescent in the active arm, a 13-year-old. And the indication is we seek approval for adults and adolescents. So that's why we want people to focus on adolescents as well.

Now, getting to this notion of power to detect. This is looking at the entire LABA database from Dr. Levenson's review. And what I have here is a hazard ratio. That's a relative risk. That's -- I have a background rate of risk of death. And how many times above that -- how many multiples of that risk do I have evidence to say I can exclude it? And what you can see is it's not until I get up to a 43-fold increase in asthma mortality risk do I actually have enough power -- comparable power to the power the company had to show that it met its FEV1 measure -- to say that

it's not that high.

The risk could be easily 25-fold or 15-fold or 10-fold increased. And this just shows you what the person years you would need to exclude the risk. And if you remember from the previous slide, we only had about 235 person years of Foradil use in children. So I think you get the picture.

We have an absence of evidence, and there should be no reassurance or assurance on the part of anyone in this room that we know anything about how bad or how high the mortality risk could be. And if we're evidence-based, my argument at least is then we need to say what is it we know? What is it we can reject? What is it we know and what is it we can reject? And if we can't reject an acceptable level of risk, then we've got a real problem, because the benefits and the risks don't balance.

Okay, now I want to talk about decision-making paradigms and public health.

And this is a log scale, and it goes from like 5 percent up to 100 percent. And then these adjectives are sort of the terminology that people might use in everyday life to interpret that level of statistical certainty. And it's kind of like the weatherman when he says it's likelihood it's going to rain today; do you bring an umbrella? You know, if he says there's an 80 percent chance of rain, you bring an umbrella.

Well, FDA and industry use this level of evidence to establish efficacy and harm. But in public health, depending on the problem they're dealing with, there's a threshold for clinical and public health significance that's important to consider and upon which decisions actually have to be made. And when you do this, then things are more balanced. And the action level that you had I believe would be inversely related to the magnitude, severity, or intensity of the

benefit.

So if I'm talking about a very large harm, I might accept that it's possibly a very large harm if the benefits aren't demonstratively very large. So it's kind of a sliding scale.

Now, this stylized slide shows the Y axis of the certainty going from very likely to very unlikely, and the X axis being basically the size or the magnitude of whatever the effect is. It can be a beneficial effect; it can be a harmful effect.

And if we were to design the ideal drug, we would have high certainty of a large benefit, and equally high certainty that we don't have substantial harm -- that harms are small and we know that with high certainty, and that the benefits are great and we know that with high certainty. That would be the ideal drug.

In the next several slides, I'm

going to try to graphically describe, integrating the data that I presented in previous tables, summarizing the asthma quality of life and the asthma scores for these various LABAs into a diagram that tries to at the same time show the benefits and risks in a common place at a common time.

What I've done here is it's a similar X and Y axis to before, but what I've done is I've reversed the direction of the log.

And I did that -- in a normal log scale as you go higher up, the marks get closer and closer together.

What I did was flip it because I wanted to magnify the places where we either have the greatest certainty or we have the greatest either positive or negative effect.

And so if you look back at the previous tables for all of the LABAs compared to existing therapies, the asthma quality of life score and the asthma scores were all in

the small to trivial range for all of those studies. They did not meet the definitions that FDA reviewers or that people who have standardized instruments for asthma quality of life thought were important or meaningful.

The reason why the certainty goes all over the board is because different drugs within the LABA class had different amounts of data that provide us with different levels of certainty about what that small -- what are the probabilities associated with that very small benefit.

With the excess harms, on the other hand, we know that from SMART and SNS that we're talking about a relative risk of about four and that that could translate into many, many deaths.

This slide, I've added one additional feature, which is this dotted line which I've labeled the threshold of public health importance. The line is not -- it's curvilinear because of the log scale. And

what I'm trying to convey here is that there's some threshold -- this is just -- I just put it there. It could be up here; it could be down there. It's really something that would have to be informed by the situation, by the benefits you're dealing with, by the public health problem. But it's for teaching, heuristic purposes -- is that there is some line beyond which if an effect is a beneficial effect, it would be considered important even if the certainty about it was low.

So if I knew that there's a drug that -- you know, cures asthma but I don't have a lot of certainty yet because there isn't a lot of data for it, well, that might go over here. And it would cross the threshold and be something that would be important to consider if some other harms came up that we needed to balance it against; likewise, with the harms. And what I'm suggesting here is that the evidence we have

on harms for the LABAs and the evidence we have on benefits are really on opposites sides of that decision threshold for public health importance.

Now, FDA, by approving the LABAs, and the company by marketing the LABAs, have implicitly stated -- or explicitly on the part of FDA -- that the benefits exceed the risks. So what they're saying basically in terms of diagrams is that here's where the benefits are for the LABAs, and they exceed the harms in some type of calculus. And the problem is, from anything I've seen today, we don't have any proof that these are where the benefits are, and certainly not from large RCTs. So I would submit that that's speculative at best.

Now, looking at our data, this should have a minus sign there -- that should be a -3, not a +3.

The question came up earlier that Advair within Dr. Levenson's review seemed to

have a lower point estimate for the composite. In fact, there didn't look like there was any risk for the composite. Well, one possibility is that the population that was studied in the adverse studies is different than the populations that maybe were studied in other studies. So what I've done over here is look at the control groups for each of the studies, and we can see what the incidence rate for the composite outcome was per 10,000 person years. And what we see is that the Advair control group was very different than the groups for the other products. So that raises the question of is it real or is it Memorex? Is the fact that Advair looked good in Dr. Levenson's analysis an actual property of Advair, or is it a property of the controls that were used in the study?

Now, what's important to note also as well, and Dr. Mosholder pointed this point in Dr. Levenson's review, is that there are

only 20 outcome events in the Advair group. Well, if you look at the data for Serevent in Dr. Levenson's review, there's about 15 or 20 hospitalizations per outcome event. So the fact that we don't see one -- that we don't see a death in the adverse study should provide no reassurance either. And I'll address that a little more next.

We talked about the asymmetry of handling benefits and risks in pivotal trials before. And what I want to summarize here is that the benefits in the Advair trial to identify a clinically important change in asthma quality of life was 88 percent. That was right out of the biostatistics part of the submission that the company sent in. For Symbicort, for their FEV1, they had 95 power. This is the power to exclude a 10-fold increase in mortality. Eight percent for Advair, 10 percent for Symbicort. Fifty-fold increase in mortality. 31 percent, 40 percent, even 100-fold. So statistical

power. Without a telescope, the moon has no craters. Does that mean that the moon really has no craters? The fact that I don't see asthma deaths with Advair because I have 8 percent power to show it, does that mean there isn't? I don't think that we can conclude that. I think that that's a presumption; that's not evidence-based.

Now, given such low power, how could we objectively conclude that either of these drugs are safe, or that their clinical benefits exceed their risks, assuming that risks haven't been adequately or accurately measured -- that we haven't even capped the risk -- unless you're willing to say that 100-fold increase in asthma mortality is an acceptable level of risk -- the benefits that Advair confers. If that's the case, then you have an easy solution to your dilemma.

Now, the level of certainty regarding asthma mortality -- this is from the entire Advair controlled database that

Dr. Levenson presented earlier. Okay, so not just -- the previous slide was clinical trials from the approval. Now with, you know, seven or eight years of additional data, we have a larger database. And this is the power to detect the hazard ratio. We've got enough power now to detect a hazard ratio of 10. We can't exclude a hazard ratio for Advair below 10.

Serevent confers something between 3 and 4. You have somewhere probably between 30 and 40 percent power to deal with that. We basically were flying blind.

So now -- I said I would focus on Advair specifically because it's the leading LABA that's marketed -- and I'll show you now the same diagram of the certainty and the intensity of the effect. Blue is clinical benefits. The dotted red lines are the mortality risk. This box here is based on the ADA power to conclude that Advair health benefit is small and not clinically

important, because that's the power that you had for asthma quality of life.

Now, mortality risk, well, you could place the box in one of two places depending on how you want to view the problem. You could place it here because you had low power to document the level of Advair mortality because the studies were small. But if you do that, then you're rewarding companies for not doing studies, because the solution to this problem is do the smallest studies you can get away with and then you don't have an answer and you're guaranteed a null result. You could put it up here because there's no proof that Advair's mortality risk is different than Serevent's. You could put it up here because ICS hasn't been proved to reduce LABA mortality -- at least not in a very large prespecified RCT.

So this is the characteristics of an ideal drug that I showed you earlier. And this is where I think we're dealing with

Advair. It is the antithesis. It is the opposite. It i the mirror image of an ideal drug. There's a small clinical benefit with high certainty. We can't distinguish Serevent from Advair. We know that the risk for Serevent with high certainty is large and it's high.

And there's no proof this risk isn't very large. So I would say that from an evidence-based perspective, that the evidence of benefit -- we know with high certainty that at least the things we can measure aren't good. It's a bronchodilator. Maybe we need better measures in the clinical trials. But the things that we've been presented with don't suggest that we're getting a whole lot. It's not the magic bullet.

So the conclusions that our group came to -- I'll go over those. Ann went over some of them as well. We believe that single entity LABA products should be withdrawn from

the market. And the reasons for that are that the clinical benefits are generally small compared to albuterol. In children, the benefit is even less. Nearly 50 percent of the single ingredient salmeterol Serevent or Foradil are used without ICS.

So we know with certainty that Serevent confers a high mortality risk. And this is an engineering solution. If we use a combination product, then nobody who uses a LABA could get it without an ICS. So from a risk mitigation strategy, if you believe that ICS cures the problem, this solves that problem.

But here's the contradiction. ICS hasn't been shown to reduce asthma mortality -- LABA mortality. So what's the rationale for concluding that ICS should be used with LABAs? Now, that first conclusion our entire group agreed with -- the four of us on the LABA OSC team. The second is one that we also agreed with, which was that the

asthma indication for use of all combination LABA products in children and adolescents should be withdrawn. From my perspective, it's been inadequately studied, the safety is unproven, and there's no evidence -- there's no proof that the benefits exceed the risk.

There's no basis to conclude that. The benefits, if any, seem to be small compared to placebo, because most of these studies in children were done against placebo. There's a high potential for substantially increased mortality risk. And we get back to this question. The absence of proof of mortality is not the same as the proof of absence of such risk. We can exclude a 43-fold increase in asthma mortality for these LABAs in children -- LABA ICS products in children. If that's an acceptable level of risk for the small amount of benefit we've had, then leave the indication there. If it's not, and we think it isn't, we believe the indication should be

pulled.

Now, the asthma indication for all combination LABA products in adults should be withdrawn. Dr. Mosholder and I subscribe to this recommendation. Dr. McMahon and Dr. Busaber didn't. And the reasons that I have for it are that while it's clear that LABA ICS is superior to ICS alone as a bronchodilator, I don't know what that means clinically. As far as I can see, it doesn't translate into something that's been measured that I can say is a clinical benefit that I can measure against the harm as measurable as mortality. Even for Advair, where the most favorable data is available, there's no evidence that asthma hospitalizations are prevented.

The LABA component of these products increases mortality, and we know that. With Advair, basically we have no evidence to say the risk isn't the same as it is for Serevent.

And then finally, additional reasons why -- to support the reason why we think it should be withdrawn in adults as well. I point your attention here to the approved indication. This is equivalent to an FDA endorsement or recommendation that a product is safe and effective for use in a specified disorder. Given what I've presented previously where we have small proven clinical benefits, how can we justify exposing millions to what we must conclude is an extremely high risk of death?

We haven't rejected -- we haven't even capped the risk at a level that's probably reasonable to accept. And yet we're concluding that the benefits exceed the risks.

To me, this question could have been answered many, many years ago if FDA had insisted that the manufacturers of Advair go out and do a really large SMART-like study comparing the combination product to ICS

alone, to scheduled albuterol plus ICS, and we'd have an answer today. But that study wasn't asked for by FDA. The company apparently didn't volunteer to do it, and so we don't have those data.

So the question then is how can we conclude these products are safe and effective if the efficacy measures don't predict clinical benefit. So at best, I would say -- I would conclude that the LABA ICS products have been inadequately and insufficiently studied to be marketed, and that their continued marketing is really in a sense a natural experiment where we don't have good data collection.

And then a couple of final thoughts. Yes, asthma is a serious disease and the therapies that we have are not adequate. And we would love to have new therapies, better therapies that work. But our desire to have better therapies shouldn't trump making evidence-based decisions as a

population -- and a population in a public health perspective.

And what we have right now is we don't have evidence, so it's all based on presumption. We assume that the drug is safe. We assume that the benefits exceed the risks, but when you test it, it's like the emperor with no clothes. There isn't substance there. So we have diamonds, we have zircons, and we have glass.

And I would say that zircon at LABA ICS are closer to glass than diamonds in terms of clinical benefits, but they command diamond prices in terms of mortality risk.

Okay, thank you.

DR. SWENSON: Well, thank you, Dr. Graham.

Well, at this point, we've heard some -- we've heard two serious talks here, and I think that we'll just break a little bit from the schedule because I'm certain there are a number of questions, and we'll

take a bit of time here to have questions for these two recent speakers.

And so let's start with Dr. Brantly. I see him first.

DR. BRANTLY: So this is a question for Dr. Graham. And again, I'd like to focus in and get into public health and the epidemiology of asthma, and I'd like to try to rectify that with the data that you've presented. And that is that, number one, you predict that there's more asthma deaths based on the LABAs than there actually are, number one.

And number two is, even with the introduction of LABAs, there's actually been a continued decrease in the deaths associated with asthma.

So the numbers don't quite add up.

DR. GRAHAM: Well, a couple things. One, the total deaths that I listed are the total deaths over all the years. There are about 4- or 5,000 asthma deaths a year, so my numbers don't exceed the number of asthma deaths

that there are, A.

B, it is true that trend for reported asthma death has declined over time, but it's an ecologic association. Nobody has shown that that decline has anything to do with LABA use. It's not done in a clinical trial setting. And as an epidemiologist, you know that's ecological.

The other thing is that 50 percent of that decline is due to the change in classification coding from ICD-9 to ICD-10. And so I think that ecologic data -- I mean, it's in the first chapter of epidemiology textbooks that you can be led astray.

DR. BRANTLY: Can I just follow that up?

I just want to say we have at least one historical example of increase in asthma deaths associated with the introduction of a drug onto the market for treatment, and that's isoproterenol, where there was actually an increase in the number of asthma

deaths associated, clearly identifying that drug as the -- as one of the -- something that was clearly just cause and effect.

I mean --

DR. GRAHAM: But here's my question back to you. Then Serevent by itself doesn't increase mortality? Because if SNS and SMART are wrong and Serevent does not increase asthma mortality, then yes, you could have your death rates going down over time or you could fail to see a spike. But what you're talking about is a very crude measure of what's going on.

The coding for asthma mortality, as you well know, is very inefficient, and very imprecise and prone to lots of error. And so unless you're prepared to say that Serevent, that SNS and SMART, that those controlled randomized trials are wrong and that Serevent doesn't increase asthma mortality, I think that your argument is lacking in strength, and I disagree.

DR. SWENSON: Dr. Goldstein.

DR. GOLDSTEIN: This is for Dr. Graham as well. I certainly don't disagree with you that the current paradigm for drug development is asymmetric, and that the approval process is different for efficacy -- that is different in terms of efficacy and safety. I think one of the questions -- and I agree with your analysis and the numbers that you showed.

I think one of the -- the main question that I have is that the current bar that's set for efficacy for this drug population, my interpretation is that it's FEV1, and it's a hard number and a physiologic process that can be measured.

DR. GRAHAM: Right.

DR. GOLDSTEIN: For other drugs in other areas, including asthma, scoring systems or surrogate markers have not been accepted. The hard markers are needed. FEV1, change in blood pressure, survival, those things are required. And therefore, when a drug company designs a trial for a primary outcome variable,

they use these hard primary outcome variables to power their study design.

To then go back and say that efficacy was really not demonstrated because even though they met the primary outcome variable, the secondary outcome variables were really not all that significant and they are now more important than the primary outcome variable, A, doesn't seem fair because you can't change the rules after the game is over.

And B, the study wasn't designed with those secondary outcome variables as the primary, so they really weren't powered to show differences in those.

DR. GRAHAM: Right.

DR. GOLDSTEIN: I just wanted your comment on that.

DR. GRAHAM: Well, everything that you've said, I agree with, but what I would point is the following: That there's a big difference between efficacy and effectiveness,

between efficacy and benefit. We see that with other drugs.

If I had a statin -- I mean, you know, we're pushing to look at clinical outcomes. If I lower your cholesterol level but it doesn't translate into improved cardiovascular survival, have I accomplished anything? So there's a difference between efficacy, which is the standard that FDA uses, and benefit, which when you're talking about whether a drug should remain on the market or not, there you're talking about benefits and risks. You're talking about, at the most simplistic level, how many lives do I save, how many lives do I take.

And here, it's not changing the rules. It's saying an extraordinary situation has arisen. We now know with high certainty that LABAs increase asthma mortality. Do the health benefits justify that? Is it justifiable? Does it make sense to pay $10,000 for a piece of glass or

$10,000 for a diamond? Now, you could say, well, free choice, and everybody should have options and do what they can, but there are certain exchanges that just aren't reasonable. And I believe it's the role of regulatory agencies to set a bar about what's acceptable.

But if people disagree, then what I would say is you have to be very explicit about what you're doing. And based on the data we have here, that would mean saying that for children, an increase in asthma mortality of 43-fold is dominated by the health benefits that that drug confers to children; and that a morality increase of tenfold with Advair justifies what appears to be small clinical benefits.

