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 TWO

Rockville, Maryland

Thursday, December 11, 2008

PARTICIPANTS:

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE

Voting Members:

DAREN KNOELL, PharmD
The Ohio State University

Temporary Voting Members:

JOHN HOIDAL, M.D.
Salt Lake City, Utah

FERNANDO MARTINEZ, M.D.
University of Arizona

MARK BRANTLY, M.D.
University of Florida

ANDREA HOLKA (Patient Representative)
Attack on Asthma Nebraska

LEE NEWMAN, M.D.
University of Colorado-Denver

JESSE JOAD, M.D.
U.C. Davis Medical Center

DAVID SCHOENFELD, Ph.D.
Massachusetts General Hospital

ERIK SWENSON, M.D. (Acting Chair)
University of Washington

PARTICIPANTS (CONT'D):

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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SEAN HENNESSY, Pharm.D., Ph.D.
University of Pennsylvania

JUDITH KRAMER, M.D., M.S.
Duke University

SYDNEY WOLFE, M.D. (Consumer Representative)
Health Research Group of Public Citizen

Non-Voting Member:

D. BRUCE BURLINGTON, M.D. (Industry Rep)
Gaithersburg, Maryland

Temporary Voting Members:

SEBASTIAN SCHNEEWEISS, M.D.
Harvard University

DEBORAH SHATIN, Ph.D.
Shatin Associates, LLC

JULIE ZITO, Ph.D.
University of Maryland

DAVID MARGOLIS M.D., Ph.D.
Hospital of the University of Pennsylvania

EDWARD KRENZELOCK, Pharm.D.
University of Pittsburgh Medical Center

JACQUELINE GARDNER, Ph.D.
University of Washington

PARTICIPANTS (CONT'D):

PEDIATRIC ADVISORY COMMITTEE

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Michigan State University

AMY CELENTO (Patient-Family Representative)
Nutley, New Jersey

AVITAL CNAAN, Ph.D., M.S.
Children's National Medical Center

CARL D'ANGIO, M.D.
University of Rochester

MELISSA HUDSON, M.D.
St. Jude Children's Research Hospital

KEITH KOCIS, M.D., M.S.
University of North Carolina

DANIEL NOTTERMAN, M.D.
Princeton University

GEOFFREY ROSENTHAL, M.D., Ph.D.
Children's Hospital Center
Cleveland, Ohio

ELAINE VINING (Consumer Representative)
Silver Spring, Maryland

Non-voting Member:

BRAHM GOLDSTEIN, M.D. (Industry Representative)
Princeton, New Jersey

GUEST SPEAKER (Non-Voting)

ROBERT LEMANSKE JR., M.D.
University of Wisconsin-Madison

PARTICIPANTS (CONT'D):

FDA PARTICIPANTS (Non-Voting):

JOHN JENKINS, M.D.
Director, Office of New Drugs
CDER/FDA

BADRUL CHOWDHURY, M.D., Ph.D.
Director, Division of Pulmonary Drug Products
CDER/FDA

SALLY SEYMOUR, M.D.
Deputy Director for Safety
Division of Pulmonary Drug Products
CDER/FDA

ANN McMAHON, M.D.
Acting Director Division of Pharmacovigilance II
CDER/FDA

HENRY FRANCIS, M.D.
Deputy Director
Office of Surveillance and Epidemiology
CDER/FDA

DIANNE MURPHY, M.D.
Director, Office of Pediatric Therapeutics
OC/FDA

ROBERT NELSON, M.D., Ph.D.
Bioethicist, Office of Pediatric Therapeutics
OC/FDA

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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 begin our second day here of this Joint Advisory Committee Meeting. Just to remind you, this is a combined meeting of the Pulmonary Allergy Drugs Advisory Committee, the Pediatric Advisory Committee, and the Drug Safety and Monitoring Advisory Committee.

To begin with, I'll ask Kristine Khuc here to clarify our Conflict of Interest.

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 representatives, 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 special financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion 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 the 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 Federal Food, Drug, and Cosmetic Act to Dr. Fernando Martinez.

Dr. Martinez is a member of an 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 had 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, AstroZeneca, 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 630 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. Bob Goldstein and Bruce Burlington are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Drs. Goldstein's 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 our 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 record.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have

with any firms.

DR. SWENSON: I'd like to reiterate what I said yesterday. For the topics that we're discussing today, there are very commonly some strongly held opinions, and these may be very passionately debated. But our goal in this meeting will be to have a fair and open discussion, and that we allow all individuals to express their views without interruption.

Thus, as a reminder, individuals will be allowed to speak into the record only if they're recognized by the Chair. We'll be keeping track of people as they wish to raise questions, so please don't interrupt; we'll call on you.

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're aware that members of the media are

anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. And I'd again like to identify the FDA press contacts, Ms. Sandy Walsh and Karen Riley. If they would again stand and show themselves. Thank you.

I'd like to remind everyone present to please silence your cell phones or any other electronic devices if you haven't already done so. And for the Committee members, again, please refrain from discussing any business of the meeting during breaks and lunch.

And at this stage, I'd like to call on Dr. McMahon for some opening remarks.

DR. McMAHON: Good morning. I know you all had a long day yesterday, and today, there's a lot on the agenda, starting with the open public hearing. This will be followed by questions and clarification and summary remarks.

And then a reading through of the questions that were mentioned and discussed yesterday a little bit. This will be followed by a discussion of the questions and voting.

And I want with further ado to turn the meeting over to Drs. Swenson and Rappley.

Thank you.

DR. SWENSON: I'd like to ask Dr. Diane Murphy then to give us some remarks, particularly as it relates to the focus in part of this meeting, particularly the pediatric issues.

DR. MURPHY: Thank you. In response to a number of concerns or questions raised yesterday, I'm going to attempt to put some context about why we have three committees here, and what we expect for you all to provide us at the end of today. In other words, the path to this meeting. I hope it will be helpful to do that.

Historically, pediatric drug development is different. 75 percent of

products that are used in children have not been studied in them, and when you get to certain subpopulations, we're talking 100 percent down to the neonate. It has required fundamentally acts of Congress to get products studied in children. Now, those different acts have provided an incentive and a requirement, and that has been how we've been able to move forward getting products studied in children.

Next slide, please. Do I have a way of doing this up here? Okay. Which one?

Okay, thank you.

This is -- just to give you an idea, under the exclusivity component of the trials that have been requested by the Agency, and the sponsor has to do them as to what has happened. And I put this up here only for one reason -- to show you that out of the -- we've asked for 360 products to be studied. We've had studies submitted and labeled for 149 products as of June. It's

actually higher than that now. What the information that we obtained from these studies, when we were able to get them, is that you'll notice out of the 149, safety and efficacy were not established. And these are products that have almost universally -- not always, but by far -- have been established as having efficacy in adults.

So we really don't know children are going to respond the same. Sometimes this happens because the effect size is different, and that's what we find out. Sometimes it happens because we don't have as good validated endpoints because we haven't been, studying kids, et cetera. But the point being it's not unusual to find when you do pediatric studies in products that have been approved for adults, that we don't find that same effect size, or aren't able to prove that they're as efficacious.

The other thing -- it may be that you have the wrong dose, and that's another

thing that we find out. Children can't always -- even with the pharmacokinetics, you need really good pharmacokinetic assessments to be able to determine whether you're going to get the right dose for kids.

And the other point on this slide is that if you look at safety and efficacy, it was 46, but if you look down at new enhanced safety information, 43 out of the 149 products that we brought in. The point being that we're finding in children, when we study again products that have been studied in adults and we know that they work and we know the safety profile, that we may have a different safety profile or a more severe adverse event profile in children.

So that's the reason I wanted to bring this information to you. What we're seeing is not that unusual -- that children are different.

Congress also legislated that we have a focused pediatric safety review. If

we're going to require these studies -- as everyone knows, pediatric studies are more difficult for lots of reasons. And they have ethical challenges, et cetera.

If you want to not find something -- you know, it is that the pediatric adverse event reporting we know is a very small percentage of the overall adverse event reporting, which we know is a very small percentage of what goes on. You won't find a signal if you don't go in and look for the pediatric-specific signal. So that's what you have to do.

So Congress mandated that we do that. And you can see we've had -- it's now over 90 products have been brought to the Pediatric Advisory Committee to look at the adverse event reporting for children. They have to go in and pull out the pediatric-specific data to look at that.