And if you're prepared to say that and to enunciate it so that the world can see and scratch their head and say does that make sense to them, then I can sit down because then I don't have an argument anymore. But

where I would place the balance and the exchange is much lower than 43-fold increased death in children or tenfold increase with Advair.

DR. GOLDSTEIN: I appreciate that. Quickly, I just would comment that because I think the studies that we would ideally love to see have not been done, that's why I asked Dr. Lemanske earlier what would be the burden on the patients if these drugs were removed? And specifically referring to children.

DR. GRAHAM: Right.

DR. GOLDSTEIN: It was just a comment.

DR. GRAHAM: Right. Well, if I can respond to that question, I think for children, since they're not deriving much, if any, clinical benefit, it's hard to imagine that there would be a harm that would occur as a result of withdrawing the indication. If anything, we're going to have fewer asthma deaths in children, which I would think is a good thing.

In adults, I would argue the same thing. I would also argue that at the very end of Dr. Lemanske's presentation, where he was presenting data on use of albuterol and ICS, and suggesting that albuterol and ICS may actually -- even if it's used as a rescue therapy, might actually be beneficial, that it might have promise. The problem is nobody's compared those therapies.

We know that albuterol, scheduled albuterol, is safer than Serevent. SNS tells us that. And so the question in my mind is, is that the fact that we don't have those studies would mean that I would go to the thing that, based on the comparisons, looks to be safer, which would be albuterol and inhaled corticosteroids.

And yes, there are going to be individual patients that are in control, that are controlled by LABAs, but the question is do you expose the entire population to that so that you can get the occasional patient

that responds that way? Because we have no way of identifying who's going to have that miraculous response to Advair, just as we have no way or predicting who's going to end up in the cemetery because of Advair.

DR. SWENSON: Dr. Kramer.

DR. KRAMER: This is not specifically for David Graham, but for the FDA in general. I'd actually like a response from both the Pulmonary and Drugs Division as well as the Office of Surveillance and Epidemiology.

I'd like to step up at a higher level about what these three different advisory committees are being asked to do today. And I've been growing -- I was concerned when I reviewed the material in advance, and as the presentations have gone on, I've gotten increasingly concerned.

My understanding -- first of all, we've got a disease that in itself is a very serious disease. And I think at the end of these two days, we've got patients and

practitioners waiting with bated breath for what this group is going to do, which is why I'm asking this question this way.

As I understand it, from as far back as 2005, both the label and increasingly guidelines have advised against monotherapy. And in 2007, as I understand it, the Pediatric Advisory Committee asked for a follow-up update on the safety in children and continued update on safety in general.

And yet my understanding of what we've been presented and what's continuing to be presented here is, first, a meta-analysis that is heavily dominated by the old data on monotherapy, and the quantitative estimates heavily dominated by the monotherapy arms of these trials.

And now, in the last presentation, we're having a philosophical debate about the basis for approving drugs in this country in the context of three advisory committees trying to decide on the proper treatment for

patients with asthma. And I think that this is an impossible task that you're asking us to do. And I just wonder how you could give us some guidance.

I'd like FDA to be clear about what new data are we being asked to look at that wasn't present in 2007, that we're reviewing now. And what are -- you know, are we really going to opine and decide different criteria for basis of approval of drugs at this meeting?

(Applause)

DR. JENKINS: Okay. I'll be brave and try to answer that. The issue that we fundamentally want this committee to advise us on today and tomorrow is the question of do the benefits of these products exceed their risk, such that they should remain on the market? And if so, how should those risks be managed to try to maximize benefit and minimize risk?

You say you have an impossible task. We have the same task, so we're asking

you to give us advice. I think the main new data that you have in front of you is the FDA meta-analysis that Dr. Levenson presented earlier. That's the main question we want you to address.

We're not here to address comments or concerns about the approval standard for drugs. It's not only in the United States, by the way. That's the way drugs are approved around the world.

This should really focus on benefit versus risk for LABAs and the LABA combinations. Do you think that the population benefits and the individual patient benefits warrant keeping these available given the known risk of serious adverse reactions with these drugs?

DR. KRAMER: Then why didn't the FDA present us with data to come to bear with the current guidelines on how asthma's treated?

DR. JENKINS: Well, I think you're going to see some of that in Dr. Chowdhury's

presentation, which is coming up next. So you haven't see all of the presentations and you obviously haven't seen the sponsors' presentations either, because they probably have some viewpoints on this issue as well.

You know, one thing to keep in mind is that the analysis that you just saw is probably true for any chronic symptomatic therapy that has a known serious risk. It's probably true for NSAIDs, where you're treating -- using them for symptom relief, not disease modification. You're not expecting to cure osteoarthritis by using an NSAID chronically, but you know they carry a risk of -- serious risk of GI bleeding and even potential death. You can make this construct for any of those.

Tylenol, you could make the same construct for acetaminophen about the benefits, and yet it's the number one cause of drug-induced liver failure in the United States every year.

So you've got to look at what are the benefits in your mind for the population as a whole and individual patients? What are the risks? Are those risks acceptable and manageable? And if so, how should we do that management? That's the fundamental question that we're asking the committee to opine on.

I mean, we don't have a lot of disagreement, I don't think, within the FDA that the risk is real. The real question is, you know, does the risk mean that these drugs are unacceptable for marketing, or is that risk acceptable in your mind given the benefits that are accrued to patients individually and collectively? And that's what we'd like to hear your opinion on.

You're hearing different opinions from within the FDA. It's not surprising that you're hearing different opinions. It's a very complex data set. To some degree, it is a philosophical question, as you said. So hopefully, that helps you understand what

we're trying to achieve.

DR. SWENSON: Well, at this point, I think it would be appropriate that we move on with Dr. Chowdhury's comments. And we will have quite a bit more time tomorrow to discuss these very important aspects.

DR. CHOWDHURY: Good afternoon. I will be speaking about the risk-benefit assessment of long-acting beta agonist bronchodilators in the treatment of asthma.

Before I start, I would like to thank members of my division for the work that I'm presenting. Particular thanks to our statistical team leader, Dr. Chen Lee (?). Thanks to the medical reviewers, Dr. Seymour and Dr. Kalimisha, Dr. Michel, Dr. Boskin, Peter Stowick (?), and others. I also thank Dr. Rosebrough and Dr. Jenkins of the office for their oversight and support.

Here is the outline of the presentation. I'll initially make some introductory comments, then talk about risks

of LABAs in adults and children, benefits of these drugs in adults and children, risk-benefit assessment, and then I'll reflect on some of the comments that you heard from our OSE colleagues. And finally, make some concluding remarks.

First, let me go through some introductory comments and then talk about the risks and then benefits. As you have heard in the discussion just preceding my talk, got into that, that there were differing views on managing risks from inhaled LABAs in the treatment of asthma. And the views that were expressed by our OSE colleagues and us in the Division of Pulmonary and Allergy Drugs are somewhat different on how to manage these risks.

You have heard unanimous recommendation from our colleagues in the OSE which goes for withdrawing medication for all long-acting beta agonists for patients below 18 years of age and removal of asthma

indication and contraindicate its use as single-ingredient agents for all ages. In other words, what will remain are combination products only for managing asthma above the age of 18. The rest will all go.

From our viewpoint, we think the products containing long-acting beta agonists should continue to be in the market, and the safety risk should be managed through labeling. And some of this labeling and other ways of managing risk has been expounded by Dr. Seymour, which includes various aspects such as: Labeling changes, which you have seen; medication guides; directions for appropriate use; particularly that long-acting beta agonists should be used only as additional therapy for patients not adequately controlled on other asthma control medications such as inhaled corticosteroids.

And I'd like to add that opposition is consistent with major asthma treatment guidelines, such as those of the NAPP of NIH

and also the GENA (?), which is the Global Asthma Treatment Guidelines.

Now you have heard what asthma is. In the top bullet, I give some features of asthma which is generally accepted, which includes shortness of breath, wheezing, chest tightness, cough, airflow obstruction, and, of course, bronchial hyper-responsiveness and underlying inflammation. As you can see, many of these are symptoms because of airflow limitations that these patients have. A long-acting beta agonist dilates airways and relieving their symptoms.

It was heard in the early presentation that asthma is classified based on level of symptoms, awakenings, short-acting beta agonist use, and interference with normal activity and lung function. And asthma is classified as intermittent or persistent, and the persistent being mild, moderate, severe.

And as you have also heard in the

morning, asthma is not a fixed disease and not exactly the same disease in everybody. And patients with asthma can move down in severity or move up in severity. In other words, the disease is very variable in patients.

Now, what are the current treatment choices that we have for treating asthma? Well, asthma treatments can be classified in two categories: The quick relief medications, which include short-acting bronchodilators for all practical purpose in the U.S. -- this means inhaled albuterol -- and (inaudible) corticosteroids. For the very mild asthma, short-acting beta agonists or inhaled albuterol is all the patient may need.

The long-term control medications as classes are listed here. And let me go through these classes one by one so that you understand what the choices are. These are listed alphabetically.

First, there are or soon will be (inaudible) inhaled cromones. These drugs are propelled by CFCs and are to be phased out because of CFC and these have not been reformulated with alternate propellants. The drugs in this class were nedocromil and cromilin.

Then we have immunomodulator that we heard before. The trade name is Xolair. This drug is specifically for patients who have got asthma with an allergic component, specific levels of IGE, more directed for more severe patients, and have serious risk. The two warnings: Malignancy and anaphylaxis.

Third, we have heard about inhaled corticosteroids and heard a lot about it. Then there are liquid modifiers. There are practically two in the market: Montelukast, we have heard in the morning how effective these are; and also zileuton. Zileuton can cause liver injury. And the product label

asks for periodic monitoring of blood for its safe use.

Then, of course, we have long-acting beta agonists, which we're discussing now. And then the methylxanthines or theophylline, which we all know what the safety profiles of these drugs are. For theophylline one needs to do periodic blood monitoring to ensure safe use. Theophyllines are quite narrow drug. And of course, we have systemic corticosteroids coming under both. And systemic corticosteroids has their well-known, well-characterized safety profile, including metabolic effects. And keep in mind, inhaled corticosteroids, even at high doses, can have systemic effects.

So these are the drugs that we have. For really all practical purpose, the main drugs that currently are used by patients with asthma are albuterol, inhaled corticosteroids, and long-acting beta agonists. These forms the main banquet for

asthma treatment today. What particularly what we're talking about is removal of this.

The removal of long-acting beta agonists as a group, as recommended by our colleagues in the OSE, will force patients who are not adequately controlled on ICS to use other medications. Since LABA are symptom relief medications effects that are acutely noticeable by patients, patients are likely use -- are likely to use inhaled short-acting beta agonists or albuterol chronically and perhaps at high doses, and also, burst of oral (inaudible) steroids.

As I'll discuss later, you will appreciate that chronic high-dose short-acting beta agonist also has risk of its own, which goes back to what the risk with long-acting beta agonist is, which is asthma-related death. Oral and (inaudible) steroids have known risks that you're aware of.

Now, asthma-related death with

short- acting beta agonists is not new. There were some discussions on this a couple minutes ago. It goes back over 50 years. And here is a slide that I borrowed from a publication, Lancet, showing similar well-described population-based risk, which we heard about a minute ago, with some of these drugs.

The first that we saw was with epinephrine in 1940s and '50s in some countries. The countries in the slide are New Zealand, England, and Wales, and Netherlands -- the U.S. is not here -- and there was an increase with asthma-related death that was thought to be linked to epinephrine.

Second, in 1950s, we heard just a comment before about isoproterenol resulting in increased death. The publications out there going back about 50 years, which describes this death. Then there was a high-dose formulation of isoproterenol

introduced to the market in some countries, resulting in quite high increase and, again, population-based increase in death.

Then finally, in these -- I would point out the well-described cases with fenoterol and other short-acting beta agonists. Initially, the risk was seen in New Zealand. And subsequently, the risk was characterized in population-based studies conducted in Saskatchewan, Canada. And in this analysis the authors actually looked at albuterol and concluded in the articles in different journals on this that, based on exposure, it is possible, but albuterol at high doses can carry the same risk. And that led to the use of albuterol, which currently we use today, which is more of as-needed use and not chronic high-dose use.

Now, going back to a question that was posed early in the morning, what are the mechanisms of asthma-related death? The short answer is we do not know.

The couple of factors that we should consider or think about what we know. First, there are some contributing factors. Use of high-dose beta agonist drugs can cause problem. And we saw that, as I showed in the previous slide, with isoproterenol. It was also (inaudible) with a case with fenoterol. And also we have data from recently the case with the long-acting beta agonist formoterol.

Second, use of less selective drug can contribute, and we have seen data with isoproterenol and, again, fenoterol.

Now, there are also some hypothesized mechanisms that can contribute to this. First, which we heard about earlier, is reduction of protection against bronchoconstrictor stimuli. In other ways, if patients are on these drugs, then the responsiveness to a bronchoconstrictive agent may be blunted. And this has been tested with various agents and shown to be the case. And agents included, the published articles

on these, using methylcholine, histamine, adenosine, exercise, cold air, allergen.

The other thing which we've also heard is masking symptoms of worsening asthma. In other ways, the patients taking long-acting beta agonists can have asthma worsening, which they would not really respond to and seek treatment because with the long-acting beta agonist on board, the symptoms are controlled. And by the time they seek help, perhaps inflammation is too advanced.

Now, we have heard about phenogenetic studies and things for the future, but at this time, we do not have any certain length of phenogenetic marker or phenotypic marker (inaudible) patients who are at risk. And in my summary documentation for the briefing package I've listed some of the studies which has tested for the possibility of looking for a genetic link for this asthma risk, and we do not have one.

Now, mechanistically one can think the mechanism by which inhaled short-acting beta agonists and long-acting beta agonists cause asthma-related death are not known, but maybe they're likely to be similar because the basic action of both these drug classes are the same. They're basically both bronchodilators and really do not have any market effect of inflammation -- on inflammation.

Now, what are the risks of long-acting beta agonists in adults? I'll go over the next couple of slides talking about adults and then come back and comment about pediatrics.

Of course, the main risk is asthma-related death, which we have been talking about, and serious exacerbation. In addition, there are other effects with these drugs that are well-known and they're listed here. The systemic effects which I'm listing on the slides are rare with inhaled drugs

because the inhaled doses are lower than the doses known to cause the systemic effects. And local irritation of airways are also seen with this drug. So for today, for a more practical purpose, what we're talking about are asthma-related death and serious asthma exacerbation.

Now I'll go over some of the safety data and safety findings with the two long-acting beta agonists: Salmeterol and formoterol. For this section, I'll go through my slides pretty quickly because most of this has been described earlier, and I'll just make some comments which I may want to make on these studies.

As we have heard, for salmeterol there are two studies: SNS and the SMART study. And we have seen the results of the SNS study showing the death risk with the risk of 3. And we have heard about the SMART study design, which was a study comparing salmeterol versus placebo. I'll not go into

the design in this slide any further.

And we have heard about the conduct of the study, the powering of the study. The main point is that it was powered to rule out three times increase in asthma death. The number three comes essentially from the SNS study. And the primary endpoint and the important endpoint of death is shown in this slide. You also have this slide in my briefing document and has been presented earlier, so I'll not go through the details here. The main point, which we all know, there were 13 deaths with Serevent versus 3 with placebo. And it seemed to be more in African-Americans. All the Caucasians had the same risk with death.

Two of the slides quickly, secondary endpoints on the death. The first one was a question that we have addressed already, whether inhaled corticosteroids protects or not.

And here is the data broken down by

use of inhaled corticosteroid at baseline versus no, and the numbers are here. And if we really look at the African-Americans, it doesn't seem to be much different, three versus one, four versus zero.

Another question came up in the morning regarding the phases of the study and, yes, it was done in two phases. And the first phase, which was in these four years, patients were recruited primarily through advertisements from their essentially home or are patients and not necessarily through physician contact.

In the second phase, to encourage enrollment, patients were actually (inaudible) through physician's office. Patients coming in Phase II were actually seeing physicians for the asthma control in most cases.

And as expected, the number of events were high in the Phase I, where patients would be coming in, if you would

call it, from the wild. The numbers were different. The green is salmeterol and the yellow is placebo. There were 10 versus 3 deaths.

The second phase, which the patients were under physicians' control, also have events; much less, and three events were with salmeterol.

Now, let me go over again very quickly with the formoterol studies. You've seen the studies presented before. I'll go through them pretty quickly.

As you've heard, there were two Phase III studies in patients 12 and above, one Phase III study in patients 5 to 12, and one Phase IV study, 16-week study duration, in patients 12 years of age and older. I'll show all those studies in one slide.

And here is the result. You have the same slide in my briefing document. And I'll not go through the numbers here because the numbers have already been presented. The

main point is there was serious asthma exacerbations that were seen with formoterol. The numbers were higher than albuterol and the placebo. And there seemed to be a dose ordering.

Now, I want to touch on, briefly, about the combination product, Symbicort Phase III NDA study, and bring out one safety finding from this -- these Phase III studies. There are two Phase III studies that supported approval of Symbicort in the U.S.: Study 1 and 2 done in patient with moderate to severe asthma and mild to moderate asthma. The two co-primary endpoints, as you've heard, are (inaudible) present, which was based on FEV1. And patients who satisfied predefined asthma worsening criteria were required to be withdrawn. And I'll show these patients were withdrawn and make some comment here.

Here are the number of patients and percentages who were withdrawn from these

studies because of asthma worsening. Again, you have the slide in the briefing document. But I want to highlight here that these, of course, are efficacy parameters and also they can be used as safety parameters.