That brings us to where this Pediatric Advisory Committee was last

November. When this happens -- and we just had a paper with our Duke colleagues on what happens when we bring these pediatric -- do these pediatric safety reviews -- there is a certain percentage of the time that we do find new information that needs to be provided either in the label or other communications. Next slide.

So how do we assure pediatric safety? Well, as I said, the Congress said we will have a focused assessment looking at children. And the problem is, and this Committee has been -- the Pediatric Advisory Committee has been struggling with this since 2002 -- is everyone knows the limitations of adverse event reporting; right? And I just told you that even less of it is pediatrics.

So this Committee over time has said we can't -- we can't really deal with this issue if you don't put it in context. You need to provide us the safety information from the controlled trials, which I've just

told you are going to be limited. We need you to put it in the context of what's happening with adults, because that is where you're going to have a larger amount of information, realizing that children may react differently, but still, you need to have that information.

And that you may need to combine studies into a meta-analysis. So that's the clue to say, well, what happened at the last Pediatric Advisory Committee? Someone said, what's new? What happened at the last Pediatric Advisory Committee is we looked at -- and I'm not going to go through it; I promise you -- we looked at the adverse event reporting, and we always look at the use data.

We can see, as it was pointed out, there's more -- there seemed to be more adverse event reporting than the younger age groups for these products. And you saw the meta-analysis that was presented to the

Committee in November, which raised questions. Okay, that's the point. These meetings often raise questions. So the Committee then has to ask for more information, make recommendations on labeling.

And just for your information, this Committee is mandated by law to do labeling changes and they get special training in it, and they've done a fair amount of it.

Or what other extra communication should we make? The Committee's decision was we need more information. And that's -- the Agency went out and asked for those additional trials, brought them in, analyzed them before we try to make a decision about what we should be doing with this information.

The other point being that -- you know, they're struggling with -- and I just use this slide as an example. If we're putting out a public -- if we're putting it

in a label and we're putting out a public announcement about the risk in a subpopulation which was by race, and then we have a possible signal in kids that's even higher, what do we do with this?

So that is one of the reasons we have three groups here today. We have the Pediatric Advisory Committee, which has been dealing with these issues of safety, that brings that expertise to the Committee. It's the Pulmonary Advisory Committee, which brings the disease-specific expertise to the Committee, and the Risk Committee, which is bringing how do we communicate this?

We don't want -- we don't want this to be a sensational scare message. We want it to be a balanced message about what it is that we know, and how do we best inform practitioners from the pediatric perspective of how to use these products. And that's why your questions today -- we from the pediatric aspect really want to hear your thoughts in

that arena of what do we think of these signals, what do we say about them, and how do we communicate them?

Thank you.

DR. SWENSON: Thank you, Dr. Murphy. At this point, we'll now proceed to the open public hearing portion of the meeting. The FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure that such transparency exists at the open public hearing session, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages those speakers at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in

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

The FDA and this Committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this Committee and our Committees in this consideration of the issues before them. That said, in many instances and for many topics, there will be a wide variety of opinions. One of our goals today in this open public hearing is that it be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, I ask you to please

speak only when recognized by this Chair. And I appreciate very much your cooperation.

So to begin, we will have Anne Dorsey and Julian Dorsey come to the microphone.

MS. DORSEY: Good morning. My name is Anne Dorsey. I'm Julian Dorsey's mom. Julian is a 13-year-old. He's one of my four children, three of whom have special needs, but Julian has life-threatening asthma. Nobody has paid me or taken care of me in any way. I have no investment in any drug companies.

My name is Anne Dorsey and I'm the mother of Julian, a wonderful 13-year-old boy with life-threatening asthma. On July 11, 2006, I was watching television with Julian and my three other children. Julian looked at me in panic, clutched his throat, and said please help me. Please don't let me die. I put Julian on his nebulizer. His eyes rolled back in his head. I called 911.

I watched my son turn gray and then

I watched him turn pale and almost a bluish. I handed him lifeless to the paramedics. They worked on him; they bagged him, to no avail. My three other children watched while we were in the ambulance. We rode into Sinai Hospital in Baltimore. I tried to call our priest.

At one point I was told I could talk to Julian, but he could no longer hear me, as he was beginning to pass away. He did come back to consciousness after a long time. He was up in the Pediatric Intensive Care Unit, and then I was told he wasn't out of the woods.

I crawled in bed with my son and I just prayed. At 4:00 in the morning, he tapped me on the shoulder and said, mom, I have to go to the bathroom. There are no better words that a mom could have heard. My son goes to Pikesville Middle School in Baltimore. He's gifted. He's talented. He's compassionate. He's everything any mom

would want. Julian is so used to giving up things. He's a child of a single mom on a teacher's salary. I have to ask you not to let him perish.

When Advair -- and I'm not -- I have no affiliation with Advair -- 2006, Advair came out with a pump. It was lactose-free. And his allergist and the pulmonologist at Hopkins worked with his pediatrician at Sinai Hospital, and they put him on this pump. My son is so used to traveling in ambulances, out of school -- had to leave a gifted school because there was no air conditioning and he almost died. With the Advair and a combination of other drugs used twice a day, my son is still here, as you see. He spent Thanksgiving in the hospital.

He spends most of his winters in and out of hospitals. And he got out of the hospital Tuesday evening because he felt it was important to come down and tell you his

story.

I ask you when you consider the goal of your considerations, until we find a cure for this insidious disease, to please keep my son -- allow him to take these drugs. I think he's worth it, and I need -- as a mom, I can't bear the thought of losing him. I've almost lost him.

Thank you. I'm going to let Julian have a little bit of time to talk to you.

MR. DORSEY: Good morning. I'm Julian Dorsey and I'm an asthmatic. I spend a lot of time in hospitals and I got a lot of IVs and blood gases. But when I took Advair, it was almost cut in half how much time I spent in the hospital. And life got a whole lot easier, and without Advair, I don't know what I'd do.

Thank you.

DR. SWENSON: Well, thank you very much, Julian and Ms. Dorsey, for those words.

Our next presenter is Dr. Stanley Szefler.

DR. SZEFLER: Thank you, and good morning. It's an honor to speak on behalf of my two societies -- the American Academy of Allergy, Asthma, and Immunology, and also the American College of Allergy, Asthma, and Immunology.

And as you just noted, in those two organizations, the word asthma has been included. That occurred about 15 years ago, because the Academy and the College recognized that asthma is an important disease. At the time, a major concern about asthma was asthma deaths. The asthma deaths were increasing, and it was recognized that a large amount of the asthma deaths were due to under-treatment. Some major things happened, one of which was the introduction of the Asthma Guidelines.

And I also sit on the Asthma Guidelines panel. And also what developed was a number of asthma networks -- NIH asthma networks that are focused on asthma studies.

So what I'm going to do is kind of talk to you with a number of hats on, but speak for both societies. To answer Dr. Goldstein's question yesterday, if this drug -- the long-acting beta agonist was removed from asthma treatment, it would be a disaster. You just heard from a parent and a child how important this intervention was. That's one individual. I can speak on behalf of six million patients that you heard about yesterday, that if this drug was removed, it would make a difference.

This is the fourth meeting that you've had now on this topic, and so you're going to be asked to make some very critical decisions. And I would say if you make a decision to take this drug off the market, it would be a major decision. I don't think you want to have a panel that's going to walk away from this meeting and have a headline that this panel decided to draw back asthma to 20 years ago.

I'm going to take you down Memory Lane, because I've been involved in asthma research for 30 years now. When I came to National Jewish in 1982, the wards were full of over 100 patients who were there to be housed for severe asthma. Many of those patients refused to take the main drugs that they were taking, which was namely theophylline and oral steroids. There was the advent of inhaled steroids, but many patients had to take high doses of inhaled steroids. And they had to take this four times a day.

With the advent of fluticasone and long-acting beta agonists, many of those drugs that I spent many hours dealing with attorneys in terms of adverse effects of those medications, we no longer have to deal with. Those two drugs are theophylline and oral steroids.

I have not received a call from a lawyer for over 10 years to testify on behalf

of a physician for using any of these drugs. And that's because their use is very limited.

I'll give you the case experience that I had of a patient who was a very severe asthmatic. And I talked to the physician and encouraged them to use theophylline. And this was a physician that was very knowledgeable in the use of that drug. This patient went home.

The next time I heard from them, he was admitted for theophylline toxicity, because the physician prescribed Biaxin, which had a significant drug interaction. Physicians don't know how to use this drug anymore. Residents ask me what is theophylline. I feel like I'm an elderly statesman now talking about theophylline.