On the safety side, if you look at the studies -- for example, study 1 -- there are more patients on formoterol alone who have withdrawn due to decrease in FEV1, peak flow, and clinical exacerbation. The numbers compare to placebo. The point here is that these are very effective bronchodilator drugs, but also a small percentage of patients have worsening of their asthma with this drug, and this is what we're talking about. It comes out in multiple studies, including in these studies.

Now, let me just briefly comment on the inhaled LABAs risk in children. For ages 12 and above, it's the same as older children and adults because the safety studies were conducted in this age group. For children 4

to 11, as we heard before, there are no large safety studies and Phase III studies did not show any asthma death. Ages below four is not relevant because the drug is not approved at this age group.

Now, keep in mind for these drugs there actually were studies done in 4- to 11-year-old children, for example, with Serevent, Advair, Foradil. Each have studies with children in this age group, ranging in number between 200 to approximately 500 patients.

Another comment about the risk in children: Products containing inhaled LABA for now carry the same labeling warning irrespective of age with the conclusion that asthma-related death seen in studies conducted in adults and adolescents, in patients 12 years of age and older, apply to patients below 4 years of age. Therefore, we have taken a conservative view.

A couple of points here. Based on

the control trials, the available data do not suggest that the safety risk with long-acting beta agonists is higher in children four years of age and older. And we also need to consider that patients four years of age and older as they compare to adults, as far as the disease is concerned, the disease is the same. Asthma, the pathophysiology also is the same.

The target of the beta agonists, the beta receptors, function similarly. Therefore, the response to long-acting beta agonists is expected to be the same.

Now, our OSE colleagues concluded the safety risk is higher in children. This conclusion is not based on death, but on hospitalization. And I'll comment further on that conclusion later in my presentation.

You have, again, seen this slide before, which is a risk interpretation. And the point that I want to make here is the risk in a population basis, based on the

SMART study, is 8 per 10,000 over 28 weeks. And we are to keep in mind that for the SMART this perhaps is the worst-case scenario. The LABA in the study was used, in many cases, without controller medications. Time has moved. Management has moved. The treatment of asthma has moved.

In real life, long-acting beta agonists mostly, as we'll see in slides, are used by controller medications such as inhaled corticosteroids. And the question came up how does this risk really translate into asthma mortality in the U.S. on a population basis? And you've seen before by presenting the population data with some other short-acting beta agonists drugs.

For the long-acting beta agonist drug, as we see now, it doesn't seem to have translated to increased mortality.

Here's the mortality shown over age, over years, rate, and number. And if we look at -- approximately late '90s, it has

changed. And this is the ICD-9 to code -- to 10 code change. And of course, there was a decrease here. But all the ICD-10 code it seems to continue the gradual decline. And this is in spite introductions of the drugs that we're talking about here today.

Inhalation aerosol in 1994. Two years later, the Diskus formulation. A couple of years later, Advair Diskus, inhalation aerosol, and lately Symbicort. And the use of these drugs also per volume is increasing as you've seen in some slides before.

Now, what are the benefits of LABA in adults? I'll go through this pretty quickly, and you've heard this before. LABAs were approved for use in asthma, EIB or exercise-induced bronchospasm, and COPD. And some of them, as you heard before, of course increases quality of life, specifically the ones which are combination products containing LABA and inhaled corticosteroids.

The reason I bring up quality of life, because we've heard a lot of discussions around it and to keep in mind the AQLQ for an instrument to be used in trials was really not validated up until late '90s and old trials do not have much AQLQ data. And also to keep in mind that AQLQ itself was validated based on FEV1 measure and (inaudible) challenge, which is also based on FEV1. So some was circular.

The benefits of LABA in children for ages 12 and above we concluded it is the same as older children and not necessarily any worse. And there are studies 4 to 11 showing efficacy, and ages below 4 is not relevant.

And again, for -- same as on the safety side, on the benefit aspect of it, the same logic that I applied for the safety applies here. The disease being the same, the target being the same, the response being the same. So there shouldn't be really much

reason to believe that efficacy will be substantially different. Nevertheless, in children studies were done and shown efficacy.

As far as combination product goes, we have heard before the combinations are combinations of convenience. So they did not necessarily require the same level of study to show efficacy of the combination product. The point here is does the combination give the same two active ingredients? And it is true for Advair the number of studies are limited. But again, they're based on multiple studies done with the single-ingredient products in children.

For example, in Advair, in children there was one study primarily for safety, which also showed efficacy, but this was built upon multiple studies. For example, with fluticasone, there are three studies with Flovent Diskus in patients 4 to 11, involving approximately a thousand patients.

There was one study with Flovent (inaudible) involving about 250 children. There was also another study involving over 200 patients with Flovent inhalation aerosols. There are also similar studies with salmeterol. So, therefore, the point I'm making is the combination Advair has multiple studies with single ingredients, which supports the approval and the combination is built on those studies.

Now, on the benefits, just to summarize then, LABAs are effective for asthma in terms of improvement in FEV1, peak flow, rescue albuterol use, symptom control, nocturnal awakenings, and others. And you have seen a summary of the studies presented by Dr. Sally Seymour and others. In addition, you have seen many of the studies which have been done in the public domain by either public funding or private funding that has been summarized Dr. Lemanske before. And I'm naming some of the major studies here

that includes combination products, including formoterol and budesonide, salmeterol and (inaudible), salmeterol and fluticasone. And these all show the benefit of these combination products over single ingredients.

And I would like to use one study which is a widely quoted study conducted over multiple years.

And this is a GSK-funded study which showed the contribution of combination product over inhaled corticosteroid. And the next three slides I'll walk through the study to make the point.

The goal study involved approximately 3,400 patients, ages 12 through 80, group, multinational. And it compared step-wise increase of doses of fluticasone or fluticasone plus salmeterol in achieving asthma control. And the asthma control here, which I show based on daytime symptoms, rescue drug use, morning peak flow, nocturnal awakenings, exacerbations, emergency visits,

and treatment of adverse event, these come out from the (inaudible) document. So these are combinations of asthma control.

The design was somewhat complicated. The patient were broken up into stratus 1, 2, and 3, based on the severity, 3 being more severe. And patients entered into phases of trials, which is called Phase I and Phase II. And the aim for these phases was to stabilize patients on a dose of fluticasone or a combination product and achieve control. If control was achieved, maintain that. If not, increase the dose of the steroid complement and go up on that. It's basically the way asthma is managed and this allows comparison of fluticasone and salmeterol versus fluticasone in different levels of asthma severity.

Here is a summary slide. On the left-hand side, I'm showing patients achieving well-controlled; on the right-hand side, patients achieving totally controlled.

Without going into the details you can see that there was more patients or there was more control achieved by the combination product over fluticasone. And this is not based on FEV1, the base on asthma control, which I defined earlier. And the numbers are right here across the strata. And the sicker the patients, there's more improvement.

And also note that totally controlled asthma, which we tried to achieve was not really achieved in about half of the patients. So we have good drugs, but not necessarily that get us there. And now we're talking about removing salmeterol and formoterol from these choices.

Now I'll talk about the risk/benefit assessment and then come back and comment on some of the OSE comments here.

On the risk side, the main risk, of course, is asthma-related death. On the benefit side, it is that most patients derive symptomatic benefit in the form of various

control measures that we have talked about this morning. The main thing is how to balance this risk against the benefit.

Patients, health care providers, and society have accepted serious adverse reactions and even death in a small number of patients for symptom control in a large number of patients. And just a couple of minutes ago, we have heard two examples: Acetaminophen and NSAIDs.

These control -- these drugs provide symptom control, minor aches, and ailments, but have serious adverse reactions. So our view from the division side is that the safety risk of long-acting beta agonists can be managed through labeling to inform health care providers and patients of the risk and thereby directing use of these drugs to the appropriate patient population. And our position is consistent with the recommendation from the July 2005 Advisory Committee meeting. And as I said earlier,

also consistent with the U.S. asthma guidelines from NIH and also the global guidelines, the GENA document.

Now, let's think through some of the consequences of removal of asthma indication for long-acting beta agonists. It will reduce choice (inaudible) unable to control patients' asthma on ICS alone. The drugs are listed here, and I've mentioned the limitations of these drugs earlier.

Since LABAs are symptom relief medications, effects that are acute and noticeable by patients, patients will most likely use short-acting beta agonists chronically and at high doses and oral steroids with or without theophylline. This will shift and push back the asthma treatment and asthma care to where it was about 20 years ago. This shift will not reduce mortality, but may increase it. As we know, short-acting beta agonists itself may have risk of asthma-related death. And oral and

(inaudible) steroids have known safety risks. Theophylline is a narrow therapeutic index drug.

Now, another concern will be inappropriate use of long-acting beta agonists in patients with asthma. You need to keep in mind long-acting beta agonists are also proved for (inaudible) to the bronchospasm and for COPD. Therefore, health care providers and patients will have access to the medications and these can continue, although off-label use. And we have seen OSE's presentation commenting about the labeling and how effective it can be. And also keep in mind with the removal of the asthma indication specific recommendation regarding appropriate safe use of LABAs in asthma will also be removed from the label.

We have often heard about the possibility of removal of asthma indication for single-ingredient LABAs in favor of the combination products. Again, it would reduce

choice, choice for inhaled corticosteroids. Because what we'll have now are the two corticosteroids: Fluticasone and budesonide, which are available as combination products. And also, it will preclude combination use of inhaled LABAs with other long-term control medications other than corticosteroids. And, of course, we have heard about that there's no data that such combination can mitigate the risk.

Now let me move on and reflect on some of the comments that we have heard from our colleagues earlier in the session. Now, a couple of brief points about limitations of meta-analysis, and what I'm commenting here is for any meta-analysis be it for safety, be it for efficacy.

First of all, when meta-analyses are done they're very, very useful to overcome the problem of reduced surgical power in studies with some small sample sizes by pooling similar studies in appropriate,

orderly way. A weakness in meta- analysis is that any source of bias in the various original studies is carried forward. And one has to be very careful about the critical issues and lack of control of these can lead to bias. For example, how and what studies were selected, their heterogeneity in the results, conduct design of the studies, patient populations are all information that one needs is available and was an appropriate analysis performed.

And generally, a large, controlled, randomized clinical study is the gold standard of obtaining information of a specific question. And with long-acting beta agonists, we have the luxury of having two such studies.

But for rare events, the same points that I made earlier applies, and even can get magnified because they're even so small. And for rare events meta-analysis can actually become important because of lower

signals and lower sample sizes. But for these rare events, conclusions should be based on endpoints, and these require a good understanding of all potential bias introduced in meta-analysis.

Now, let me talk about a few points about the FDA meta-analysis. I'm just using the term OSE up here just to point out, but this is actually FDA meta-analysis conducted by our Office of Biostatistics. One point is that patient dropout is important and can confirm results. Differential dropout in placebo arm or less effected treatment arms compared to more effected treatment arms may result in patients staying longer in the active treatment arm or more effected treatment arm and, therefore, provide more adverse events of interest.

An example, if you look at the SMART trial, the number of dropouts in the placebo arm was 535 patients compared to 434 in the salmeterol arm, a difference of

approximately 100.

As for the comparators, no LABA which has been used as a comparator in the FDA meta-analysis is informative, but, again, has some limitations. It depends what question one is answering -- is asking. For example, to understand if LABA risk is mitigated by inhaled corticosteroid, the right comparator arm is ICS plus LABA versus LABA.

The fact that many studies were designed to address objective meta-analysis is not an issue of meta-analysis in general. The important point is whether data is ready for analysis.

Two of the points to keep in mind is whether the risk difference is constant or variable over time, and thus -- this -- and how this effects the selection of studies based on 30-day ration as a cutoff. We have seen the cutoff used in the FDA meta-analysis.

Another point to keep in mind, is it reasonable to exclude doses of drugs higher than labeled dose, which has been done in some meta-analysis? It's general knowledge that safety risk is generally dose-related with higher dose giving more safety findings.

Now I'll comment on meta-analysis for asthma-related death. And the question is really, what is the role of meta-analysis when large control studies are available? And they are. Risk can be diluted by inclusion of studies with limited duration of exposure at a low, even rate. Heterogeneity of patients, such as milder patients or patients on adequately controller drugs on board, we have low risk and can dilute the findings. And, of course, the non-LABA as a comparator would have the same effect.

Now, hospitalization is a very important consideration for asthma and is a major cause of asthma morbidity. The FDA

meta-analysis did a remarkable job to get data on this important endpoint. There are some points that you need to keep in mind as you review the hospitalization data in the FDA meta-analysis and other meta-analysis and see how informative these are.

The general expectation is that the asthma-related hospitalization will track with asthma-related death and intubation, if one is to believe that these are spectrum of LABA risk. In the FDA meta-analysis, this did not track. And all potential biases should be controlled, and we talked about the biases earlier.

And one important point is that the underlying cause of the hospitalization, as much as possible, should be obtained because it is very informative. Because the number of hospitalization events without accounting for the underlying cause of hospitalization does not provide a complete picture of the risk.

Now, you have seen part of this slide before at least twice. And what I'm showing here is the FDA meta-analysis, the primary endpoint stratified by age, the risk difference, and (inaudible) per thousand subjects, LABA versus no LABA. You have seen this before, which is a composite endpoint showing that the risk is high in the younger patients. You've also see and heard before that the risk is driven primarily by hospitalization. And there are some limitations in the hospitalization data which has commented -- which I commented to earlier.

For asthma death or asthma death and intubation, the FDA meta-analysis indeed does dilute the death signal seen in SMART. The asthma death risk difference in SMART is about .8 per 1,000. Overall risk death difference in this meta-analysis is approximately half of that. The overall death difference of -- in patients were

largely seen in patients 18 to 65 years of age and virtually not seen in younger patients.

In the same FDA meta-analysis Symbicort seemed to have the worst risk of all products, even worse than the single ingredient formoterol or Foradil here. This finding goes against other observation that the risk of asthma death and other related outcomes are seen more in patients with single-ingredient LABA products compared to patients on LABA plus ICS.

The two other points I would like to briefly make is in this slide. One, one needs to consider what patients are included under combination products Advair and Symbicort. To get a complete risk assessment, patients treated with fixed-dose combination products, as well as patients receiving both individual components contained in those fixed-dose products, should be included under the combination

product groups. Because the risk to patients is the same, whether they receive Advair Diskus as a single product or they receive Advair Diskus plus the steroid formulation.

Second point, the number of patients in this analysis and some of the published meta-analysis are different and we have seen some explanation before. And you need to understand to make sure that there's no potential bias introduced in selection or exclusion of studies.

In the FDA meta-analysis the number of patients in the two formoterol-containing products are very low compared to some published meta-analysis. To (inaudible) complete risk assessment study using all relevant products, either marketed in the U.S. or internationally, should ideally be included. And I believe the product Oxis, a Turbuhaler, which is a (inaudible) formulation of formoterol, which contributed about 8,000 patients, were not included.

The final couple of slides here, the unanimous OSE recommendation that you have heard before needs to be considered carefully in light of all existing data. As I discussed before, it is sort of questionable whether there's conclusive data that shows long-acting beta agonists below patients 18 years of age are more riskier. Withdrawal of drugs or contraindication of drugs are serious recommendations. With withdrawal, these drugs will not be available for patients. And contraindication would mean that these drugs should not be used because the risk of use clearly outweigh any possible benefit. It simply means do not use the drug, there's no benefit that can overcome the risk. And the consequences of removal you've heard before.

Briefly, some reflections on some OSE comments which you heard before and also in the briefing documents. One question is which benefit might outweigh the risk?

Again, this is a judgment call and we are asking you to opine on that. Again, the benefit is in larger number of patients who take these drugs. The risk is real and the numbers you have seen before.

And you have seen comments that LABA are more risky and less effective in patients below 18 years of age compared to older patients. And this is mainly driven by hospitalization. And conclusions and recommendations based on hospitalization from meta-analysis has many problems, as I discussed earlier.

On the efficacy side, I would like to comment that paucity of evidence does not mean that the drug is less effective. And, in fact, they have data down to four years of age that shows similar efficacy profile across ages.

And one point is that long-acting beta agonists and short-acting beta agonists are not necessarily fully interchangeable.

These are drugs that belongs to different classes. And in the current asthma treatment paradigm falls into categories: Short-acting pain reliever drugs for as-needed use; long-acting pain controller drugs, although the science in the future going forward may change. And perhaps some of the changes may come from the discussion here.

I'd like to reflect on the two large remaining questions that our colleagues in the OSE poses in the briefing document. And the questions are, which we have heard before: How does the safety and efficacy of short-acting beta agonists plus ICS compare with safety and efficacy of long-acting beta agonists plus ICS?

Again, as I said earlier, this goes somewhat different than the current paradigm of asthma treatment and APB and GENA, which recommends albuterol to be (inaudible) as-needed basis.

And the second question which I

think is quite important is, does concomitant ICS use mitigate the LABA risk in other patients? Our colleagues have proposed large safety studies of Advair and Symbicort to answer these two questions. And the proposed comparators are short-acting beta agonist plus ICS as a control arm, ICS as a control arm.

As one looks into this proposed study, there are a couple of thoughts that come to mind. Short-acting beta agonist plus ICS is not necessarily the standard of care. And it raises the question of using short-acting beta agonists chronically, perhaps on top of it using short-acting beta agonists on an as-needed basis for patients who are not adequately controlled.

Second, if short-acting beta agonist is found to be safer than low-acting beta agonist it will be very hard to imagine combination products containing albuterol with formoterol -- with, sorry, fluticasone

or budesonide, which are the steroids in Advair and Symbicort. Because the dose and frequency of albuterol is four times a day, whereas the steroids are four times a day. So we'll not really have (inaudible) with these specific steroids.

And another point is that the second question, which is a rather important question, is not going to be addressed by this design because of appropriate control in the LABA arm is missing. Based on NIPP and GENA guidelines and product labels for these long-acting beta agonists, it is unlikely that a large study with single-ingredient, long-acting beta agonists with mortality or other serious safety endpoint is actually even visible.

Some concluding remarks with the last two slides. Risk with long-acting beta agonists is real. Their mortality, serious risk. It happens in a number of patients, one can call it small, but the numbers are

all there. The worst-case scenario is from the SMART study and SNS study.

The benefit, which is, again, real, is in most patients. One way to vanish is to accept the risk and manage the risk by appropriate labeling, including dose warning, medication guide, inform patients and practitioners how to safely use this drug, and to label the drug for appropriate and safe use.

And finally, for our position has been that for patients four years of age and older LABAs should be used in patients not adequately controlled on other asthma-controller medications; e.g., low to medium dose ICS, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Long-acting beta agonists should not be used in patients whose asthma can be managed by the ICS alone with occasional use of inhaled short-acting beta agonists. For patients less than four years

of age, this is not approved.

Thank you very much.

DR. SWENSON: At this time, since we are behind schedule, we're going to shorten the scheduled break to ten minutes, and I'd like everyone back then to resume in ten minutes.

That will be 3:50.

(Recess)

DR. SWENSON: We'll begin this last portion of the meeting today with a first overview of Asthma Guidelines in the Diagnosis and Management, by Stuart Stoloff.

Dr. Stoloff?

DR. STOLOFF: Good afternoon. I'm Dr. Stuart Stoloff. I'm a family physician from Carson City, Nevada. I have practiced as a family physician, as a solo physician, for over 30 years. During that time, I have provided care, and continue to provide care, daily for infants, children, adults, pregnant women, and people that I put in the "older age group"; other people put them in the geriatric age

group.

For the past 15 years, I have also been a member of the expert medical panel for the Guidelines for the Diagnosis and Management of Asthma, of which some of my other colleagues are in the room at the present time.

Because of this special interest, it has allowed me to increase my practice in this field, and I presently have over 2,000 infants, adults, pregnant women and older individuals in my practice with that disease. So it's my pleasure to have an opportunity today to extend the comments that Dr. Lemanske started with, provide some other information. And I appreciate the opportunity.

What this next slide shows you is the United States, and what's going on on a daily basis in the United States. Asthma is not only common, it's a chronic disease, and when you look at it, about 5,000 people every

day end up in the emergency room in this country.

Additionally, 63,000 people miss work or miss school. And in fact, asthma is the number one reason why children miss school in the United States. Additionally, ten people a day die in the United States. So the death rate is not 5,000, the death rate is not 4,000, the death rate is somewhere between 3,400 and 3,600 in the United States.

So what is this disease? Well, this is a picture diagram you can look at, and the number one thing that you see is it is a bronchoconstriction. Now, for those of you not in medicine, what I'd like you to think of is a hose, and the outside of the hose has got a smooth area but you don't have a nozzle to turn off that hose, so what you do is you clamp it down with your hand. That is bronchoconstriction.

At the same time, unfortunately,

one of your kids got dirt and pebbles inside that hose, and that's inflammation. And these two components, this smooth muscle dysfunction, combined with the inflammation, can and do occur concurrently in asthma. And that's asthma. That's the pathophysiology.

So we have the guidelines. Well, the guidelines are actually a developmental process. The first guideline was in 1991, and in August 2007, as you heard, we released the third expert panel report, which utilized a strictly evidenced-based approach to care. It is a group of which I'm part of, and other members here are of -- 18 experts, and we worked for 3-1/2 years, and what we reviewed when we started was over 15,000 articles with over 2,100 full text reviews and approximately 80 percent -- somewhere between 50 and 80 percent looked at specifically therapeutics, pharmaco-therapy.

Now, we have evolved from that first version in 1991 that was a

consensus-based, to an evidence-based process. We have recognized that this disease is heterogeneous.

It involves, as I stated, both airway inflammation and a dysfunction of the smooth muscle that surrounds the outer airway. We do make our therapeutic decisions based upon how this airway inflammation and smooth muscle dysfunction play out and affect the patient. It is no longer a disease driven by severity; it is a disease for which it is driven by control.

And really, that should make sense to everyone in this room. When we think about high blood pressure, when we think about diabetes, when we think about hyperlipidemia, what are we really thinking about is what does it take to gain and maintain control. And these are chronic diseases, and asthma is a chronic disease. That's how we should look at this disease of asthma.

Now, as part of that, as for other chronic diseases, education by the clinician, and engagement of the patient with this education, is imperative. This therapeutic relationship of the patient, the physician, and the family is a key component, and it is a strong component in our guideline.

So where are we? Well, this is a picture that was just shown to you, but I've added some to this. This is the latest mortality data in the United States, and as you can see, the mortality incidence is diminishing. The height of it was approximately 1995, 1996. With the introduction of long-acting bronchodilators in approximately 1994, we have seen a change.

Is this change entirely due to a drug? No. The improvement is due to, one, education; two, a better understanding of the disease; and additionally, the improvements in the medications that we utilize. Educational efforts of the National Heart,

Lung, and Blood Institute, coordinated by the National Asthma Education and Prevention Program, have facilitated both the development of the guidelines as well as the dissemination of these guidelines.

Now, despite all these efforts, we still have approximately 10 people a day in this country dying from asthma.

So here are the definitions, and Dr. Lemanske put them up for you. We think of severity as the intrinsic state of the disease, and we define severity actually like a runner who's in the starting block at the start of a race. Before the gun goes off, that's severity. The minute he takes or she takes that first step, all we are interested in is gaining and maintaining control to meet our goal, the goal devised by the patient and the clinician, the physician.

We define severity most easily in patients who have a diagnosis of persistent asthma but are not on a controller therapy.

Control is defined by looking at the two domains: that is impairment and risk. And that is the key, looking at the present impairment and risk for the future. The decisions that we make, both pharmacologically as well as other therapeutic decisions, are based upon gaining and maintaining control, the same way we do in the other chronic diseases, as I discussed.

So what is the goal of therapy? Well, the goal is really gaining and maintaining control of the disease. It's established during a patient/physician dialogue. For any patient, regardless of the severity of the disease, we are always looking at both decreasing impairment and risk.

What's impairment? Well, impairment is the daytime symptoms, the nighttime symptoms, the use of quick relief inhalers, and most importantly, quality of

life for the patient.

We want, and our patients want, to be able to sleep, to work, and to play to their full capability. In addition, we want patients to have near normal or preferably normal lung function. At the same time, we look at risk. We want to reduce risk. Risk is an asthma exacerbation. We define an exacerbation in our document as an emergency room visit, a hospitalization, and use of oral corticosteroids. That's exacerbation. And regardless of the severity, we are always stating that the goals of therapy are the same -- a well-controlled individual.

So to help you with this, I'm going to tell you about a patient of mine. This is CJ. I've been taking care of him for quite some time. He's nine years old and he was given a diagnosis of asthma at approximately age two in another practice. He has symptoms during the viral season, which is actually right now. When he plays, and we'll talk

about this further, he has some difficulties especially when he's tried to play soccer. In addition, he is atopic with multiple allergies.

He came to me on a low dose inhaled corticosteroid, which is and was the appropriate therapy. He had also received quick relief medications. What I found out, however, on further questioning, was that he was having to use his quick relief medications unrelated to exercise three to four times a week. He had received two bursts of oral corticosteroids each for seven days in the past year, and he had to miss five days of school because of asthma attacks, as he called them.

He loved to play soccer; he could not play soccer anymore. He really wanted to play on the soccer team, but in fact when he could play, the only position he could play -- goalie. Now, he had relatively normal lung function, as you can see in the

bottom, an FEV1 of 88 percent predicted.

So CJ came in on this therapy, and once you're on a controller therapy, we assess control rather than severity to determine treatment, and what you see here are the two domains -- the domains of impairment and risk in his age group for assessing control. And if you remember, CJ was using a quick relief medication, what has already been called appropriately SABA, short acting bronchodilator, and he was using it regularly three to four times a week.

Looking at this figure, what you will see is, he falls in this category of not well-controlled. The category which is most severe when you look at controlled is where you define the level of control. So according to the guideline grid right here, he is not well-controlled despite being on what many would perceive appropriate therapy, a low dose inhaled corticosteroid.

I did a questionnaire on him, a

validated questionnaire. I used the childhood asthma control test. He scored 18. That is consistent with not well-controlled, so that went along here. In addition, I said he got oral corticosteroids, two bursts in the past calendar year. Right here, again, not well-controlled.

So what did I do for CJ? Well, I looked at our algorithms for care -- and this is exactly what I did, following the guidelines that we all wrote. He is no longer Step II. He is in Step III therapy. We had to step up. We talked about this as someone who was not well-controlled regardless of age, we need to step up therapy.

And for stepping up, I went to combination therapy. CJ got a combination concurrent of a low dose inhaled corticosteroid with a long-acting bronchodilator. And what you also see are some letters here, and these letters are

associated from the alphabet with the recommended therapy. These letters relate to the quality of the evidence to support our therapeutic recommendations.

A, low dose inhaled corticosteroids are double blind, randomized, placebo controlled trials in very large populations with a lot of wealth of data; B are double blind, randomized, placebo controlled trials but with much smaller populations with a limited body of data; C are observational and non- randomized studies. And D, when we see D, this is called panel consensus. So for our group of 18, based upon an extensive review of the literature, we determined what the preferred therapy was for each level of severity and control.

The preferred therapies were distinguished from alternatives. Inhaled corticosteroids plus a long-acting bronchodilator are preferred therapies at Step III, and in fact are the only preferred

therapies at Step IV through Step VI in children five to eleven.

What about for 12 and above? For ages 12 and above, the data is more robust. As you can see, evidence A here, for concurrent combination, low dose, inhaled corticosteroids with a long-acting bronchodilator, and these are based upon large, randomized, placebo controlled trials with a wealth of data.

What about the alternatives, down here? There is insufficient data, when we reviewed all the literature, to tell us which of the alternatives should be a preferred alternative. Therefore, we listed all the alternative therapies in alphabetical order, as shown in the figure.

Once you treat the patient and make a change, you need to have them controlled a minimum of three months. We looked at all the data in the world and found out that the key was three months. If you step down

therapy at an interval of less than three months, the risk of exacerbation increases. So I put him -- I put CJ -- on combination therapy.

Now, I previously discussed that we looked at a lot of robust data. Among the data we looked at was the Cochrane analysis, meta-analysis, written in 2005, and it provided us insight into how to make our decisions for the populations who were not well-controlled on monotherapy with a low to high dose inhaled corticosteroid.

And this looked at all the English language studies to the time. The combination of an ICS and a long-acting bronchodilator versus monotherapy with an ICS resulted in statistically and clinically less exacerbations requiring oral corticosteroids, as the first portion of the upper portion of the slide. The bottom portion of the slide shows you that the withdrawal rate is much less in the population who gets combination

therapy versus low to increasing to medium or high dose inhaled corticosteroids as monotherapy.

So what's happened to CJ? Well, CJ now is 10 years of age. I saw him this past month. I see patients every day when I'm not on the road. He's been on concurrent therapy of a low dose inhaled corticosteroid with a long-acting bronchodilator for over 10 months. So what's happened to him since I put him on this therapy? And that was changed about the middle of last year in the school year. Number one, he has no exacerbations. Number two, he has not missed a school day. Number three, the most important thing to CJ is, he's on a soccer team, he's on the traveling soccer team, he does not play goalie. He runs up and down the field.

So where are we? Well, we're with a disease that has 20 million individuals who have the disease at the present time.

Additionally, approximately 9.2 million children under the age of 18 have this diagnosis. That is one out of every eight children in the United States have a diagnosis of asthma. In the past decade, the mortality rate has decreased 35 percent.

Why? Better education, better understanding of the pathophysiology of the disease, and better therapy. We have a much better understanding of what appropriate therapy, including all medications, should be for the population.

So where are we? Well, just as in CJ, the concurrent use of an inhaled corticosteroid, combined with a long-acting bronchodilator, is an effective and safe treatment option for patients who are not well-controlled on monotherapy with low dose ICS, or if they come to me or any other clinician physician with a severity, a classification of moderate persistent asthma, not on controller therapy or on a controller

therapy but not well-controlled, our guideline recommendations are that therapy should be instituted with a low dose inhaled corticosteroid combined with a long-acting bronchodilator.

Today, CJ is well, but my concern for CJ and hundreds of my other patients like him is what options will be available to him and other children and adults if there is any restriction to access for long-acting bronchodilators.

Thank you.

DR. SWENSON: Thank you, Dr. Stoloff. We'll go now to GlaxoSmithKline, and Dr. Jones, who will start off.

DR. JONES: Good afternoon. My name is Elaine Jones, and I'm vice president of Regulatory Affairs at GlaxoSmithKline. On behalf of GlaxoSmithKline, I would like to thank the Agency and the Advisory Committees for this opportunity to participate in the review of the efficacy and safety data for salmeterol.

Our review of the benefits and risks of salmeterol will encompass data from all approved salmeterol-containing products. Current products available are Serevent Diskus, which contains only salmeterol, and Advair Diskus and Advair HFA, both of which contain salmeterol with the inhaled steroid fluticasone propionate in a single device.

As we have heard, after the first approval in 1990 in the United Kingdom, two large surveillance studies of Serevent were conducted. They were the Serevent Nationwide Surveillance Study, or SNS, and the Salmeterol Multicenter Asthma Research Trial, or SMART. In these two studies, there was an increase in serious asthma-related outcomes of Serevent, which helped contribute to the lingering concerns around the safety of salmeterol.

These studies did not mandate the concomitant use of inhaled corticosteroids, and their use was not monitored. However,

the results suggested that when Serevent was used in patients reporting inhaled corticosteroids at baseline, the risk of serious asthma-related outcomes was mitigated.

Immediately following termination of SMART in January 2003, an ADIA health care practitioner letter was distributed informing of the findings. A box warning was subsequently incorporated into the labeling for Serevent and Advair describing the asthma-related deaths in SMART, and suggesting that African-Americans may be at higher risk.

As Dr. Seymour presented earlier, in July 2005, the Pulmonary-Allergy Drugs Advisory Committee reviewed salmeterol data including SMART, and comprehensively evaluated the benefit/risk profile of salmeterol in the treatment of asthma. The result was a unanimous vote confirming the positive benefit/risk profile of long-acting

agonists for the treatment of asthma in patients four years of age and older.

As a result of recommendations of the Committee, additional labeling revisions were made for both Serevent and Advair advising that long-acting beta agonists should only be used in patients when a single controller agent is not sufficient. In addition, a medication guide was approved for distribution to patients.

In November 2007, the Pediatric Advisory Committee evaluated the spontaneous adverse event data obtained in the one-year period following the granting of pediatric exclusivity for salmeterol and to the Best Pharmaceuticals for Children's Act. The Committee concluded that no new safety signals were identified in the year following the granting of exclusivity. However, evaluation of pediatric hospitalizations from SMART, and studies with formoterol, resulted in the recommendation that a further

evaluation of the benefit/risk profile of long-acting beta agonist-containing products was appropriate.

In preparation for this Advisory Committee, GSK has extensively evaluated the benefits and risks of salmeterol-containing products. To explore the benefit of adding salmeterol to an inhaled corticosteroid in the treatment of asthma in adults and children, all clinical studies that were specifically designed to measure efficacy between salmeterol plus inhaled corticosteroids compared with alternative treatment options were analyzed.

In July this year, we submitted to FDA a safety database of GSK randomized control trials, including over 200 studies with a salmeterol-containing treatment arm, representing over 100,000 patients. GSK reviewed other databases to fully elucidate the benefit to risk profile of salmeterol-containing products.

Dr. Kate Knobil, head of Respiratory Clinical Development and a pulmonologist, will now present the evaluation of the benefit to risk of adding salmeterol to an inhaled corticosteroid in the treatment of asthma in adults and children.

DR. KNOBIL: Thank you, Dr. Jones. Today, I will discuss the safety and efficacy of salmeterol-containing medicines for the treatment of asthma, which includes both Serevent and Advair.

20 years of clinical experience, comprising nearly 60 million patient years of exposure, has demonstrated substantial efficacy and no significant increased risk of asthma-related events when salmeterol is used appropriately with an inhaled corticosteroid.

First, I will review the efficacy of salmeterol-containing products when used appropriately with an inhaled corticosteroid, which will include both Serevent and Advair.

Then, I will review the methodology for the main safety analysis, followed by the data for Serevent and then for Advair.

After the review of the data, Dr. Jones will return to discuss GSK's recommendations.

Here is a representative study that shows the benefit in lung function of adding salmeterol to an inhaled corticosteroid. This study compared Advair, shown in yellow, to fluticasone propionate, in green, Serevent in blue, and placebo in white. These graphs show the serial FV1 response to treatment over time, with Day One on the left and Week Twelve on the right.

As shown on the left, the onset of action after the first dose of salmeterol was within 30 minutes, and the duration of action was at least 12 hours. Shown on the right, lung function improved after chronic dosing with salmeterol, with no diminution of effect. At week 12, the FEV1 response for

Advair was over 600ml, which is a substantial improvement in lung function. Also, note that the effective FP never obtained the same benefit as Advair.