They ask me, how do you use it? I'll have to go back to my slides and pull out my slides and remake them if I have to go back and educate physicians on how to use this drug.

Will it happen? I don't know. The advent of the asthma guidelines made it very critical where these drugs play a role. You didn't hear yesterday -- another thing you didn't hear yesterday -- this was a hot topic for the Asthma Guidelines. We spent hours arguing over it personally, poring over literature. We created evidence-based tables.

If you want to go back, look at them. Many of you are not asthma specialists. Many of you are not old enough to go back and kind of see what happened during the '80s with these drugs. I would encourage you to do that as you make your decisions.

I'm not going to read my statement. I'll let you read that. It has much more information. But I would -- if you're not awake now and the coffee hasn't set in, I would read this statement, listen to the presentation that you're going to hear the

rest of the day, argue as much as you want, but when it comes down to it, you're going to have some very critical decisions to make. And I would ask you to do due diligence to the asthma -- the people that sat on that Asthma Guidelines Committee and made up those decisions on where to place these drugs. They were placed in steps. They were placed because of efficacy and concerns for adverse effects. You could look at those statements. Read the guidelines very carefully. They have very cautious statements in there.

I think our two societies -- without hearing Dr. Chowdhury's presentation yesterday -- we would align very carefully and support what he told you yesterday, in that we will try to educate physicians as much as possible to be careful about the use of these drugs. I will go back to my societies and relay the messages if you make that decision to step up their educational processes.

I thank you very much for your attention. If you want to ask me any questions, I would be welcome to take any questions.

DR. SWENSON: Thank you, Dr. Szefler.

Our next speaker will be Dr. Carolyn Britton.

DR. BRITTON: Thank you very much. I am president of the National Medical Association. The NMA is a 501(c)(3) education organization founded in 1895, and it is the largest and oldest national organization, representing 30,000 African-American physicians, and the more than 10 million patients they serve.

Thank you for the opportunity to discuss the burden of asthma in African-Americans and other underserved communities, and the NMA's position on long-acting beta-2 agonists for the treatment of asthma.

The NMA supports the FDA mission of

assuring the availability of safe and effective medication for all Americans. We have specific concerns, however, about the modification of guidelines and warnings for use of long-acting beta agonists in asthma treatment. We are concerned about the possibility for adverse outcomes in minority communities if a successful therapy is withdrawn, or its use unnecessarily curtailed.

More than 26 million Americans have asthma. Both the prevalence and severity are worse in the African-American community compared to the Caucasian community. African-Americans represent 12 percent of the U.S. population, 26 percent of the deaths from asthma. The asthma attack prevalence rate in African-Americans is 37 percent higher than in Caucasians. African-Americans have nearly four times as many asthma-related emergency room visits.

African-American children are three

times more likely than Caucasians to die from asthma. So it is a serious disease in our community.

The racial differences in asthma prevalence, morbidity, and mortality among minorities are highly correlated with poverty, urban air quality, indoor allergens, lack of patient and physician education, inadequate medical care, misuse of medications, and lack of available community resources.

Inadequate provider and caregiver education on controller therapy also contribute to unsuccessful treatment. Efforts to date, including programmatic initiatives and resource expenditures, have failed to reduce the incidence, morbidity, and mortality of asthma in the minority community.

The economic and social impact of asthma is considerable. In 2002, the National Institute of Health and Centers for

Disease Control reported 477,000 patients were hospitalized for the disease, with an average length of stay of 4.06 days. Total estimated costs of asthma care, $10.7 billion. Direct cost for medical care, including pharmaceuticals, $6.1 billion. And indirect costs due to lost school days and lost work days, $4.6 billion. Additionally, asthma accounted for approximately 11.8 million missed school days in children age 5 to 17, and 8 million lost work days for adults.

The NMA and its member physicians are committed to the elimination of health disparities among minority populations, especially African-Americans. Of the 23 medical specialties represented in the NMA, primary care is among the largest. Practice surveys show that NMA members choose to practice in medically underserved areas.

Their patient populations are among society's most vulnerable, and include the

poor, uninsured, underinsured, and/or Medicaid or Medicare beneficiaries.

Among these vulnerable populations, primary care specialists provide a significant proportion of asthma care due to the lack of sufficient specialists to meet community needs. The common challenges physicians confront in asthma management include accurate diagnosis, assessment of control, and utilization of best practices for consistent care. These are magnified in the African-American population because of frequent under-diagnosis, high prevalence rates, and increased risk of asthma-related morbidity and mortality.

Primary care physicians treating specialty diseases such as asthma are often cautious in medical management. Black box warnings for asthma medications are a potential deterrent to their use by non-specialists. This has the potential to increase adverse patient outcomes due to

limited use of an appropriate therapy. The use of black box warnings must be carefully considered with regard to data supporting their necessity, and should be supported by solid evidence.

There is long-standing concern about the safety of long-acting beta-2 agonists, especially in children, and you've heard lots of testimony about that. The SMART study was stopped early due to excess deaths, especially among African-Americans.

However, subsequent analyses show that the study was flawed due to the high rate of inappropriate medication use, and the failure to use an inhaled corticosteroid. Later monitoring of the beta-2 agonists and inhaled corticosteroid use in African-Americans has not clearly substantiated an excess death risk.

Current data show that when used appropriately in concert with inhaled corticosteroids, beta-2 agonists improved

control of moderate to severe asthma. Although asthma-related side effects may be observed, the efficacy of these medications for control of moderate to severe asthma is well-established.

The NMA and its allergy and asthma specialty section join our colleagues in the American Academy and American College of Allergy, Asthma, and Immunology in recommending that beta-2 agonists continue to be made available for use in conjunction with inhaled corticosteroids.

The guidelines for their use should be clear and unambiguous. Data collection on outcome should be continued, especially for children and the African-American community. We underscore the disproportionate impact of asthma morbidity and mortality in the African-American community, and ask the Committee to carefully consider any decision that removes an effective class of treatment.

Thank you for the opportunity to

share our concerns.

DR. SWENSON: Thank you, Dr. Britton. Our next speaker is Dr. Shelley Salpeter.

DR. SALPETER: Do I have my slides that I can use? Wonderful. Okay. Thank you.

Today, I will be presenting updated pooled data on the effect of long-acting beta agonists on asthma intubations and deaths. I know you've heard a lot about that already, but I will try to give a slightly different perspective.

I have no financial ties with the pharmaceutical industry; however, I have provided expert testimony on a litigation case involving a long-acting beta agonist, and I was paid on an hourly basis.

For this presentation, I have pooled data from all available sources on long-acting beta agonists with variable ICS and concomitant ICS, to evaluate the risk of the composite outcome of life-threatening or fatal asthma events, defined as asthma

intubations or asthma deaths. Unlike the FDA meta-analysis that was presented yesterday, I am not looking at hospitalizations, nor am I looking at active comparator controls.

In addition, I have pooled data from all available sources, including FDA-approved and non-approved doses, and industry-sponsored and non-sponsored trials. And I'm evaluating risk using odds ratios instead of the absolute risk difference. In addition, I performed subgroup analysis to compare the results between variable and concomitant ICS use, salmeterol and formoterol, adults and children, and between life-threatening and fatal events.

In 2006, my colleagues and I performed a meta-analysis on the effect of long-acting beta agonists on asthma hospitalizations, intubations, and deaths. The included trials compared long-acting beta agonists with placebo and had varying amounts of concomitant ICS use. We found that

long-acting beta agonists were associated with a two-to-fourfold increased risk for serious life-threatening and fatal asthma events compared with placebo. On average, 50 percent of the participants received concomitant ICS.

Now, in 2008, five more meta-analyses have been published on the effect of long-acting beta agonists on intubations and deaths. Most of these were sponsored by the pharmaceutical industry, and each of them only looked at one part of the picture.

Today, what I'm going to do is pull together all available data from drug-sponsored and non-sponsored trials on the effect of salmeterol and formoterol with and without inhaled corticosteroids on asthma intubations or deaths in children and adults. I have contacted the investigators of these other analyses to attain additional information on their trials and events

reported.

This slide shows the pooled results. For long-acting beta agonists and variable ICS, there is a twofold increased risk for asthma intubation or death compared with placebo, with a PTO (?) odds ratio of 1.94, and a p-value for overall effect of 0.05. The greatest weight in this analysis came from the large SMART study. If that trial were removed from the analysis, there would be a fivefold increased risk for asthma intubation or death for long-acting beta agonists compared with placebo, with a p-value of 0.01.