While not shown, symptoms in Albuterol use were also significantly improved over FP alone. This is just a single study, but all of the studies that have compared the efficacy of salmeterol plus an inhaled corticosteroid have consistently shown a benefit over ICS alone.

This slide includes all studies in adults and adolescents that were specifically designed to measure efficacy between salmeterol plus ICS compared with alternative treatment options. Each bar represents treatment difference in an individual study. For mean change and morning peak flow, the additional improvement provided by salmeterol added to ICS over that seen with ICS at the same dose is shown in yellow, over higher dose ICS in blue, and over ICS plus add-on

therapy with either Theofolin or Montalucast in white and purple.

In all of these studies, there was a statistically significant improvement in lung function for patients receiving salmeterol plus ICS over the alternative treatment options. These data show that salmeterol is a very effective bronchodilator, but that is only one measure of asthma control.

All patients with asthma should be provided a short-acting bronchodilator to relieve acute symptoms. Shown here as the percentage of days that patients receiving salmeterol plus ICS did not require rescue Albuterol to treat acute symptoms compared to patients receiving other treatments. In all of these studies, there was a statistically significant improvement in rescue-free days for patients receiving salmeterol plus ICS over alternative treatment options.

Extrapolating these data, adding

salmeterol to inhaled corticosteroids would result in two fewer months per year in which patients require rescue medication to treat asthma symptoms.

Finally, asthma exacerbations are an indicator of loss of asthma control, and as such, a reduction in exacerbations is one of the most important goals of asthma therapy. Shown here is a fourth plot of a meta-analysis of risk differences, which included 24 studies assessing severe asthma exacerbations requiring oral corticosteroids. Each study is listed on the left with the corresponding risk difference and confidence intervals plotted to the right.

An effect that favored the addition of salmeterol is to the left of zero, and an effect that favored ICS alone is to the right. The combined result, shown in yellow at the bottom, indicated that salmeterol added to inhaled corticosteroids, significantly decreased the risk of severe

exacerbations. The risk difference was minus 250 per 10,000 patients.

This means the 10,000 patients receiving salmeterol plus ICS would experience 250 fewer exacerbations than 10,000 patients treated with ICS alone.

The authors also reported the odds ratio for this outcome, which was .65, representing a 35 percent reduction in asthma exacerbations.

For the efficacy review in children, we included studies compared salmeterol plus ICS compared with a higher dose of ICS. This is consistent with the Advair label, which states that children must be symptomatic on an ICS before stepping up to alternatives like Advair. This representative study in children aged four to eleven years compared Advair in yellow to twice the approved dose of FP, shown in blue.

Treatment with Advair resulted in significantly improved lung function, and the

results for asthma symptoms and rescue-free days showed similar trends. Therefore, higher doses of inhaled corticosteroids may not provide better asthma control.

Exacerbations of asthma are the leading reason for missed school days in children, and that is one reason why preventing exacerbations is so important in this age group. Shown here are the exacerbation rates for all pediatric trials comparing Advair with the same dose or higher dose of inhaled corticosteroid. With the exception of one trial, treatment with Advair resulted in a similar or lower rate of asthma exacerbations. The three trials at the bottom of the table compared Advair with a higher dose of ICS.

Because of the risk of dose-related adverse events with ICS such as growth suppression, guidelines recommend that after achieving asthma control, ICS should be titrated to the lowest effective dose. The

addition of salmeterol to ICS allows for better overall asthma control and a lower dose of ICS.

In summary, results from randomized control trials consistently showed that Advair, or the combination of salmeterol plus ICS, provided better overall asthma control compared with alternative treatment options. As you heard in CJ's case from Dr. Stoloff, improvements in lung function, a decrease in the need for rescue medications, and the prevention of serious asthma exacerbations allows patients to achieve and maintain normal daily functioning, and reduces the number of missed school and work days. For these reasons, evidence-based asthma treatment guidelines place long-acting agonists plus ICS as preferred medications for treating patients with persistent asthma.

Before reviewing the safety data for Serevent, I will examine how salmeterol is used in clinical practice today. I will

then describe the methods of the meta-analysis of GSK clinical trials.

When Serevent was introduced in 1994, the role of inflammation and the pathophysiology of asthma was not as widely appreciated, and bronchodilators were often prescribed alone. As shown on the left in 1994 to 1996, only about one third of Serevent was dispensed with a concurrent inhaled corticosteroid. Another third was dispensed with no other controller medication at all.

The current understanding of asthma has changed since the 1980s and '90s, and now, asthma treatment guidelines and clinicians recognize that all patients with persistent asthma should be treated with an anti-inflammatory agent, preferably an inhaled corticosteroid. Today, for asthma, as shown on the right, salmeterol is dispensed with an ICS over 98 percent of the time, with the majority of this in the form

of Advair. Currently, 97 percent of salmeterol use is in Advair.

The safety data considered for analysis included all GSK-sponsored clinical studies of salmeterol which were randomized, controlled, double blind, and chronic dosing and design. The outcomes of interest were adjudicated by independent, external physicians based on blinded case narratives. If, in the clinical judgment of the physicians, the outcome could reasonably be considered asthma-related, then it was adjudicated as asthma-related.

Today, my review will focus on asthma-related death and hospitalization. Although I will not discuss asthma-related intubation and all-cause death in detail, the results are included in your briefing document.

The analysis populations constructed from the studies in the database allow for appropriate comparison of safety

outcomes between the treatments of interest. The comparison of salmeterol-containing treatments versus non-LABA treatments contain 215 studies, representing over 106,000 patients. The non-LABA group excluded any LABA treatment, and includes all other treatments, such as ICS, Theofolin, and placebo. This population is the most heterogeneous.

To aid in the interpretation of a potential treatment effect of salmeterol, more homogeneous populations were constructed. The groups shown on the far left evaluated salmeterol in the absence of ICS, compared with placebo, also with no ICS. To evaluate the effect of salmeterol in the presence of ICS, the populations were grouped by the way they received ICS in the study, corresponding to the degree of control of the use of ICS; therefore, the level of confidence and adherence to ICS increases as you move from left to right.

In the first, salmeterol was added to background inhaled corticosteroids. It is important to understand the difference between ICS given as a background medication and ICS administered as a study drug. Background ICS refers to patients who reported taking an ICS prior to the screening visit and who were instructed to continue that ICS throughout the study. However, there was no systematic reinforcement or any measure of continued adherence to the ICS.

The confidence in the adherence ICS as a background medication is lower than in the other treatment comparisons.

ICS administered as a study medication with salmeterol in separate blinded inhalers is the next treatment comparison. In this comparison, there was systematic reinforcement of adherence. However, patients could selectively discontinue either one of the inhalers.

Finally, salmeterol and ICS could

be administered as a blinded study medication in a single inhaler as Advair. Only this last analysis population evaluated outcomes when the concurrent use of salmeterol and ICS was assured.

For safety, I will first review the data for Serevent in the overall population. For our meta-analysis, risk differences will be expressed per 10,000 patients, to be consistent with the way results from SMART have been incorporated into the Serevent and Advair labels. FDA reported results as risk differences per 1,000 patients, and in general, the results reported by FDA and GSK were consistent.

The first outcome that I will discuss is asthma-related death. For all of the risk difference comparisons I will show you, the analysis populations and corresponding outcomes will be listed on the left, and the risk differences per 10,000 patients will be on the right.

For salmeterol versus non-LABA-containing treatments, there were 28 asthma-related deaths in patients receiving salmeterol and seven asthma-related deaths in patients receiving non-LABA. Of note, all but five of the 35 total asthma-related dates occurred in SNS and SMART. These studies were initiated in the early to mid-1990s, which was a time when inhaled corticosteroids were not as routinely used as they are today. Since this top population is the most heterogeneous, the treatment comparisons below this one are more informative for specific treatment regimens with Serevent.

It is now well-accepted that Serervent should not be used with without an anti-inflammatory medication in persistent asthma. The data showed that Serevent, when used without an inhaled corticosteroid, had a risk difference of nearly nine per 10,000, and this increase in asthma-related death is already described in the product label.

As we move down the next three analysis populations, the confidence and adherence to ICS increases. When Serevent was added to background ICS, which was not dispensed as part of the study, there were five asthma-related deaths on Serevent and three on ICS. All of these events occurred in SMART.

When Serevent and ICS were both given the study medications in separate inhalers, there was one asthma-related death with Serevent, and none with inhaled corticosteroid.

As a point of reference, Advair data are included on the slide, and I will discuss these data in more detail later in my presentation. When concurrent use of ICS was assured, there were no asthma-related deaths for patients receiving Advair.

There were more patients with an asthma-related hospitalization, so this outcome was more amenable to analyzing the

more homogeneous treatment comparisons. For Serevent compared with placebo, each without ICS, which again is not acceptable management of persistent asthma because it does not control inflammation, the risk was elevated.

Why would the risk be elevated versus placebo? Serevent is an effective bronchodilator, and chronic use may blunt the patient's awareness of worsening underlying airway inflammation, and could lead to a delay in seeking appropriate medical attention. This behavior is an established risk factor for untoward outcomes in asthma.

Similarly, when comparing the use of Serevent added to background ICS, with background ICS alone, the risk difference was also elevated. This was an unexpected finding, and a possible explanation for this increased risk may be that patients, because they feel better, selectively discontinued non-study ICS during the clinical trials.

Why would patients taking

salmeterol with background ICS have worse outcomes than background ICS alone? These data from table two in your briefing document show that even in the absence of Serevent, the risk of hospitalization was five times greater in patients reporting background use of ICS compared with patients receiving ICS as a study medication. There was also an increase in asthma-related death in this population. These data suggest that patients discontinued their background ICS during the study which resulted in severe asthma outcomes. Using an effective bronchodilator like Serevent improves symptoms, and patients may be more likely to discontinue their inhaled corticosteroid.

This leaves inflammation untreated which is associated with an increase in serious asthma morbidity and mortality. Thus, the inappropriate treatment of asthma, specifically under-use of inhaled corticosteroids, can lead to an increase in

asthma-related outcomes.

If we now examine the population where Serevent and inhaled corticosteroid were both administered as study drug in separate devices, there were 16 hospitalizations in patients receiving Serevent plus ICS, and 14 hospitalizations with an ICS and study drug. This was a difference of two events in nearly 6,000 patients.

When salmeterol and inhaled corticosteroid were administered in the same device as Advair, there was no increase in risk.

I will now review similar safety information in the pediatric population. For the majority of studies, these patients were between the ages of four and eleven. The review of Serevent data included 37 studies in over 7,400 children. There was one asthma-related death, and this occurred in a patient that was receiving Albuterol four

times daily.

Although not discussed in detail for the overall population, we felt it also important to mention the occurrence of intubations in children, since it may be considered a surrogate for risk of asthma-related death. There were two asthma-related intubations in children. One occurred in a patient that was receiving Albuterol four times daily in a different patient than in an asthma-related death, and then the other occurred in a patient receiving Serevent. None of the children experiencing these events were receiving concurrent inhaled corticosteroids.

An examination of asthma-related hospitalization found similar results in children as in the overall population. If we look at the specific treatment comparisons for Serevent compared with placebo, the number of events was low, but resulted in an elevated risk difference. When comparing the

use of Serevent added to non-study background ICS with background ICS alone, the risk difference was also elevated in this population.

The most plausible explanation, as discussed for the overall population, is that more patients on Serevent selectively discontinued their background inhaled corticosteroid during this study, thus leaving airway inflammation untreated.

If we now examine the population where Serevent and ICS were both administered as a study drug in separate devices, there was one hospitalization in children receiving Serevent plus ICS, and two in the children receiving ICS alone. Similarly, there was one hospitalization in children receiving Advair compared with two receiving ICS alone.

Concurrent use of Serevent and inhaled corticosteroids was shown to be highly effective for the treatment of asthma in adults and children by demonstrating

substantial improvements in lung function, decreased symptoms, and a decrease in asthma exacerbations. A fixed dose combination may not meet the needs of all patients. There are patients who need a different ICS than fluticasone propionate, or need a different dose of ICS than is available in Advair. It also allows for easier titration of ICS for patients who require frequent changes in their regimen. Although it may be a relatively small number, it is important that those individuals who cannot use a combination inhaler have effective options available to them. There was an increased risk of serious asthma outcomes with Serevent when ICS use was not controlled. However, there was no safety signal when Serevent was used concurrently with inhaled corticosteroids.

GSK acknowledges that there is a question as to whether Serevent should continue to be indicated for the treatment of

asthma. Removing the asthma indication and thus restricting the use of salmeterol and asthma to the combination product Advair would ensure the appropriate use of Serevent with ICS. However, this would limit choice for physicians and patients and could have a negative impact on patient care.

Balancing these considerations, we favor continued availability, and have proposed the labeling changes and will discuss a plan of action to reinforce that Serevent should only be used concurrently with inhaled corticosteroids.

Patient safety is our top priority, and we believe that the benefits demonstrated by Serevent, used concurrently with an inhaled corticosteroid in asthma, outweigh the potential risks in the population of patients who need broader treatment options.

You've already seen some of the data with Advair, and now I will provide a more comprehensive review. Since the

majority of current salmeterol use is in Advair, the meta-analysis of safety data from the Advair clinical trials is more reflective of how salmeterol is used today. The results of the meta-analysis of the Advair data for the overall population are shown here.

There were no asthma-related deaths in over 22,000 patients receiving Advair or ICS. Further, there was no increased risk of asthma-related hospitalization in this population. Although not shown on the slide, there were no asthma-related intubations in patients receiving Advair.

I will now review the meta-analysis results for Advair in children. Similar to the overall population as shown on the previous slide, the results for Advair in children were positive. There were no asthma-related deaths in over 2,400 children receiving Advair or ICS. Further, there was no increase in risk of asthma-related hospitalization in children. Although not

shown on the slide, there were no asthma-related intubations in children receiving Advair.

African-Americans experience comparatively greater asthma morbidity and mortality than Caucasians and other ethnic groups. SMART found an increased risk of serious asthma-related outcomes for African-Americans receiving salmeterol, and nearly all of these events occurred in those not reporting use of ICS at baseline.

In response to SMART, GSK conducted a yearlong study in African-Americans to examine the rate of asthma exacerbations between Advair and FP. The results showed no significant difference in the rate of asthma exacerbations in patients receiving Advair compared with FP, demonstrating that appropriate use of salmeterol with an inhaled corticosteroid was not associated with an increased risk of exacerbations in African-Americans.

We also examined the number of asthma-related hospitalizations in all African-American patients in all studies comparing Advair and ICS. There was no increase in asthma-related hospitalizations with the addition of salmeterol to ICS. These results were similar to the overall population. There was no evidence to suggest that African-Americans are at increased risk for serious asthma-related outcomes when using Serevent or salmeterol concurrently with ICS.

I will now move to the results of studies of use of Advair in clinical practice. For observational studies of Advair, odds ratios were reported, so they'll be presented here in the same manner.

In order to assess the overall effect of the use of Advair in adults in clinical practice within the U.S., a meta-analysis was undertaken of all observational cohort studies that compared

Advair to ICS. A total of four studies comprising nearly 83,000 patients met the a priori criteria for study inclusion, with 59,000 receiving Advair. Treatment with Advair resulted in a combined odds ratio of .84, which corresponds to a 16 percent decrease in patients with an asthma-related emergency department visit compared to patients treated with ICS.

For asthma-related hospitalizations, the combined odds ratio shown in yellow on the lower half of the screen was .85, corresponding to a 15 percent decrease in patients with asthma-related hospitalizations with Advair compared to patients treated with ICS. These data show that Advair significantly reduced severe events over and above that seen with ICS alone.

In pediatrics, a similar meta-analysis was performed, including over 43,000 children and adolescents, with over

16,000 receiving Advair. The analysis included diverse populations ranging from Medicaid patients to patients with mild asthma. Due to the low frequency of asthma-related hospitalizations observed in these studies, only the combined endpoint of asthma-related emergency department visits and hospitalizations is shown.

The studies above the dotted line compared Advair to ICS alone. The combined odds ratio was .91, which corresponds to a 9 percent decrease in the number of patients with an emergency department visit or hospitalization. This analysis showed that Advair was significantly more effective in reducing this outcome in children than ICS alone.

The studies below the dotted line compared Advair to ICS plus Montelukast in children. The combined odds ratio was .46, which corresponds to a 54 percent decrease in the number of patients with an emergency

department visit or hospitalization, again showing that Advair was significantly more effective than the combination of ICS plus Montelukast in reducing this outcome in children.

For Advair, the benefit to risk profile is positive for adults and children. Advair is highly effective in the treatment of asthma, and has demonstrated substantial efficacy in improvement in lung function, decreased symptoms and a decrease in exacerbations.

Use of Advair was also associated with significant reductions in emergency department visits and hospitalizations versus ICS alone in adults and children, and also a reduction in a combined emergency department visit and hospitalization versus ICS plus Montelukast in children. Therefore, alternative treatment options may not be more efficacious.

The combination of salmeterol and

FP in a single device ensures concurrent use of the ICS, and does not allow selective discontinuation of ICS. There is no evidence that Advair is associated with the risks identified in the early studies of Serevent. This comprehensive review of Advair, which included nearly 18,000 patients from randomized clinical trials, as well as over 75,000 patients from observational studies, did not identify any increased risk associated with Advair. There were no asthma-related deaths reported in children or adults taking Advair, and there was no increase in asthma-related hospitalizations. While I did not show the data, there were no asthma-related intubations and no increase in all-cause death.