For long-acting beta agonists with concomitant ICS, there is a sevenfold increased risk for asthma intubation or death, with a combined regimen of long-acting beta agonists and ICS, compared with ICS alone, with a PTO odds ratio of 7.34 and a p-value of 0.02. In this analysis, the LABA ICS combinations could be in a single or in

multiple inhalers.

When all trials are pulled together, there is a twofold increased risk for asthma intubation or death for long-acting beta agonists, compared with no long-acting beta agonists, with a p-value of 0.001. As you can see in the figure, there is little to no heterogeneity in the results between trials, with all trials reporting more events in the long-acting beta agonist group.

In fact, if the SMART study were removed from the analysis, all events are in the long-acting beta agonist group, and zero events in the control group.

In subgroup analysis, there was no statistically significant difference in the results for all subgroups analyzed. Similar results were seen for trials with variable and concomitant ICS use. There was no evidence here that concomitant ICS protected against the increased relative risk

associated with long-acting beta agonists. In fact, the odds ratio for long-acting beta agonists with ICS was higher than or variable ICS, although the difference in the results between these two subgroups was not statistically significant. In addition, no significant differences in results were seen for life-threatening and fatal events in trials with and without concomitant ICS.

In further subgroup analysis, similar increases in risk were seen for salmeterol and formoterol and for children and adults in trials with and without inhaled corticosteroids. As you can see here, the combination of salmeterol and ICS as is contained in Advair was associated with a tenfold increased risk for asthma intubation or death compared with ICS alone, with wide confidence intervals, as you can see.

These results were similar to that seen with the combination of formoterol and ICS, as contained in Symbicort. Also, you

can see here that there's not a substantial difference in the results between adults in children, at least with the life-threatening and the fatal events.

In conclusion, pooled data show that long-acting beta agonists carry significantly increased risk for asthma intubation or death, even when used with concomitant inhaled corticosteroids. There was no evidence of a protective effect of ICS on the increased risk associated with salmeterol or formoterol.

However, we cannot assess the absolute increase in risk in this analysis, as only those trials with at least one event were included. It is possible that the baseline risk for life-threatening and fatal events is lowered by the use of inhaled corticosteroids in both the treatment and the control groups, so that the absolute increase in risk associated with the addition of a long-acting beta agonist to an inhaled

corticosteroid is lower than that seen with long-acting beta agonists alone.

Thank you.

DR. SWENSON: Thank you, Dr. Salpeter. Our next speaker is Ms. Nancy Sander.

DR. NOTTERMAN: Dr. Swenson, since we weren't given an opportunity to see this information and digest it before this presentation, would it be possible to ask Dr. Salpeter some questions about it for clarification?

DR. SWENSON: Yes, I think that would be fair, but let us finish this, and then in our first question session, if she's willing -- and I hope she will be -- that we can pose questions to her.

DR. NOTTERMAN: Thanks, Dr. Swenson.

DR. SWENSON: Ms. Sander.

MS. SANDER: Good morning. Thank you for the opportunity to share patient perspectives that support the continued availability of pediatric and adult single and

combination formulations of 12-hour bronchodilators.

I'm Nancy Sander. I'm president and founder of Allergy and Asthma Network Mothers of Asthmatics. I'm also a founding member of the NAEPP Coordinating Committee. But most of all, I stand before you as a parent of four now-grown children, three of whom have asthma, and also as a person who has dealt with asthma most of my life as well.

Allergy and Asthma Network Mothers of Asthmatics since 1985 has been the leading national grassroots family-to-family patient education advocacy and outreach organization. We're a 501(c)(3), and during our 23-year history, I have solicited and received grants and funds from all three companies whose companies are under review today. These funds were used to support our education and outreach efforts, many of which are award-winning.

I paid for my own travel here today.

People who call our organization have a long wish list of things they'd like to see different in their lives because of asthma. It's things that most of us take for granted, such as the ability to go to work or perform your normal household chores, to be able to play with your friends, or to sleep through the night without symptoms. Children tell their own stories in our book, How Asthma Makes Me Feel. And in your packets that you were given today, you will see on the left-hand side there's an illustration done by an eight-year-old who described asthma feeling as if an elephant was sitting on his chest.

And you'll notice that he drew a ghost of his body, or his spirit leaving his body. And we know that children really do fear death in the nighttime. They do feel the isolation of asthma, and often don't have

a good way of expressing it.

But even though asthma is a complex, serious, and potentially life-threatening disease, it is possible today -- thank goodness today -- for patients to lead productive and fulfilling lives with minimal impact from symptoms. I know. I've been in that same line of history with Dr. Szefler -- what it used to be like to take theophylline, to watch my daughter curl up in a ball grabbing her stomach from the pain that she would have in her stomach after taking theophylline. I understand and remember the days of oral corticosteroids.

But when patients talk -- when they talk about their struggles, we show them practical ways to overcome, using the principles detailed in the NAEPP Guidelines Expert Panel Report III. We understand their challenges and we know that when prescribed as part of the comprehensive treatment plan, 12-hour bronchodilators have given back to

patients the ability to work, climb stairs, attend school, sleep through the night, and compete in sports without symptoms. And these are things that most other people take for granted.

The key word here is "when used as prescribed." Like many young people with asthma, 15-year-old Stephanie underestimated asthma, and didn't use her 12-hour bronchodilator inhaled corticosteroid medication on a twice daily basis as instructed. And while in swimming class at school, she had an asthma attack and died. Had she been using her twice-daily medication as prescribed, and had she kept her albuterol inhaler at poolside instead of her locker, this story could have had a very different ending.

Her mom and family is grieving today, and they came to us asking to help them get the message out that using these medications on a regular basis, as prescribed

by your physician, is incredibly important. And stopping and starting them at your own discretion can be deadly.

In fact, when the SMART study was halted and news reports were released that 12-hour bronchodilators could be deadly, many patients with asthma and/or COPD, and parents of children using these medications, called our office panicked. Some of them had said they'd stopped using their 12-hour bronchodilators because they feared the medication more than the disease.

Others were afraid to stop taking it, but afraid that they would also have some kind of fatal reaction as a result of taking it. In each case, we educated and counseled these patients to follow-up with their health care professionals. We published two articles -- they're in your packets as well -- in our magazine and our newsletter, and we posted them on our website to answer patient questions.

And they are still there today. And we also provide a patient support center, staffed by a registered nurse who is also an asthma educator.

But when we looked at all the research on all the studies that were presented here today or yesterday, we had many questions that we felt were not answered. You know, whenever someone dies of asthma, it is tragic, because in most instances, it's a preventable death. But in these cases, we don't believe that questions were asked deeply enough of the patient families, such as what happened? Was the patient a good candidate for the medication that was prescribed?

Did the patient receive a complete evaluation to identify and address co-morbid or medical conditions that may stimulate or masquerade as asthma symptoms? Did this patient have a written asthma management plan and were they able to follow it? Did the

treatment plan address both the symptoms and the smoldering underlying components of inflammation? What other medications were they supposed to be using, and were they using them? Did the patient know the name, the purpose, the frequency, and the correct use of medications? Or were they handed a prescription that they picked up at the pharmacy with no further instructions on how to use the medication?

I want to ask two important questions. You know that albuterol or levalbuterol inhalers that these patients were using to treat breakthrough symptoms -- were they using empty inhalers? Did these devices have dose counters on them? Contents remain in the inhaler long after the medication -- the usable doses -- have been gone. Could this have been a contributing factor?

Also, did the patient have realistic expectations about what these

medications were supposed to do, or the differences between their 12-hour bronchodilators and their short-acting bronchodilators? For example, were their short-acting inhalers called rescue medication so they waited until the very --

(Interruption)

DR. SWENSON: Thank you, Ms. Sander. Sorry about the slip there.

Our last speaker is Dr. Alfred Munzer.

DR. MUNZER: Good morning. I'm delighted to speak on behalf of the American Thoracic Society.

And I want to disclose that I have no financial interests in any of the products we discussed today.

On behalf of the American Thoracic Society, I'd like to express our appreciation of the continued interests of the FDA to this issue. The safety of patients, we treat as a

shared concern of the ATS and the FDA. There is conclusive research evidence supported by years of clinical experience that demonstrates that adjunct of long-acting beta agonist use is effective in controlling asthma symptoms, especially in patients who do not achieve good control of their asthma just using inhaled corticosteroids.