The case for Advair is clear. Substantial efficacy has been demonstrated, and there is no increased risk of untoward asthma outcomes. The case for Serevent is more complex. We know that it is

inappropriate to use long-acting beta agonists alone to treat asthma, and the data show that the use of Serevent alone is associated with increased risk.

However, there was no significant increase in risk when Serevent was used concurrently with inhaled corticosteroids. For the relatively small number of patients who deserve access to guideline preferred therapy, but whose needs cannot be met with Advair, it is important that Serevent remains available.

I would now like to turn the podium back over to Dr. Jones, who will discuss the actions that GSK is recommending to ensure appropriate use of this important medication.

DR. JONES: As Dr. Knobil has shown, there is a positive benefit to risk profile when salmeterol is used concurrently with an inhaled corticosteroid. The most effective way to ensure the concurrent use of inhaled corticosteroids is by the fixed-dose combination

products.

While Advair meets the medical needs of most patients, there are some that require separate inhalers, and for these individuals, it is important that Serevent remains available. Therefore, GSK recommends the following actions to prevent inappropriate use of Serevent in the treatment of asthma.

The first action, already undertaken, was submission of a labeling supplement. This action was taken in September and is currently under review. The indications section was revised to restrict the use of Serevent in patients with asthma to concomitant therapy with an inhaled corticosteroid.

Also, information concerning the risk of asthma-related hospitalizations was added to the box warning that already included a warning for asthma-related death.

Finally, for patients, the

medication guide was strengthened to reinforce that if using Serevent Diskus to treat asthma, an inhaled corticosteroid must be used every day. It also emphasizes that patients must continue taking an inhaled corticosteroid every day, and must not stop or decrease the dose even if they feel better.

The next step is the enhancement of our risk management approach, which builds on the important changes to the label that I've just reviewed. The comprehensive plan targets health care providers, pharmacies, and patients. For health care providers, in addition to the labeling revisions, GSK is proposing to communicate with all health care providers who prescribed or dispensed Serevent in the last year, emphasizing concurrent use of Serevent with inhaled corticosteroids. In addition, we will initiate educational programs emphasizing that Serevent should only be used with an

inhaled corticosteroid.

Next, GSK will work with managed care and pharmacy benefit management organizations and retail pharmacies. This initiative will change fulminary (?) Algorithms, update pharmacy computer systems, and inform physicians of these changes. This would result in the pharmacist being alerted that Serevent is being prescribed without an inhaled corticosteroid and should have contact with a physician.

Finally, to communicate to patients directly, in addition to revisions to the medication guide, GSK proposes changes to the packaging for Serevent Diskus, alerting patients that in the treatment of asthma, Serevent must only be used as concomitant therapy with an inhaled corticosteroid.

This risk management plan will enable the safe and appropriate use of Serevent in the treatment of asthma.

In conclusion, we have presented

data showing Advair and Serevent plus inhaled corticosteroids provide substantial benefits to patients with asthma, and these medicines have significantly advanced the care and well being of both adults and children. These medications remain a preferred treatment option in the NHLBI evidence-based asthma treatment guidelines. Denying access to these life changing medicines would be extremely detrimental to patient care. It is critical that these medicines continue to be available to maintain the high standard of care that is currently available to patients with asthma.

Thank you.

DR. SWENSON: Now we'll turn just with a slight departure from the schedule, to the representatives from Novartis, who I think we'll begin with Mathias Hukkelhoven to begin the presentation.

DR. HUKKELHOVEN: Dr. Swenson, Dr. Rappley, members of the three Advisory

Committee meetings, members of the FDA and guests, good afternoon. My name is Mat Hukkelhoven. I'm the Global Head of Drug Regulatory Affairs at Novartis. It's a pleasure to present today on behalf of my colleagues -- and Linda Armstrong will present as well -- the safety and efficacy data for Foradil.

To begin with, I will present the regulatory history of Foradil, part of which has actually already been very well-explained by Dr. Seymour.

Foradil was first approved in 1990 in France, and is currently approved in over 80 countries. In the U.S., Formoterol was approved in 2001 under the tradename Foradil Aerolizer for the maintenance treatment of asthma in patients five years of age and older, for the acute prevention of exercise-induced bronchospasm, and for the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD).

Foradil Aerolizer consists of capsules for oral inhalation containing 12mcg of Formoterol and a delivery device, a single-dose dry powder inhaler, the Aerolizer. The approved dose is 12mcg twice daily, which corresponds to a total daily dose of 24mcg. In the U.S., Novartis is the NDA holder for Foradil Aerolizer, and Schering-Plough Corporation markets the product. In addition, Foradil Certihaler, a multi-dose dry powder inhaler which contains 10mcg of Formoterol per activation, is approved at the dose of 10mcg BID, corresponding to a total daily dose of 20mcg.

It was approved in 2006 for the maintenance treatment of asthma five years of age and older, but it is not marketed. I mention the total daily dose, TDD, as this is how the results of the clinical data analysis will be presented.

Outside of the U.S., Foradil Aerolizer is approved in many countries at 12

to 24mcg BID, which corresponds to a TTD of 24 to 48mcg for the prophylaxis and treatment of asthma in patients five years of age and older, for the prophylaxis of bronchospasm induced by inhaled allergens, cold air, or exercise, and for COPD.

Note that the 24mcg BID dose which is twice the approved dose in the U.S. is only recommended in adults.

In some countries, Formoterol is also approved as an inhalation aerosol in the MDI, and as Foradil Certihaler which is also not marketed ex U.S. Although Formoterol is approved for multiple indications, the focus of today's meeting is of course asthma, and the analyses to be presented are based on the studies in asthma.

Events leading up to the meeting today following approval of Foradil Aerolizer in 2001 include the Pulmonary Advisory Committee meeting in 2005 to discuss the safety of LABAs, and the subsequent labeling

revisions for Foradil in 2006. In 2007, the Pediatric Advisory Committee meeting raised, as has been discussed before, concerns about safety of LABAs in pediatric patients with asthma, and recommended that this be further discussed at a subsequent meeting. As a result, early this year, FDA requested information regarding controlled clinical trials conducted with LABA for manufacturers of LABA containing products. Dr. Armstrong will be presenting this data, specifically the events of interest identified by FDA which we have termed "serious asthma exacerbations."

I would like to focus for a moment on the 2006 labeling revisions. At that time, a box warning was added to the Foradil label. The box warning addresses the possible increased risk of asthma-related death for LABA as a class based on the signal seen with salmeterol in the SMART study. It also clearly advocates the concomitant use of

inhaled corticosteroids with Formoterol.

The label revisions of 2006 also included the addition of data on the incidence of serious asthma exacerbations from the three pivotal Foradil registration trials, including data from the one-year pivotal pediatric study which you see here, and where we did observe a higher incidence of serious asthma exacerbations in the Formoterol groups compared to placebo.

Note that all three registration studies were conducted in the 1990s before inhaled corticosteroids became the standard of care. Please also note that the incidences of serious asthma exacerbations outlined in the label differ from those outlined in the briefing document provided by Novartis in preparation for this meeting. Those in the label include all events up to 30 days following the end of treatment, and those in the briefing book included events to the end of blinded treatment, as requested by

FDA.

The label update also included the results of two pivotal registration studies in adolescents and adults, and in these two trials, we saw no difference in serious asthma exacerbations in the 12mcg BID group compared to placebo. However, since there was a small increase in serious asthma exacerbations in the highest dose, the 24mcg BID, FDA asked for a post-marketing study specifically investigating serious asthma exacerbations at the approved dose and twice the approved dose.

In this slide, you will see the labeling resulting from this post-marketing study which was completed in 2004. As you can see, there was no dose response observed, and the incidence of serious asthma exacerbations was actually very low.

Since approval of Foradil Aerolizer, a number of activities have been completed or are ongoing to evaluate and

minimize the risk of serious asthma exacerbations. These include a post-marketing commitment study that I just mentioned, which is reflected now in the label and will be discussed in greater detail by Dr. Armstrong in the next presentation.

Also, we did pharmacogenetic analysis looking at polymorphesence (?) in the receptor from two Phase III Formoterol studies which was submitted to the FDA through a voluntary genomic data submission; epidemiological studies to investigate the incidence of serious asthma exacerbations, asthma related emergency room visits, hospitalizations, and intubations; global pharmaco-vigilance to review and assess events, with a focus on asthma-related serious adverse events, and that for Formoterol, revised labeling as explained as well as the addition of a medication guide in 2006 to reflect the potential risks and to describe the appropriate use of Formoterol.

And finally, education and communication of risks through a website that educates prescribers and consumers on the appropriate use of Formoterol.

Our clinical presentation by Dr. Armstrong will show that based on a review of clinical data from Novartis and publications for Formoterol, in the context of the current treatment guidelines and the approved label, and based on our post-marketing surveillance data both from the Novartis ARGUS database as well as the FDA AERS database, we conclude that Foradil continues to exhibit a favorable benefit/risk ratio. Please note that no deaths or intubations were observed in children in any of our controlled studies with Formoterol, so all serious asthma exacerbations were hospitalizations.

Furthermore, Formoterol remains an important therapeutic option in the treatment of patients with asthma. Further, that the

continued availability of non-combined LABAs provide flexibility in choosing the type and dose of inhaled corticosteroids, and that the appropriate use of Foradil is adequately outlined in the current labeling.

Based on the outcome of this Advisory Committee meeting today and tomorrow, we will work with FDA to update the label and medication guide as appropriate.

Dr. Linda Armstrong from our Clinical Development and Medical Affairs Department at Novartis will now present our clinical data on Foradil. In addition, Dr. Gary Cook from the University of North Carolina and Dr. James Kemp, clinical professor of pediatric oncology, are also attending on behalf of Novartis and are available to answer any questions.

Dr. Armstrong?

DR. ARMSTRONG: Thank you.

As Dr. Hukkelhoven has just mentioned, our data support that Foradil,

when used according to the product label and treatment guidelines, continues to have a positive benefit/risk profile, and should remain available for the treatment of asthma.

I will start with a review of the efficacy and safety data from the three pivotal trials that were the basis for Foradil's approval in 2001, and a safety study that was conducted as a post-marketing commitment. I will then describe the pool data that Novartis provided to the FDA. I will review the use of the drug in the United States and reports of spontaneous asthma-related events. And finally, I will address the overall benefit/risk profile of long-acting beta agonists, including Foradil, in the treatment of asthma.

The asthma treatment paradigm has evolved, and the treatment guidelines have been updated over the 17 years in which Novartis has conducted Foradil trials. When the pivotal trials were designed and

conducted between 1995 and 1998, inhaled corticosteroids were not yet considered the standard of care for asthma, and in fact, regularly dosed Albuterol was widely used to treat patients with persistent disease and was used as an active comparator in many of our trials.

As Dr. Lemanske stated, regularly dosed Albuterol in the Baggs and Barts Study was found to be no more effective than PRN dosing, and might be harmful in some patients.

These are the three pivotal studies that supported the registration of Foradil. Remember that given the time frame in which these studies were conducted, only about half the patients reported inhaled corticosteroid use at any time during this treatment period.

In these trials, approximately 500 adolescent and adult patients, randomized to receive Foradil either 12mcg twice daily, the approved dose, 24mcg twice daily, Albuterol,

dosed regularly four times a day, or placebo. Patients in all of the treatment groups were to remain on their stable controller medications, including inhaled corticosteroids, and were permitted to use Albuterol as needed.

As you can see from the results of Trial 40, Foradil showed superior efficacy compared to placebo and Albuterol after 12 weeks of treatment. This improvement was measured by lung function, improved symptom control, and decreased use of rescue medication.

After 12 weeks, even before treatments, patients treated with Foradil 12mcg, shown here in green, demonstrated a significantly higher baseline FEV1. After dosing, FEV1 remained significantly higher than placebo, which is shown in white. In contrast, patients treated with Albuterol, shown in blue, had an initial improvement after dosing which returns to baseline within

four hours. Note the troughs with Albuterol. These may be associated with increased symptoms during the course of the day or overnight.

On average, patients treated with Foradil demonstrated a 22 percent improvement in FEV1 from baseline. A responder analysis showed that within 60 minutes of dosing, 89 percent of patients demonstrated an improvement in FEV1 that was clinically significant.

This improvement in lung function was also associated with improvements in other measures of asthma control, including asthma symptoms and rescue medication use. The Y axis shows the median symptom score which was measured on a five point scale from zero to four. At baseline, the median score was one. Patients treated with Foradil had a 30 percent reduction in symptoms.

This improvement was associated with a decrease in rescue medication use. In

contrast, patients treated with Albuterol had a smaller reduction in symptoms, and as expected, patients on placebo remained symptomatic.

In this graph, the Y axis is median inhalations of rescue medication. At baseline, most patients use between one to two inhalations during the day. By the end of the trial, rescue medication use was 60 percent lower in the Foradil group compared to placebo.

A similar trend was seen for nighttime symptoms and rescue medication use. Because many patients with asthma are troubled by symptoms at night, the impact of a medication on nocturnal symptoms and rescue medication use is of particular clinical interest. Here, the Y axis shows the median symptom score for nocturnal symptoms. At baseline, the median score was .7. Patients treated with Foradil had a 70 percent reduction in symptoms. This was associated

with fewer nocturnal awakenings and a decrease in rescue medication use.

In the Y axis of the next graph, the median inhalations of rescue medication during the night are recorded. At baseline, again, most patients use one to two inhalations per night. By the end of the trial, rescue medication use at night was 70 percent lower in the Foradil group compared to placebo. Although not measured in this study, patients treated with Foradil had demonstrated significant improvements in quality of life compared with placebo in other clinical trials.

Turning now to safety, there were no asthma-related serious adverse events in patients receiving Foradil 12mcg twice daily. There were four asthma-related serious adverse events in the 48mcg group, two in the Albuterol group, and no events in the placebo group. In the other pivotal trial, there was one event in the approved dose group, five

events in the higher dose group, none in the Albuterol group, and two in the placebo group.

These are the results of the trials that were the basis for the adult and adolescent approval in 2001. What does the pediatric data look like?

Novartis has conducted seven trials in children to support approvals. Most of the placebo controlled data comes from Study 49 which was a one-year study conducted in children five to twelve. 518 children were randomized to four 24mcg twice daily, 12mcg twice daily, or placebo. Patients were required to use concomitant anti-inflammatory medications, although compliance with these medications was not monitored.

75 percent reported using inhaled corticosteroids at any time during the treatment period and mostly they were on low dose becla-methasone, triamcinolone, and budesonide. As with the overall population

in our studies, pediatric patients treated with Foradil in Study 49 demonstrated significant improvements in average FEV1. Patients treated with 12mcg BID demonstrated a 150ml improvement over placebo, which is a 10 percent improvement in lung function. This improvement was shown after 12 weeks of treatment, which is the primary endpoint, and maintained throughout the one-year trial.

12 micrograms twice daily was selected as the lowest effective dose with the greatest benefit/risk profile. Although higher doses are approved for adults in some countries, 12mcg twice a day is the maximum daily dose for children worldwide.

The overall improvement in pediatric patients was confirmed in analysis of daytime symptom reduction. Throughout the one-year trial, Foradil decreased daytime symptom scores by more than 50 percent. This improvement in symptoms was accompanied by a similar reduction in rescue medication use.

Patients did not have to be symptomatic for inclusion in this trial, which explains the relatively mild symptoms at baseline, but in those patients with baseline symptoms, the reduction in symptom and rescue medication use is clinically relevant.

Deterioration days is a composite endpoint that was used in this study to describe days in which patients use more than four puffs of rescue medication, had a symptom score greater than one, or used additional controller medications. Patients treated with Foradil had a 45 percent reduction in deterioration days, confirming the benefit in this population.

Once again, Foradil also decreased nighttime symptom scores by almost 50 percent, and additionally decreased the use of nighttime rescue medication. These improvements persisted throughout the one-year trial.

In the safety analysis of 49, there were more asthma-related SAEs among patients receiving Foradil compared with placebo. Note that there were no asthma-related SAEs among patients randomized to placebo. This is unusual, as other long-term studies in children have demonstrated asthma-related hospitalization in the 1 to 4 percent range for placebo-treated patients. Eight subjects randomized to 12mcg twice daily, and 11 randomized to 24 experienced asthma-related SAEs throughout the course of the one-year trial. There were no deaths or intubations during this trial.

Although there were no SAEs among the placebo patients, the premature discontinuation rate was actually higher among placebo patients than those who were treated with Foradil. These patients were quite symptomatic, often describing severe symptoms with increased rescue medication use and significant reductions in peak flow, who

required multiple courses of oral corticosteroids.

Patients who discontinued were not followed after dropping out of the trial. A disproportionate dropout in patients may have lead to a healthy survivor effect in the placebo arm, meaning that better-controlled patients remained in the study and were less likely to experience serious adverse events. These limitations do not fully account for the imbalance that we saw in Study 49; however, they do make it more difficult to fully assess the magnitude of risk associated with Foradil in this study. This study was the basis for approval for Foradil in patients five to twelve, and is reflected in the current label.

Studies 40, 41, and 49 were conducted 15 years ago. After approval, Novartis conducted Study 2307 as a post-marketing commitment. It was designed to further assess whether an imbalance in

asthma-related hospitalizations, seen between the 12 and 24mcg doses, would be confirmed in a larger safety study.

Four times the number of patients in the pivotal trials were enrolled in this study. 2085 patients 12 years of age and older were randomized to receive Foradil 12mcg twice daily, 12mcg twice daily plus PRN Foradil, Foradil 24mcg twice daily, or placebo. The inclusion and exclusion criteria were matched to approximate the populations enrolled in the earlier studies.