Recent evidence, however, suggests that asthma treatment using LABA as a monotherapy is associated with a small but statistically significant increase in mortality. Meta-analysis also suggests that asthma-related adverse events, including hospitalizations and intubation, are increased by LABA use.

The increase in all asthma-adverse events, including death, intubation, and hospitalization, appear to be greatest in women, children, and those individuals of African descent.

Although increased mortality is not

apparent in combination therapy with Advair or Symbicort, increased hospitalization and intubation do occur with LABA even in combination with corticosteroids based on meta-analysis studies with Symbicort. Since these studies, however, were not designed to detect mortality, the lack of finding does not preclude a mortality risk associated with the use of LABA in combination with corticosteroids.

These studies, however, were not designed to detect mortality, and were limited by the lack of information on individual patients in terms of dropouts, asthma severity, control, and compliance with study medications. These findings touched off a controversy within the field of asthma researchers and clinicians. While the expert opinion is divided, the American Thoracic Society believes the following recommendations are supported by the existing data, clinical judgment, and prudent

risk/benefit management.

First, long-acting beta agonists in combination with inhaled corticosteroids should remain on the market for the treatment of asthma. Research evidence and years of clinical experience demonstrate that the use of long-acting beta agonists is the most effective add-on therapy for control of asthma in patients already on inhaled corticosteroids.

Should FDA remove long-acting beta agonists from the market, patients would be denied the most effective combination therapy for uncontrolled asthma.

While we appreciate the increase of asthma-adverse events associated with LABA, there is no apparent mortality risk with combination inhalers. Although the lack of finding a risk is not equivalent to the absence of risk, there is clear known mortality risk associated with poorly controlled asthma. Thus, patients, in

consultation with their providers, should retain the option to weigh the benefits and risks of using long-acting beta agonists in combination with inhaled corticosteroids to achieve maximum control of asthma.

The NIH NHLBI-sponsored National Asthma Education and Prevention Program discussed at length the mortality findings associated with LABA, and their guidelines support the use of LABA as stepwise combination therapy as an essential element of an asthma-treatment program. The addition of LABA to inhaled corticosteroids is the recommended therapy for asthma that is poorly controlled by inhaled corticosteroids in adults and children under the age of 12.

Second, single agent long-acting beta agonist products should remain on the market for asthma. LABA products are currently available on the market in a single agent formulation and in combination with steroids. It is reasonable for the Advisory

Committee of the FDA to discuss the removal of a single agent LABA product from the market, but we know that the Pediatric Advisory Committee considered taking this measure at a previous meeting but did not make that recommendation.

We are concerned that removing a single agent LABA product would send a confusing signal to patients and providers about the risks and benefits associated with the step care approach for LABA use would increase the patient out-of-pocket expenses for those forced to switch from single agent corticosteroid and LABA to combined products, and may lead patients to deviate from prescribed treatment plans for asthma control.

In addition, removal of the indication for asthma would not lead to the removal of the product from the marketplace since it is being used for COPD. But labeled indication for asthma and recommendations

regarding use would be removed from packaging; i.e., the black box warnings. Thus, off-label use might often occur inappropriately. While we do seek to minimize the potential risk associated with long-acting beta agonist use, we continue to believe that it remains an effective clinical tool in a step care approach to help establish control of asthma symptoms.

Third, any further changes or enhancements to the existing black box warnings for long-acting beta agonists should be consistent with the NAEPP recommendations. The Advisory Committee may consider making changes to the existing black box warnings of LABA products to make clearer to clinicians and patients the potential risks and benefits associated with long-acting beta agonist use.

Additionally, if LABA is considered appropriate as adjunctive therapy only for asthma control, that ATS would welcome any labeling change that more effectively conveys

this information to patients and providers. Recommendations for changes to black box mitigate risks may include warning of increased hospitalizations in children ages 4 through 12 with LABA, warning of increased risk of hospitalization and death of women and African-Americans.

Further research on LABA is needed, and the ATS recommends that further research is needed on a number of topics which are in my written statement.

Thank you very much.

DR. SWENSON: Thank you, Dr. Munzer. The open public hearing portion of this hearing is now concluded, and we will no longer take comments from the audience.

The Committee now will turn its attention to the task at hand -- careful consideration of the data before the Committee as well as the public comments.

We will now open up a general discussion. And what I would like to ask of

all the Committee members is that if they would tell us by lighting their microphone -- we'll be watching for you, and as you get recognition that we see you, would you then turn off your light and we'll call you in turn.

Questions. Let's see. I'll recognize -- I don't see your name.

Dr. Notterman. Okay.

DR. NOTTERMAN: Can you hear me?

DR. SWENSON: Dr. Salpeter. She's coming.

DR. NOTTERMAN: I have a question about the data you presented.

Thank you for doing it.

DR. SALPETER: Yes.

DR. NOTTERMAN: Thank you. In evaluating or comparing the treatment in control groups across the various studies, do you know if the authors took into account the underlying disease severity of the LABA plus ICS versus the ICS groups?

DR. SALPETER: When you mean the authors, do you mean the authors of the meta-analysis that pool the data, or the original investigators of the trial?

DR. NOTTERMAN: Well, I guess I mean was that information available in the original trials, and then did it flow through to your final conclusions?

DR. SALPETER: It certainly didn't flow through to the meta-analysis. It's very hard, as we heard yesterday, to be able to quantify the disease severity in some meaningful way for a meta-analysis.

Certainly, each of the trials -- the individual trials -- they're all published or available on the FDA website -- do have descriptions of disease severity. And of course, they're all randomized trials, so that the different treatment groups have the same disease severity.

Does that answer your question?

DR. NOTTERMAN: I think it does. And then the second question I wanted to ask relative to it is what's your assessment of the possible role of publication bias among studies in which serious adverse events or deaths were shown in the LABA?

DR. SALPETER: Actually, really the opposite has occurred here, because essentially, none of the life-threatening and fatal events were even reported in the trials. Most of these were drug-sponsored trials, and the information on asthma intubations and deaths were not available in the published trials. It's actually taken a few years now, along with the help of the FDA requesting that information, that we could start getting unpublished data about the catastrophic events in each of these trials. So I don't believe publication bias is involved here.

DR. NOTTERMAN: Thank you very much.

DR. SWENSON: Dr. Margolis.

DR. MARGOLIS: Thank you. I'd like to

get back to some issues that were brought up yesterday about the effectiveness and efficacy of the drugs. There were at least two individuals from the FDA who pointed out that Asthma Quality of Life didn't change in most of the original studies, and questioned the use of FEV1.

I was wondering if, either as an expert on the panel, and perhaps Dr. Lemanske from yesterday, could comment on the usefulness of the Asthma Quality of Life tools and whether or not they're reflective of how people do have asthma versus FEV1. And in the same vein, there was also an issue brought up about effectiveness and efficacy.

And there is obviously differences between the efficacy -- how well something does in a clinical trial versus the effectiveness of how well something does in the community. And whether or not there's differences between those individuals who enroll in asthma trials versus those

individuals who are treated in the community.

DR. SWENSON: Dr. Martinez, do you want to address some of those issues? And then if Dr. Lemanske is here, I think the question was also posted to him.

DR. MARTINEZ: Is he here? I don't think he is.

DR. SWENSON: So we will not have him.

DR. MARTINEZ: First of all, it's very important to understand the complexity of the clinical expression of this disease. Let me illustrate that with the results of studies that have been recently performed that were not quoted yesterday in which -- in very large samples of asthmatic subjects, the everyday symptoms -- lung functions, exacerbations, and other manifestations of the disease, were correlated.

And what was found was that there is very little correlation between these different manifestations. In other words, there are groups of subjects who have severe

exacerbations, others who have everyday symptoms, others who have low lung function. And it is not very easy to predict which subjects are going to have either of this based on the other manifestations. To say it in a different way, it is not true that all those subjects who have very severe daily symptoms, for example, are the ones who are going to have the most severe exacerbations.

Moreover, some of the medicines that we have -- for example, inhaled corticosteroids or long-acting beta agonists, or even leukotriene receptor antagonists -- may have effects on some aspects of the disease but not on others. And therefore, when you create a composite index like the ones we have talked about and you give a certain weight to each of these, that may be good for one aspect of the disease but not for others.

And let me illustrate this very briefly with a paper that was not coded

yesterday which I think is very important, which is impressed in the Journal of Allergen Clinical Immunology, with respect to exactly what I'm saying, which is a paper by Thomas and co-workers.