Patients were to continue their anti-inflammatory medications. 70 percent were taking inhaled corticosteroids, compared to 50 percent in the earlier trials. The number of events was lower than anticipated, and the differences between the treatment groups were similar. There were three events in the 12mcg group, one in the 12mcg plus PRN group, two in the 24mcg group, and one in the placebo group.

These four studies are the largest studies included in the pooled data set requested by the FDA. 45 clinical trials met the FDA's pre-specified criteria. They were randomized, blinded asthma studies in which Foradil was delivered by the Aerolizer or the Certihaler devices. More than 8,000 subjects were randomized in these trials.

Approximately 5,300 received Foradil, 2,000 received placebo, and almost 1,000 received Albuterol, delivered primarily as a 180mcg four times a day.

In all groups, patients were permitted to use Albuterol PRN and continue their controller medications. Foradil was studied at three dose strengths, 12mcg total daily dose, which was studied as either 6mcg twice daily or 12mcg as a single daily dose; 24mcg total daily dose, the approved dose in the United States studied as 12mcg twice daily or 24 as a single daily dose; 48mcg, studied as 24mcg BID. We'll focus on

comparisons between the marketed dose of Foradil with placebo and also regularly dosed Albuterol.

Although the pooled safety database provides important information, it doesn't address the question of whether or not any inhaled corticosteroids mitigate the risk of serious exacerbations. As you may recall, most of the Novartis studies occurred prior to the time when ICS became the standard of care, and in our database, inhaled corticosteroid use was permitted in 41 of the 45 trials, but were required in only four studies, including only two multiple dose studies. In all the other studies, ICS were not provided by the sponsor, nor was ICS compliance monitored.

The focus of the pooled analysis is the asthma composite endpoint, which was defined by the FDA as asthma-related deaths, intubation, or hospitalization. This differs from events described in our label in that

asthma-related SAEs may also include other medically important events such as ER visits.

Events occurring between randomization and the final day of double blind treatment for parallel group studies, or the end of the first period for crossover studies, were identified by blinded physician review of the clinical trial database.

In contrast, our label includes SAEs reported up to 30 days after discontinuation of the study medication. In our analyses, we've compared Foradil to placebo and regularly dosed Albuterol, while the FDA has compared LABAs to non-LABAs.

In the 45 trials, there were no pediatric deaths or intubations. There was one asthma-related adult death. A 66-year-old woman had a fatal asthma exacerbation 19 days after randomization to Foradil 48mcg, the higher dose, which is not approved in the United States.

So what is the effect of Foradil on

non-fatal asthma exacerbations? This slide shows the incidence and rate of the asthma composite endpoint for patients overall and for different age groups. Events are presented here as the incidence or percent of patients with events, and the rate corrected for exposure presented as events per 100 patient years. Among patients randomized to the 24mcg total daily dose, the approved U.S. dose,.7 percent met the asthma composite endpoint, compared to .4 percent of placebo-treated patients. One percent of regularly dosed Albuterol-treated patients experienced serious asthma exacerbations. When corrected for exposure, there were 2.7 events per 100 patient years in the Formoterol group, compared to 1.4 in the placebo group, and 4.5 in the regularly dosed Albuterol group.

If we assess asthma composite endpoints by age, among adults greater than 18, there were similar event rates.

0.4 percent of patients in the approved dose met the endpoint with 1.9 events per 100 patient years, compared to .3 percent of placebo patients with 1.4 events per 100 patient years, and .7 percent of Albuterol treated patients with three events per 100 patient years.

Adult studies generally enrolled subjects greater than 12. We analyzed adolescents separately.

There were relatively few patients in this age group, but the number of events is similar across all treatment arms.

Among children five to twelve, the number of patients who met the asthma composite endpoint was increased among patients receiving Formoterol and regularly dosed Albuterol compared to placebo, 2.4 percent of patients randomized to Formoterol experienced events, with 5.2 events per 100 patient years, and 3 percent of patients randomized to Albuterol, with 16

events per 100 patient years, compared to only .3 percent or .5 events per 100 patient years in placebo.

This is a forced plot of the crude odds ratio versus placebo for all subjects by age. The scale on the X axis is logarithmic. An odds ratio favoring Foradil is on the left and placebo is on the right. Overall for Formoterol, the odds ratio versus placebo was 1.7. The same is true for patients older than 18 years. The odds ratio is about 1.3. For children 13 to 18, relatively small numbers and low number of events make confidence intervals quite wide.

In the five to twelve year age group, the odds ratio was 8.4. For all ages, the odds ratio of regularly dosed Albuterol versus placebo was greater than Foradil.

To better align our data with the data presented from the pooled analysis with that shown in our label, we also performed an analysis including events that occurred

during the observation period 30 days after the last dose. Most events occurred in the observation period occurred within five days of the last dose of the double blind treatment period. Six additional events in the Formoterol group occurred in the observation period, with two in children five to twelve.

With the addition of these events, the point estimate for the overall analysis and the analysis by age are 2.2, 1.7, .3 and 10.5 in the five to twelve year age group. These numbers are consistent with the analyses presented in the Novartis and FDA briefing box.

Next, we will review how Foradil is used in the United States, and spontaneous reports of asthma-related serious adverse events. This morning, you heard data regarding the use of single LABA agents based on a physician's survey. I will now share with you some more specific data on Foradil

prescribing tied directly to patient records.

80 percent of Foradil prescriptions are written for the treatment of COPD. 20 percent are written for the treatment of asthma, and of these, 8 percent are written for children less than 18. Pediatric prescriptions are evenly split between children five to twelve and 13 to 18.

To determine the extent of Foradil concomitant use with inhaled corticosteroids, we analyze data from a large U.S. pharmacy benefit manager from 2006 to 2007. More than three-quarters of the members under the age of 40 who filled a prescription for Foradil also filled a prescription for an inhaled corticosteroid within one year. The percentage of concurrent prescriptions in children five to twelve was 84 percent. The majority of the patients filled an ICS prescription within 30 days of the Foradil prescription.

The FDA adverse event reporting

system, or the AERS database, includes all spontaneous reports from U.S. sources for all marketed drugs. Reporting is voluntary for physicians and patients and mandatory for manufacturers. We searched the AERS database for cases in which Foradil was identified as a medication and an asthma-related serious adverse event was reported.

Approximately 1,000 events of any kind were reported from January 1, 2001 until March 31, 2008. The reporting proportion shown here is the number of asthma-related serious adverse events per 100 adverse events of any kind. Since a peak in 2003, there's been a slow decline in the number of spontaneously reported serious asthma exacerbations. Since Foradil was approved until the first quarter of this year, there were seven reports of asthma-related serious adverse events, and no asthma-related death in children. Overall, the post-marketing safety data do not show new findings that

heighten concern regarding the safety of Foradil in patients of any age.

With this data in mind, Novartis remains committed to the ongoing assessment and mitigation of risk for patients using Foradil. We are fielding an epidemiological study of seven state Medicaid databases to better understand drug utilization and risk associated with the use of Foradil with various treatment regimens. Our labeling and medication guide accurately and clearly reflect our current understanding of the class risks of long-acting beta agonists, and the safety data from the Foradil trials. We're committed to working with the Agency to address any questions or concerns that arise from these proceedings.

We highlight the appropriate use and risk in all asthma promotional and educational materials, and continue to monitor spontaneous and post-marketing surveillance data for these events.

We've reviewed the efficacy and safety data from Foradil, discussed the pooled clinical trial data, and shared data from the FDA AERS database. Given what we know about the efficacy and safety of LABAs including Foradil, what's their benefit/risk profile and how do they compare to other available treatments?

These are the updated treatment guidelines that Dr. Stoloff presented earlier and that you've seen a couple times today. As you know, inhaled corticosteroids are foundation for asthma treatment. As add-on therapy, LABAs are recommended in Step III, with alternatives including leukotriene modifiers, theophylline and increased ICS.

It's recommended that physicians add LABAs to ICS in patients whose symptoms are not controlled on ICS alone. Once the symptoms are controlled and lung function is near normal, guidelines recommend that the patients step down to less therapy. Of note,

the use of non-combined LABAs and inhaled corticosteroids allow for greater choice for physicians, and facilitates the step-up and step-down approach that's recommended by the NHLBI.

If the indication for LABAs were withdrawn, what alternatives would be left? In short, as discussed earlier, the alternatives provide a less favorable benefit/risk profile than LABAs. LABAs have superior efficacy compared to the other therapies in Step III. They're a more effective add-on than leukotriene modifiers, more effective than increasing the dose of inhaled corticosteroids, or the addition of theophylline.

Several alternatives to LABAs have significant adverse events -- theophylline has toxicities that include cardiac arrhythmia, seizures, and death. Systemic monitoring is required for theophylline and also for zileuton, which is associated

hepatotoxicity. In pediatric studies, there's less data overall. In several pediatric studies, doubling the dose of inhaled corticosteroids has not been shown to improve lung function or symptoms. There's very little data on the efficacy and safety of theophylline in children, and little data on montelukast as an add-on to inhaled corticosteroids.

Among LABAs, Foradil provides the only non-combined Formoterol option for asthma treatments in the U.S. today. It gives physicians the flexibility of adding Formoterol to any of the approved inhaled corticosteroids delivered by an array of devices across a range of doses. In terms of ICS choice, not all patients have the same treatment response to a given ICS, and as a result, there are eight inhaled corticosteroids available for the treatment of asthma.

If Foradil were no longer

available, patients currently taking any of the other improved ICS other than Fluticasone and budesonide would be required to alter their inhaled corticosteroid regimen when stepping up therapy with LABAs, and then would be required to do so again when stepping back down.

Children five to twelve would have even fewer options, since Advair Diskus is the only combination of LABA and ICS that's approved for this age group.

Many patients have difficulty using metered dose inhalers or have a device preference that makes Foradil's single dose dry powder inhaler an attractive option.

In conclusion, Foradil improves lung function, reduces symptoms, and reduces a need for rescue medication. When used as directed, in addition to inhaled corticosteroids, it remains an important and effective option that should remain in the therapeutic armamentarium with other

recommended alternatives.

Foradil, like all LABAs, may be associated with an increased risk of asthma-related serious adverse events. Our data from more than 3,000 patients across 45 studies with the approved dose shows this potential signal. The current label and medication guide address the risk of asthma-related serious adverse events in adults and children -- the increased rate of asthma hospitalizations observed among children five to twelve in the pooled analyses. This finding was primarily driven by Study 49, in which a differential dropout rate may have contributed to the imbalance.

Beyond the clinical trial data, spontaneous reports resulting from almost five million patient years of exposure do not suggest a risk of hospitalization in the pediatric age group that's greater than the other age groups.

It's the opinion of Novartis that

the totality of evidence supports the appropriate use of Foradil as an effective bronchodilator, and provides benefits for asthma patients of all ages. Foradil remains an important option for physicians and patients.

Thank you for your attention.

DR. SWENSON: Now I'll ask the team from AstraZeneca to be first seated.

This must be Catherine Bonuccelli.

DR. BONUCCELLI: Thank you and good afternoon to everybody here in the home stretch of a long day. I'm Dr. Cathy Bonuccelli, and I'm the Global Product Vice President for Symbicort at AstraZeneca. I want to thank the Agency and the Committees for the opportunity to be here today to present the benefit/risk of AstraZeneca's Formoteral-containing products, with a particular focus on the combination product available in the U.S., the Symbicort (pMDI).

I will start by introducing the

expert advisors who are here with AstraZeneca today: Gary Anderson, professor of Respiratory Pharmacology and Immunology from Melbourne, Australia; Gary Cook, professor of Biostatistics from Chapel Hill, North Carolina; Craig LaForce, Clinical Professor of Pediatrics from Raleigh, North Carolina; Harold Nelson, professor of medicine from Denver, Colorado; and Malcolm Sears, professor of medicine from Hamilton, Ontario.

Multiple speakers today have reviewed the history leading up to today's meeting, so I'm not going to go through that background again. What I will point out is that both GSK and Novartis have shown you data illustrating the significant clinical benefits of LABAs, and the importance of using LABAs in conjunction with ICS.

We will now present a substantial amount of data on Formoterol used either in free or in fixed combination with budesonide, reaffirming the significant benefits of LABA

ICS combination therapy, and providing reassurances that risks are minimized in this setting of concomitant use.

Dr. Kramer asked, what new data will you show us today? While much of GSK's data for salmeterol-containing products and Novartis' data for Foradil was considered in 2005, the data that we will now show you has not been previously considered.

This is what we will take you through this afternoon. After my introduction, Dr. Thomas Anderson will review the AstraZeneca products of relevance, and the scientific evidence demonstrating the benefits that Symbicort provides for patients with asthma, both by reducing future asthma-related risks and by improving current asthma control.

Then, Dr. Kevin Carroll will review AstraZeneca's analysis of the dataset requested by the FDA, which demonstrates that there is no signal of an increased risk for

Symicort for the severe asthma-related events of specific interest today.

Dr. Carroll will also try to put the differences between the AstraZeneca analysis that you saw in your briefing documents and the FDA analysis into context with each other.

Following Dr. Carroll's presentation, I will come back and review our conclusions from this review of benefit and risk, that Symbicort is an important treatment option for patients with persistent asthma that has a positive benefit/risk when used as currently indicated, and that the current prescribing information adequately covers any potential risks of the class.

I will now introduce Dr. Thomas Anderson, the medical science director for Symbicort at AstraZeneca, to review the AstraZeneca products of relevance and the benefit data.

DR. ANDERSON: Thank you,

Dr. Bonuccelli. Just to set some context, there are three AstraZeneca products that are relevant for today's discussion. The first and most recent is Symbicort (pMDI), a fixed combination of the inhaled corticosteroid Budesonide, and the long and rapid acting agonist Formoterol, which was approved by FDA in 2006.

Symbicort is indicated for long-term maintenance treatment of asthma in patients 12 years of age and older. However, Symbicort is not for all asthma patients. You heard it earlier today, and as clearly stated in the label, Symbicort should only be used for patients not adequately controlled on other asthma controller medications, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

There are two doses of Symbicort available, with a maximum daily dose of 640mcg of Budesonide and 18mcg of Formoterol. It should be noted that the dose of Fomoterol

is the same for both Symbicort strengths.

There are two other products that are highly relevant for today's discussion. Symbicort is available outside the U.S. as Symbicort Turbuhaler. It's a dry powder inhaler. And first available in 2000, Symbicort Turbuhaler is now registered for asthma in more than 100 countries, and it has an estimate patient exposure of more than 4,400 million treatment days.

The approved Formoterol doses in Symbicort Turbuhaler are 9, 18, or 36mcg daily, expressed as delivered doses. Therefore, outside the U.S., Formoterol is approved at a higher daily dose than the 18mcg daily approved in the U.S.

OXIS turbuhaler is a fomoterol monoproduct first approved in 1996 and now registered in 79 countries outside of the U.S. It's approved also for a range of doses, and has an estimate patient exposure of more than 1,400 million treatment days.

Both OXIS and Symbicort turbuhaler are approved for children with asthma from the age of four in some countries, but mostly the age of six and upwards.

In specific studies, these products have been proven to be therapeutically equivalent with regards to the Formoterol component. Therefore, it's highly relevant to include data from all three products when determining the overall benefit/risk of Formoterol.

I will now turn to the benefits review of Symbicort. We will focus on the clinically relevant setting -- that is when Formoterol is being added to Budesonide. We will show you data on the benefits of adding Formoterol to Budesonide on reducing the future risk of asthma, such as asthma exacerbations and asthma worsenings. Also, we will show you benefits on important measures of current control, the impairment of asthma, as Dr. Stoloff told you about

before -- namely asthma symptoms, lung function measured by FV1, asthma stability measured as morning peak flow, and asthma-related quality of life.

The asthma-related endpoints that measure the future risk of the disease, such as asthma exacerbations, are being assessed today here as possible adverse effects of therapy. Therefore, I would like to start by presenting data that shows that adding Formoterol to Budesonide actually lowers asthma future risk.

This is the Facet study. It's a clinical trial designed specifically to study severe asthma exacerbations. The study included 852 subjects with moderate to severe asthma, and it compared a treatment with a low dose Budesonide to the same dose with the addition of Fomoterol.

It also compared a moderate dose of Budesonide to the same dose plus Fomoterol over the one-year treatment period. You saw

it briefly earlier in Dr. Lemanske's presentation. Facet was published in the New England Journal of Medicine -- Medical Journal in 1997, and it's a very important and groundbreaking study supporting the development of ICS-LABA combinations, and it was also the first major study to have asthma exacerbations as a primary endpoint.

Adding Formoterol to either a low or a moderate daily dose of Budesonide significantly reduced the risk of a severe asthma exacerbation compared to treatment with Budesonide alone.

A severe asthma exacerbation was defined as the need for oral steroid treatment, or a more than 30 percent decrease in morning peak flow from baseline. If we only look at oral steroid treatments, the results are the same -- numbers creep down of course. Asthma-related hospitalizations were not part of the definition of asthma exacerbations in this trial. The number of

asthma-related hospitalizations are low but go in the same direction as the main result.

In the low dose Budesonide comparison, there were three versus one asthma-related hospitalizations. In the high dose Budesonide comparison, there were four versus one, both favoring the groups treated with Formoterol.

Again, these results suggest that Symbicort reduces future asthma risk, even for the more severe events such as hospitalizations. I would like to point out that the high dose combination treatment in this figure is equivalent to the higher approved U.S. dose of Symbicort.