It's an observational study of general practice in Great Britain in which subjects in whom inhaled corticosteroids -- who were receiving corticosteroids and in whom either more inhaled corticosteroids were added or LABA were added were compared -- now, it's an observational study, and it has all the bias that observational studies have. But the results are extremely interesting to illustrate what I was just saying.

Because what they found was that when you compare in subjects who were receiving inhaled corticosteroids and where either of these two alternatives that we have today, those in whom inhaled corticosteroids were added had less effectiveness in terms of

everyday symptoms and lung function than those in whom LABAs were added. But on the contrary, those in whom inhaled corticosteroids were added had less severe exacerbations and hospitalizations than those in whom LABAs were added.

So what we're trying to -- what I'm trying to say here is the following. Asthma is not a simple linear straightforward disease. What Dr. Szefler said this morning is perfectly true. In some subjects, some medicines do better; in some subjects, some other medicines do better. So indices like the one you're referring to give us a very general and sometimes too general view of what is going on. We need to address the different aspects of the disease in a differential way.

DR. SWENSON: Dr. Schoenfeld.

DR. SCHOENFELD: I'd like to discuss risk for a minute. It seems to me that for a rare event, the best estimate of the burden of

risk of a new treatment, or of a treatment, is basically the risk difference. The ratio of risk, the relative risk, is important for a more common endpoint. Does it increase my risk by 20 percent if I have a risk? But in a certain sense -- you know, from no risk to some risk is an infinite increase in the relative risk, but it may be a very small increase in the absolute risk.

In 2005, the concern we had was that the risk difference was very, very large from the SMART trial. It was 1 in 700 per patient year. So that means that for every year, you have a risk -- an added risk -- of about 1 in 700 of dying if you took these drugs. And this is clearly -- this is clearly very serious. So there was an attempt to get some more data. And I guess the hope to get the additional data was if the additional data sort of confirmed this, then it would be sort of a no- brainer. We'd have to take the drugs off the market. And I

guess it was hoped that there would be some way that the additional data would deny this.

So what happened with the additional data -- if we divide sort of the FDA meta-analysis into SMART and not-SMART, it's roughly the same number of patients. And in SMART, we had 13 deaths in the LABA group and three deaths in the other group. And in the not-SMART trial, we had three deaths in one group and one -- three deaths in the LABA group and one death in the group. And the question is, did this confirm what we saw in the SMART trial or did it disconfirm? Or what does it add? And unfortunately, it's a somewhat equivocal kind of view, because the absolute risk difference is now not 1 in 700 but is 1 in 3,400.

And in fact, if you look at -- with ICS -- if you look at other risk difference estimates with ICCC and -- for instance, and so on. Let's say what's the risk if you take inhaled corticosteroids, at least the

calculation I do -- and I just invite people who know the numbers better than me to reconfirm this -- is again, about 1 in 3,500 is what you get if you remove -- if you just look at the people who took concomitant corticosteroids.

The problem is that I don't even know as a statistician how to get a confidence interval on a risk difference when you have small numbers. I don't even know how to design a study to detect a risk difference of 3,500. I have a feeling that it would take -- it may be impractical, but I don't really know.

So that's sort of the numbers that we have now, and I would submit -- I'd like Dr. Salpeter to say whether she gets completely different numbers for the risk difference, but maybe wait a minute. So that's the risk difference I have now. And probably from an individual point of view, that might be a reasonable thing to consider

that as the risk of these drugs.

Now, it gets a little muddier with the individual drugs, because the FDA's numbers are somewhat different than the companies' numbers, at least in some cases. So with Advair, Foradil, and Symbicort, there's no deaths at all. And that makes it, of course, difficult to talk about the risk, because we don't want -- it's hard to assume that it's zero unless there's a huge, huge sample size.

So one rule of thumb here that's useful is that if you see nothing, what's the upper 90 percent confidence interval on how many things you might have seen? Okay. And luckily, that's really easy to compute. That's three. So anytime you walk out and you see nothing, you can say, okay, well, at worst, I could have seen three. I'm not going to see more than three. Okay. And so you can divide the amount of exposure by three and you get an upper limit.

And I'm not sure whether the upper limit is a reasonable thing to use. Maybe you should use a somewhat lower limit, but maybe if you want to use two, you could use two, and maybe if you want to use four, you can use four, depending upon how conservative you are.

But the problem is that there's a little bit -- so if you look at the upper limits, it varies between what the FDA decided and what the companies came up with, at least in certain cases. So if you look at Advair, the FDA considered less trials. And it's upper limit of the risk of Advair would be about 1,100. And the company's upper list would be about 1,800. Okay. So there was a difference there, depending upon which trials were used from the company.

I'm not sure I understand the reason for the difference -- why -- whether I should use the 1,800 or the 1,100. But I think for a patient, maybe 1,800 and 1,100

are relatively close. But it is a factor of two.

For Symbicort, it's a much bigger problem. The FDA upper number is 127. So that is the upper limit is one death in 127 patients. That's a pretty high risk that we haven't ruled out, while from the company data, the upper number is one death per every 2,100 patients. So there's a huge discrepancy there. And I think it would be nice for that to be cleared up if we're going to look at these drugs one at a time, which I guess we haven't decided to do -- whether or not we're going to do it.

And for Foradil, there's -- the upper is about -- is again a factor of two. The FDA upper is about 271, and the company upper is about 466. Both reflecting that we don't have a lot of data on Foradil. Now, the problem is that I really think we have to somehow look at these risks and say, okay, so there is one out of 3,400 -- unless somebody

can come up with a better number. Is the benefit better? And that's the place that as a statistician I have a great deal of trouble, because it's very, very hard for me as a statistician to understand the benefit. You know, and that's where I hope that we can get some elucidations from people in the trenches, because I have no experience with this. And so it's very hard for me to understand.

Thank you.

DR. SWENSON: As I see it, I think you wanted some comment from Dr. Salpeter and perhaps from the two companies that had a combined preparation. Am I right?

DR. SCHOENFELD: I think the FDA -- in terms of the problem with those three drugs that had an estimate of zero and the problem in the difference in the denominators, the FDA may have a better idea of what the -- I would think the FDA would have the best idea of what the discrepancy is, and which denominator we ought

to accept or what the pros and cons of each denominator is. And I think that this makes, of course, most difference with Symbicort, but it does make a difference with some of the other preparations as well.

Dr. Salpeter, I'd like to have her comment on what the absolute risk difference is.

DR. SWENSON: Let's have you come first, Dr. Salpeter. And then we'll have the FDA.

DR. SALPETER: Thank you. Well, I'd love to hear Mark Levenson present the data, because of course, he was working on risk differences and I was working on odds ratios.

I would love to work together so that we can pool all of our data together and probably get a more accurate estimate of the risk difference associated with long-acting beta agonists and ICS compared with ICS alone. My philosophy when we are dealing with rare events like that is to try to pool

as much data as possible together, especially if there's little heterogeneity.

So my approach would be then to take all of the data we have on long-acting beta agonists plus ICS, which is what I did for my odds ratios. And then combine all of the data without events. So Dr. Levenson has got all of the trials that have zero events, which is what you need to do in order to calculate risk differences. And then be able to calculate a pooled risk difference for long-acting beta agonists plus ICS together. If there's little heterogeneity in the results right now, we can start off with the approach that there is a class approach and then be able to treat all long-acting beta agonists plus ICS together, and get a little bit better estimate of the risk difference.

Does that -- so I'd love to hear Mark and his risk difference.

DR. LEVENSON: Excuse me. I think your primary question to FDA was why the

denominator is different.

DR. SCHOENFELD: For those three preparations.

DR. LEVENSON: Right. I think obviously, the biggest discrepancy is in Symbicort. And I tried to explain that somewhat in that flow diagram in my presentation. The big difference has to do with approved dosages. My analysis only considered approved dosages of Symbicort and only considered the combination product as Symbicort, not two separate inhalers. So that's the large explanation for the discrepancy in the trials -- and the number of trials. I don't believe there was such large discrepancies for the other drugs.

In terms of some of your estimates of how SMART differs from my analysis, I don't think you accounted for the person-years in my analysis. The risk difference is based on subjects, which on the average had roughly a half a year of exposure. So I think your estimates are off

by a factor of two.

DR. SCHOENFELD: I thought I accounted for this in my calculations. I divided -- I assumed that the SMART and not-SMART were both about a half a year, because the average was a half a year total.

And so SMART was a half a year by design. So the others would average a half a year. So I assumed -- I did multiply by two. I did multiply by two. The reason -- the way I got the 3,400 -- okay, just to do my calculations -- was I took 13 -- I assumed that the average number of patients on the treatment was 13,630.