Another key endpoint of Facet, mild asthma exacerbations, is a measure of asthma worsenings with increased reliever use, decrease in lung function, and awakenings due to asthma. For a patient, this means days with uncontrolled asthma.

As you can see from this data,

similar to the severe asthma exacerbations adding Formoterol to Budesonide significantly reduced the rate of asthma worsenings.

What you are seeing here are the results from Facet from asthma symptoms. A higher score means worse symptoms, and thus, lower is better. The results confirm that adding Formoterol to either dose of Budesonide resulted in significant reduction in asthma symptoms that was maintained without diminution over the 12 months of the study. In addition, Formoterol reduced the need for reliever medication, and improved lung function.

Four years after Facet, the Optima study confirmed the Facet result, once again showing that adding Formoterol to Budesonide reduces severe asthma exacerbations as well as asthma worsenings. Once again, asthma hospitalizations went in favor of those treated with Budesonide and Formoterol. Therefore, when rigorously studied in studies

that are designed for the purpose, adding Formoterol to Budesonide reduces rather than increases the risk of asthma exacerbations.

Study 717 is one of the pivotal trials for Symbicort (pMDI) in moderate to severe asthma in the U.S. This Kaplan-Meier curve shows asthma worsenings, and lower numbers indicate more patients with events. Asthma worsenings were predefined as increases in asthma symptoms, increases in reliever use, reduction in lung function, or clinical worsenings.

In terms of benefit, you can see that fewer patients on Symbicort, shown in green, had a worsening, and it took longer for the worsening to occur. The purple line shows the combination of separate components which had equal efficacy to Symbicort.

In terms of risk, it should be noted that this study mandated the removal of patients with worsening asthma who were then not followed further.

This makes this particular study by design less suitable for assessing more serious asthma events such as hospitalizations. However, this was one of the four trials included in the analysis provided by the FDA today. Optima and Facet was not.

This study, combined with Facet and Optima, provides strong evidence that adding Formoterol to Budesonide -- that is treating patients with Symbicort -- reduces rather than increases future risk of asthma events.

Continuing with other data from 717, I will now discuss the benefits of Symbicort on measures of current control of asthma patients. It's important to note that constricted airways and poor lung function are key burdens to asthma patients, and improving lung function is a key goal of treatments.

To the left, in green, we see the rapid and long lasting bronchodilation of

Symbicort over 12 hours, provided on the first day of treatment. I would like to point out three things on the right. First, 12 weeks of treatment with Symbicort, shown in green, improves pre-dose FEV1 more than Budesonide alone, which is shown in blue. This is a measure of the baseline lung function and asthma stability.

Secondly, the effect of LABAs used as monotherapy after withdrawal of the steroid can be seen here. Formoterol alone, shown in orange, improves lung function better than placebo, but it's less effective during chronic dosing than the combination. This also reaffirms that LABAs should not be used without ICS.

Finally, after chronic treatment for 12 weeks, with Symbicort in green, and the separate components in purple, the magnitude, the speed of onset, and the duration of bronchodilatation are fully maintained. It also illustrates, when you

look at the difference between the orange curve and the green and purple ones, how concomitant use of Budesonide maintains the responsiveness to Formoterol.

I will take the next couple of slides to put the efficacy seen in children into context with what's seen in older patients. This figure provides an overview of the seven Symbicort studies in the U.S. that included morning pre-dose peak flow, a measure of asthma stability, and the lung function, before they take their dose. The studies are arranged by age group, and includes comparison of Symbicort to Budesonide. Five of these studies included patients age six to less than twelve.

Point estimates to the left favor Budesonide, while dose to the right favor Symbicort. As shown here, the benefits of Symbicort is greater than what is achieved with Budesonide, in itself a very active and effective treatment. These improvements are

seen across all age groups from children age six and older.

Quality of life, as we heard earlier today in the presentations of Dr. Seymour and Dr. Chowdhury, it's an important overall measure of asthma control for both children and adults. As pointed out in the FDA Pulmonary Divisions briefing document, ICS-LABA combination therapies are the only asthma treatments that have shown meaningful improvements in this endpoint. In both of the U.S. Pivotal trials, Symbicort demonstrated clinically relevant improvement in quality of life versus placebo, using the Asthma Quality of Life Questionnaire, AQLQ, a validated instrument.

This morning, you saw one of the studies presented by Dr. Seymour, and here is the other one, Study 716 in patients with mild to moderate asthma.

Quality of life was improved in all active treatment groups, with the greatest

improvement from baseline observed for Symbicort. In Symbicort pediatric studies, quality of life has been assessed using the Pediatric Asthma Quality of Life Questionnaire, PAQLQ, in patients aged twelve to eleven, (?) as shown in the data to the right from a six-month study in children.

Although this study did not have a placebo comparator, the treatment differences for Symbicort versus Budesonide were similar to that seen in adults, and the improvement from baseline met the MID of 0.5. Overall, these data demonstrate improved quality of life with combination therapy, and suggest there there's similar benefits in children and adults.

So as demonstrated today, Symbicort has a positive benefit profile. The addition of Fomoterol to Budesonide as provided with Symbicort reduces the future risk to patients of asthma worsenings and exacerbations. Furthermore, Symbicort results in significant

and meaningful improvements of lung function, symptoms, reliever use, and health-related quality of life.

For patients, this means significantly more days without impairment from asthma, and for any one of you who treats asthma or who has asthma yourself, you know that this is meaningful to patients.

Finally, there's evidence that children also experience benefits similar to those seen in adults for validated measures of asthma control and quality of life.

I will now hand over to Dr. Kevin Carroll, who will present our analysis of risk with focus on the events of particular interest.

Thank you.

DR. CARROLL: Thank you, Thomas.

Over the next 15 minutes, I will present an overall assessment to risk to address the key question here today, being, does Formoterol increase the risk of

asthma-related events. The assessment will be based primarily on trials and trial data that met FDA's pre-specified criteria for inclusion as outlined in the AstraZeneca briefing document, and I will also briefly refer to some epidemiological data.

During the discussion, I will clarify why and how the analyses presented in the AstraZeneca briefing document differ from those presented in FDA's statistical briefing package.

When looking at a potential issue of drug safety, the commonly accepted practice is to consider all trial data at all doses, both approved and unapproved, in order to maximize the available information on the potential risk. Thus, in order to best assess the potential risks associated with LABAs, FDA asked sponsors to provide data from all blinded parallel group, randomized control trials conducted with a LABA in the treatment of asthma.

The data from these trials then underwent a pre-specified adjudication process for serious asthma-related events occurring on treatment. As shown in this slide, a total of 42 trials in just over 23,500 patients met FDA's predefined criteria.

As previously mentioned, the analysis provided by FDA in their materials includes only 1,270 patients from four AstraZeneca trials, meaning that 38 trials and around 95 percent of the data in over 22,000 patients have been excluded. FDA's analysis is therefore based on just 5 percent -- 5 percent of the data originally supplied by AstraZeneca.

This dramatic falloff in patient numbers is because after receiving the trial data from AstraZeneca, the Qualitative Safety and Pharmaco-epidemiology group at FDA applied additional exclusion criteria to the data, as shown on the slide. These criteria

resulted in the exclusion of highly relevant data such as study arms with Formoterol and Budesonide received in free combination at the same ratio as contained in Symbicort, in data in children less than 12, and data at doses higher than the currently approved total daily Formoterol dose.

Now, in line with comments that we heard this morning from Dr. Seymour in which the therapeutic equivalents of free and fixed combinations of Budesonide and Formoterol have been established, and also bearing in mind the comments from Dr. Chowdhury relating to the importance of looking at higher doses, be that free or fixed in combination or in terms of OXIS turbuhaler, AstraZeneca strongly believes it is essential to consider all the control trial data that were originally requested by FDA to ensure a comprehensive and thorough assessment of risk. And I shall say a little bit more about this later.

Hence, the data I'm about to show you is based on all 42 trials and 23,500 patients that met FDA's predefined inclusion criteria. The events I'll be looking at, again, as requested by FDA, are as listed on the slide. The main comparison will be for Formoterol versus non-LABA containing products, but I will also show you more refined comparisons, looking specifically at Formoterol in combination with ICS, and Formoterol at doses equal to or greater than the U.S. approved dose of 18mcg per day.

Finally, I will also show you data in the pediatric subpopulation of patients aged under 12 years.

So now I'd like to turn to the data themselves. Here, you can see that in the overall trial data set, there were seven deaths, splitting three versus four for Formoterol and non-Formoterol groups respectively. Consequently, there is little evidence for an increased risk of death with

Formoterol-containing products based on these adjudicated data. Also, there was one asthma-related intubation in the Formoterol group, and importantly, there were no asthma-related deaths.

In terms of asthma-related hospitalizations, this is the one event type occurring frequently enough to allow a detailed assessment of risk. Here, you can see that in the third line, there were a total of 161 events, giving event rates in the four line of approximately 12 and 16 per 1,000 patients per year for Formoterol and non-Formoterol groups respectively. Hence, both the relative risk and rate difference analyses show numerically lower risk of asthma-related hospitalization for Formoterol-containing products compared to non-Formoterol-containing products.

And as outlined in our briefing materials, we also looked at the data in key subgroups such as gender, race, baseline

asthma severity, and we also looked at the data in terms of longer term trials of at least six months' duration. The results of these analyses were consistent with the overall results, showing a numerically lower risk of asthma-related hospitalization for the Formoterol group relative to the non-Formoterol group.

In this slide, the hospitalization data are redisplayed as a Kaplan-Meier plot. As you would expect from the previous slide, time to first asthma-related hospitalization is longer for the Formoterol group, with the curves diverging smoothly, and no evidence of an increasing risk with time.

Now, in the previous two slides, I showed you the overall result across the 42 trials, and here, I take the opportunity to display the trial data individually. Each horizontal bar represents a separate trial, in the middle of which is shown the point estimate for that trial and at the foot of

the slide, shown in orange, is the overall relative risk and confidence interval estimate.

Symbols to the left favor Formoterol and to the right, non-LABA. As you can see, there is some variability but the confidence interval tend to include the line of unity. As before, both the relative risk and rate difference analyses show a numerically lower risk of asthma-related hospitalization for Formoterol-containing products compared to non-Formoterol-containing products.

At this point, I'd like to pause for a moment and turn back to reflect on FDA's analysis of the Formoterol data. As I mentioned before, additional exclusion criteria were applied to the AstraZeneca data, and this resulted in FDA's analysis being based on just four partial trials in 1,270 patients. That's only 5 percent of the data originally requested by FDA.

Here, you can see the four trials included in FDA's analysis, together with the corresponding relative risk result and confidence interval shown in green at the foot of the slide. Also shown in orange is a relative risk result based on all 42 trials for comparison. Note the difference in the width of the confidence interval, indicating the loss of precision in FDA's restricted analysis, which is based on just seven events.

This shows the importance of evaluating all the data that were originally requested by FDA to allow for a more complete and personal assessment of the safety of Formoterol as used in the U.S.

Moving on, and as I promised earlier, I'd now like to show you a more refined comparison looking at Formoterol in combination with ICS, which is very pertinent to the treatment of patients as outlined both in the label and in current treatment

guidelines.

A total of 29 trials and just over 18,000 patients contributed to this analysis. As you can see in our data for Formoterol, the patent for LABA plus ICS versus ICS alone is essentially the same as that seen for LABA versus non-LABA containing products.

Now, we can even further refine the analysis of Formoterol plus ICS by looking only at trials where the total daily dose of Formoterol was equal to or greater than the U.S. approved dose of 18mcg a day. For this analysis, a total of 17 trials and 7,213 patients contributed. As in the previous slide, there is no evidence for an increased risk of asthma-related hospitalization for Formoterol in combination with ICS when administered at a total daily dose of 18mcg or greater.

Now, it is important to note that this particular analysis includes all the patient data included in FDA's analysis, but

is more complete, as it also includes Formoterol in combination with ICS at doses at least as high as the approved U.S. dose.

Hence, if there was truly an excess risk of hospitalization for Formoterol in combination with ICS, this analysis, with Formoterol at doses of at least 18mcg per day, is one where we might reasonably expect to see a signal. And as you can see, no signal is evident.

To summarize, I have shown you asthma-related hospitalization data analyzed in terms of first, the LABA versus non-LABA; secondly, in terms of ICS plus LABA versus ICS alone; and finally, in terms of ICS plus LABA versus ICS alone, where the total daily dose of Formoterol is at least 18mcg per day.

The overall results of these analyses are shown on this slide for comparison.

As you can see, the data are very consistent across analyses, showing no

increase in the risk of asthma-related hospitalization for LABA-containing products. It's also a value to consider the other analyses of interest such as those provided by GSK, where data on the free and fixed combination of an ICS and a LABA are considered separately.

When we do this for Formoterol, we say there is no evidence of an increased risk of hospitalization either when Formoterol is given in free combination with an ICS or when Formoterol is given in fixed combination as in Symbicort.

On this next slide, we've looked at the number of hospitalizations as a function of accumulating Formoterol dose. As you can see in the column to the right, there's no indication of an increasing risk of hospitalization with increasing dose. Now I've added the corresponding data for the non-LABA-treated patients. You can see, in addition to there being no dose response for

hospitalizations with increasing Formoterol dose, the hospitalization rate was consistently lower than that for non-LABA-treated patients.

Now, this all strongly argues against a pharmacological dose-related risk with Formoterol when used appropriately together with an ICS.

I would now like to move on to look at the pediatric patient data. In the overall trial data, there were 3,423 children aged between four and twelve years, and around 2,150 of whom were treated with Formoterol. None of these data were included in the FDA's analysis of risk. There were no deaths or intubations amongst these patients.

Here, you can see there were a total of 39 hospitalization events in pediatric patients, given event rates of approximately 35 and 29 per 1,000 patients per year for Formoterol and non-Formoterol groups respectively.

Here, the data are displayed by individual trial. While the overall relative risk and risk difference analyses show point estimates that tend to favor non-LABA-treated patients, the confidence intervals are wide and consistent with no increase in risk, reflecting the individual trial data where the confidence intervals all include the line of unity.

As we pointed out in our briefing materials, the result here is influenced by the poor performance of a sub-therapeutic dose of Budesonide and Formoterol in Trial 673. Consequently, seven hospitalizations were observed in this trial due to a lack of efficacy. If the pediatric data are reconsidered without this sub-therapeutic dose, it is interesting to note that the point estimate reduces to .8. And I should point out that as outlined in our briefing document, our data in adolescents is consistent with the overall trial data.

To summarize then, in roughly 3,400 pediatric patients aged between four and twelve years, there was little difference in the hospitalization rate between LABA and non-LABA-treated patients.

While the data did not favor Formoterol numerically, confidence intervals were wide both for the overall analysis and for individual trials straddling the line of unity.

Moving on now briefly to look at epidemiological data, while asthma prevalence has been increasing right into the early 2000s, there is no signal of an increase in asthma mortality after the introduction of LABAs, as seen in this slide of U.S. data previously shown by Dr. Stoloff.

As a complement to U.S. data, here you can see the development of asthma mortality of the past 10 years in Sweden based on data from the National Death Registry. Sweden is the first country where

Symbicort was approved and where Formoterol is the predominant LABA. It's therefore reassuring to see that during the period with a marked increase in the use of LABAs, and of Formoterol in particular, there is no evidence of any negative trend in asthma mortality.

On the contrary, decline in asthma mortality seen is continued over this period of time strongly support the current treatment practice guidelines for the management of asthma.

I will now turn back to Dr. Bonuccelli, who will conclude today's presentation.

DR. BONUCCELLI: Thank you, Dr. Carroll.

In summary, AstraZeneca believes that the benefits of Symbicort have been shown unequivocally in controlled clinical trials in adults, adolescents and children. In asthma patients not well-controlled on ICS

alone, Symbicort improves current control of asthma, and also reduces the risk of future asthma worsenings and exacerbations.

In addition, in the FDA-requested and adjudicated data set of 23,510 patients across 42 controlled, randomized, blinded, parallel group trials, there was no evidence of increased risk of asthma-related deaths, intubations, or hospitalizations for Formoterol when used with an inhaled steroid -- that is for Symbicort. Specifically, in this data set, there were no asthma-related deaths, and asthma-related hospitalizations occurred less frequently in Formoterol-treated patients. These results are comprehensive and more precise, with narrower confidence intervals than the analysis done by the FDA, which included only 5 percent of the FDA requested data.

In conclusion then, Symbicort (pMDI), when used as indicated, is a safe, effective, and important medicine for

patients whose asthma is not controlled on inhaled steroids alone. The indication for Symbicort is appropriate, and the box warning and safety precautions in the current label adequately describe any potential risks.

Given the compelling scientific and clinical evidence supporting the positive benefit/risks of Symbicort (pMDI), we feel strongly it should remain available to patients and prescribers.

And as always, AstraZeneca is happy to discuss any additional steps that we could take to ensure the safe and effective use of Symbicort.

Thank you for your attention.

DR. SWENSON: We've heard a lot, and we're now 30 minutes past schedule. I'm sure there's still a number of questions.

And I'd like to just possibly get a sense from the panels here if they wish to at least have a few questions before we end the day here. There will be time tomorrow, but

of course, memories are fresh now from these presentations. We may not have everyone here, but could I get a show of hands of whether there's any sentiment to continued questioning here or to save it for tomorrow?

Those in favor of any further question period? Okay.

Then we meet again here tomorrow morning at 8:30.

(Whereupon, at approximately 5:57 p.m., the PROCEEDINGS were adjourned.)

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