And then I divided that by two, which was the number of patient-years. And then I divided that by two again, which was the number of the excess number of deaths. And came up with 3,400. So -- is that --

DR. LEVENSON: I don't follow it completely. Could you run through that again?

DR. SCHOENFELD: So I figured that

there was roughly 13,000 patients per treatment group in the not-SMART -- in what I'm calling the not-SMART cohort.

DR. LEVENSON: So you're trying to estimate --

DR. SCHOENFELD: The risk difference --

DR. LEVENSON: For the not-SMART.

DR. SCHOENFELD: For not-SMART.

DR. LEVENSON: Okay. Yes. Okay.

DR. SCHOENFELD: It was about 13,000.

DR. LEVENSON: Okay, now I understand.

DR. SCHOENFELD: And I divided that by four.

DR. LEVENSON: Okay, then that would be correct. Yes. I understand.

DR. SCHOENFELD: Okay. So it's 3,400 in not-SMART, and you get roughly the same number in ICS use -- you know, it's somewhat the same number with concomitant ICS. And I assume that the reason you get somewhat the same number is that it's pretty similar to not-SMART,

although it's not quite.

DR. LEVENSON: Right.

DR. SCHOENFELD: So that's where I got those numbers.

DR. LEVENSON: Then I stand corrected. I think your numbers are correct.

I misunderstood what you were trying to get at. So in terms of discrepancies, I think it's mainly due to my analysis only included approved dosages and the combination product.

DR. SCHOENFELD: What do you think -- I mean, you must have considered that very carefully to decide whether or not to do that. Do you think very strongly that we should -- do you think we should consider both analyses? Both denominators? Or do you think we should consider -- is there a real danger in considering the -- I mean, this is unusual, because more often, the pharmaceutical companies come up with an analysis and the FDA critiques it. But we haven't -- this hasn't happened

here, so it's a little -- it's not what we're used to.

DR. LEVENSON: As I said in my analysis, my analysis goal was as input into a risk/benefit analysis, where the benefits were to come from approved drugs. I actually -- when we were designing the analysis plan, I thought it would be unfair to the sponsors to include unapproved doses, so -- because we were only comparing it to approved doses. So that's how that was designed. As it turned out for some reason, the unapproved doses appear safer -- at least in terms of raw counts.

So I would say examine both sources of information.

DR. CNAAN: First, I'd like to thank Dr. Schoenfeld for his calculations.

DR. SWENSON: Move your mic closer.

SPEAKER: Close to your face.

DR. CNAAN: The FDA system has stopped working --

DR. SWENSON: Do we have a mic at the

podium that's operational?

SPEAKER: Yes.

DR. CNAAN: So I wanted to thank Dr. Schoenfeld for his calculations. It helps. I had some questions that in view of those, I will not ask Dr. Levenson, because they're sort of more detailed.

At the Pediatric Advisory Committee, typically we have small numbers, small person-years, small everything. That is a chronic problem for us.

And what the FDA has done for us in order to do something about it is that we always get reports from the AERS data and Verispan for usage. Now, it doesn't give us a denominator, but it does give us something that over time we've all learned to work with somehow.

I guess clinical trials data is better, but given some of the small person-years we saw, I wonder if we could get maybe from Dr. McMahon or somebody from her

staff some sense of what the AERS data and Verispan show. I think it might help us.

I had a question for Dr. Salpeter. My question is whether the comparisons -- it wasn't clear to me -- used both the single product and the combination products, or only the single products with then potentially inhaled corticosteroids. I'd like to understand that.

And I had a question for GSK. What I didn't hear about Advair, I think -- unless I just missed it -- is the mean duration of exposure that supported what looked like very safe data. If there's not enough exposure then it's not clear. So I'd like some information about that.

Thank you.

DR. SWENSON: Dr. Cnaan, I just want to make sure that we get your points across. So you'd like comments by Dr. Salpeter, and then GSK, and then the FDA?

DR. CNAAN: And the FDA.

DR. SWENSON: Okay. Dr. Salpeter.

DR. SALPETER: Thank you. Mine was an easy question. I included all data on long-acting beta agonists and ICS combinations. So they could be either as ICS's background use with a long-acting beta agonist as the randomized portion, or two randomized portions -- treatment portions of both the ICS and the long-acting beta agonist. Or in a combined inhaler. I used all of the data together and pooled it together to get greater power.

DR. SWENSON: Could we have a representative from GSK?

DR. KNOBIL: Yes. The mean duration of exposure for the Advair clinical trials was approximately six months. But we also thought it might be useful for you to see the exposure in patient-years for Advair compared with some of the other treatment comparisons, if that's okay.

This is Table 2, which is available

in your briefing document. There we go. There it is.

And you can see the bottom line in the top half. I don't have a pointer. The bottom line in the top half of the table shows that there's over 6,500 patient-years of exposure for Advair, which is about the same amount of exposure as we saw with Serevent in SMART. So you'll be able to compare some of the rates of events that we've seen in those trials.

SPEAKER: Is this only pediatrics?

DR. KNOBIL: No, this is for everything. I don't have it broken out by pediatrics.

SPEAKER: You don't have it broken out by age.

DR. KNOBIL: No, not for exposure.

DR. SWENSON: Dr. McMahon, I think maybe possibly this would be -- you'd be the one to handle from the Agency?

DR. McMAHON: Yes. Dr. Mosholder in

his talk yesterday presented some of the AERS data that we've most recently looked at on the LABAs. So maybe I'll ask him to make a brief comment.

DR. MOSHOLDER: Yes, we -- as you recall, we looked about a year ago at more specifically the pediatric adverse events -- asthma deaths reported with LABA products -- either Advair or Serevent. And as memory serves, there are about two dozen such cases in AERS as of last year. Some of them, similar to the early reports with Serevent were -- I think there were two in which the child was clutching an inhaler of some kind, suggesting a sort of overwhelming sudden onset fatal asthma attack.

And then most recent -- since that time, as I showed yesterday, the bar graph -- there's been additional five pediatric asthma deaths in AERS under age 12. But unfortunately, I don't have the details of those cases. I can get that if there's

interest. So I hope that -- does that address?

DR. SWENSON: Dr. Rosenthal.

DR. ROSENTHAL: Thank you. I'm wondering whether -- we spoke some yesterday in some of the discussion, some of the talks, about confounding and the difficulty with separating -- disambiguating confounding due to indication versus the effects of agents.

And as I think about these agents, there are different forms in which the medications have historically been delivered. I'm wondering whether any of the people who have gone through and produced meta-analyses of one form or another have sufficient data to help us disambiguate potential confounding by the form in which the medications are delivered from the medications themselves.

DR. SWENSON: Anybody willing to step forward here? Mark.

DR. LEVENSON: Unfortunately, in the meta-analyses we conducted, the device was not

part of the criteria. All the devices for a given drug were combined and did not look at them separately. Does that answer your question for the FDA meta-analyses?

DR. ROSENTHAL: It does. Do other people who have looked at meta-analyses have any other insight into this question?

DR. SWENSON: All right.

Dr. Goldstein.

DR. GOLDSTEIN: I just wanted to make a comment on what I think was an unintended potential slide by Dr. Chowdhury yesterday that gave the impression that the asthma as a disease was similar in children as it is in adolescents and adults. I just want to make sure -- because I know every pediatrician in the room started mashing their teeth -- that there are anatomic, physiological, and developmental changes, as Dr. Murphy was alluding to earlier, particularly in young children, that while the disease mechanisms of asthma are the same in all these age populations, the manifestations -- because

of these developmental changes in the number of asanide (?), the diameter of the airways, the number of beta receptors that are throughout the body that make the manifestations -- the severity of the disease, and the response to therapy very different in young children compared to older children and adults.

Somebody else also asked me this morning if I believed the association of an increased risk with younger age. And because I think of the paucity of data, I don't believe it per se. Nonetheless, after 25 years of taking care of children and knowing that they are oftentimes at increased risk, I cannot discount any of that data.

DR. SWENSON: Dr. Holka.

DR. HOLKA: Thank you. My question has subsequently been answered.

DR. SWENSON: Then Dr. Shatin.

DR. SHATIN: Actually, it's Shatin.

DR. SWENSON: Shatin? Forgive me.

DR. SHATIN: Actually, I'd like to

step back even further in the meta-analysis and look at the definitional endpoints. And I guess this is a question for Dr. Levenson.

I understand the composite score where each event is added, whether it's a hospitalization, intubation, whatever. My question is, we're not looking at the patient level. This number of events in the analysis reflects how many patients. So if a patient were intubated and then died, that's counted as two events. If they were hospitalized, intubated, and then died, that's three events. So I just wanted to clarify that.

DR. LEVENSON: No, in the composite, it's on the subject level. So if a subject had any of the three events, they would be counted as having an event. They would not be counted as having multiple events. So if a subject went through all three events, they would only count as one in like sum numerator.

DR. SHATIN: Okay.

DR. SWENSON: Dr. Hennessy.

DR. HENNESSY: Thank you. FDA and the sponsors both agree that long-acting beta agonists should never be used without an inhaled corticosteroid. I think that the only way to ensure against this is to remove the asthma indication from single-acting long-acting beta agonists. We know educational efforts, like package labeling and med guides, are insufficiently effective. And I've heard that some patients just won't take their corticosteroids. I think the FDA should remove the flexibility to take solo LABAs for asthma.

However, substantial uncertainty still remains about the safety of LABAs even in combination with inhaled corticosteroids. While this uncertainty does not in my view warrant the removal of combination products, it certainly warrants the conduct of pragmatic trials large enough to assess serious asthma outcomes in children and adults, including older adults.

Given the number of people taking

these drugs and $8 billion in annual revenue earned by Advair, this seems imminently plausible.

DR. SWENSON: Dr. Kramer.

DR. KRAMER: Thank you. I have a question for Dr. Salpeter as well. I wanted to highlight a statement you said at the end in terms of limitation, that only trials of at least one event were included. So presumably there was no risk in the trial. That's not even considered in your analysis. And I assume that would be addressed by your offer to work with Dr. Levenson and combine both.

So that's been addressed. But the other is the attribution of medication use in these sorts of meta-analyses. What I was wondering about (inaudible) adherence is a serious problem. And I was wondering whether a patient like Stephanie that was described by Nancy Sander -- someone who was prescribed both LABA and concomitant ICS but who stopped taking it -- could have in one of those

studies in your meta-analyses been in fact labeled LABA plus ICS.

DR. SALPETER: Yes, that certainly is possible. There weren't that many events. And going through the reports, they did adjudicate each of the events. Going through the reports, they did say that they verified that the patient had been taking inhaled corticosteroids of the events -- of those who had the event. But we don't know if that's exactly true, but they did go and adjudicate each of those life-threatening and fatal events for the LABA ICS group, to be able to verify that they were in fact taking ICS.

DR. SWENSON: Dr. Seymour.

DR. SEYMOUR: I just wanted to comment on response to something Dr. Schoenfeld mentioned, which is regarding whether the additional data on Symbicort and formoterol from AstraZeneca should be included in the meta-analysis or not. And I think it would be reasonable to consider that additional data.

During the development program, I presented yesterday that the company performs studies to evaluate the comparability of the Formoterol Oxis Turbuhaler and the Symbicort Formoterol.

And the Division considered that adequate for their development program. I think including that type of information -- it is formoterol. It is going to be the same as drug stance that's in Foradil Aerolizer. And including that information I think would be a reasonable thing to do. In addition, I think including the higher and lower doses -- that they have that information -- would be reasonable to look at.

DR. SWENSON: Dr. Chowdhury. Oh, I'm sorry. Excuse me. Dr. Schoenfeld.

DR. SCHOENFELD: I looked at -- when I did my little kind of calculations, I didn't actually -- I didn't mention the children. So if you look at the meta-analysis for children, it's again a big problem, because for children 4

to 11, there were no events in the FDA meta-analysis. But there weren't very many children. So the upper on that -- the upper limit on that is only for one event out of 266, because there were so few children in that analysis.

For children 12 to 17, it's a little bit -- there was one event on the LABA group and zero events on the other group. And one event is also a little problematic, but there's a great rule of thumb for one event also. So the rule of thumb for no events is divided by three. And the rule of thumb for one event is divide by 4.7. So if you only see one of something, the worst it can bee is 5. Okay? Just as a way of thinking about it dealing with rare events. And so you get a number there of about 1 out of 300.

So there's not much data, unfortunately, in the FDA analysis on children is the problem.

And I should say that I think I agree with you as well. I think we should probably use the industry estimates of denominator, because I think that it's so hard to figure out risk -- that especially when you're looking at absolute risk, that you should try to take as much data as you can.

I have a question, though, about these graphs of the number of dispensings versus the number of deaths, because these have come up on the screen about five times, and I have a question. And maybe the industry people can answer this question.

So it says that there's been a roughly 30 million dispensings of -- 30 million dispensings of these drugs. And there has been -- the number of asthma deaths per year is something in the order of 3,500.

So I was trying to actually see if we actually did have a death rate of 1 in 3,500 -- you know, the death rates -- you

know, what death rates are possible. But I don't know how to convert a dispensing into a patient year. Okay? Because I don't know what a dispensing is.

So for instance, a dispensing -- if you sell this by inhaler, which lasts a month -- you know, which is a prescription, then a dispensing is one month of treatment, and I should divide by 12 the 30 million. I should divide by 12. And then I get a death load of 625 deaths. If I accept that it's 1 out of 3,400 -- you know, 1 out of 4,000. I thought I'd round it, so 1 out of 4,000 is the risk for this.

And I divide 30 times 10 to the 6th by 12, and then divide it by 4,000, I get a public health cost -- you know, sort of assuming these numbers of about 625 deaths a year.

But I may be completely wrong at what a dispensing is. Am I right? Does somebody know what a dispensing is? Could

they put me straight here?

DR. SWENSON: Dr. Cnaan first, and then if she has anything to that -- if she has another point. And then we might ask the companies themselves.

DR. CNAAN: It's actually exactly to that. I want to thank Dr. -- I'm sorry, I'm a little bit sick. I want to thank Dr. Mosholder, because there was just so much information yesterday. But his slide 6 from yesterday indeed shows the 5 deaths for ages 4 to 11 in the year of '08. His slide 28 shows projected number of patients receiving LABA prescriptions essentially for the year '08. And that shows about 5.8 million. And then his slide 29 shows that about 10 percent of those are -- or 11 percent -- are ages 0 to 16.

Now, admittedly that's combining disparate resources of information, but if you say that about 11 percent of the 5.8 million patients -- not prescriptions, patients -- who received LABA in '08 were

children, so you get that maybe 600,000 or so were children. And there are reported five deaths and we know there's under-reporting. We know there's vast under-reporting. But if you believe that you would say that the death is 1 in 120,000.

Now, that has nothing to do with the 625, and the 120,000 is not true because of the under-reporting. But I would imagine that the 625 is an underestimate, given the data that we have from Dr. Mosholder.

DR. SWENSON: We had the question about dispensings, and I wonder if any of the companies might have some insight into how to calculate that.

DR. KNOBIL: I can only speak for dispensings of GSK products. But we have found in looking at some of the data that are available that for Advair the refill rate is approximately five per year, or about half of what they should. So theoretically, 12 dispensings would mean a full year, but it

probably means closer to two years in that respect.

But also, the numbers that Dr. Mosholder gave yesterday were a little bit confusing, because the total number of LABA patients on a LABA-containing product appeared to me to be not just asthma but potentially asthma and COPD. I can tell you that for Advair, the estimated number of patients is about 3.9 million last year.

DR. SWENSON: Okay.

DR. KNOBIL: Just to address Dr. Cnaan for pediatrics, it's under 300,000 on Advair.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: Dr. Salpeter's analysis this morning reminded me about some data that was provided to us in our package, which Dr. Levenson I'm sure did not have enough time to go over. And I'd just like to mention it for 45 seconds or a minute or so. It has to do with Figures 9 and 10, which were on pages 29 and 30 of the handout that we got four weeks ago. And

it's on the issue of -- which has been discussed widely -- do inhaled corticosteroids protect against the increased serious events, as in deaths, intubations, and hospitalizations, that are caused by the long-acting beta agonists.

And what these tables show is very relevant to this point. Figure 9 is based on the composite, namely intubations, deaths, and hospitalizations, by what the baseline status was of ICS. And what this analysis shows is that over half of the patients in this whole meta-analysis were already on baseline ICS, and that subgroup had a statistically significant risk difference of 2.56.

And then when you went to the next slide, which was risk difference based on any use of ICS -- either those that were designated to use it during the trial or those who had already been on baseline -- it became even higher. And you had about two-thirds of the patients were already on or

became on ICS. And again, their risk difference was statistically significant, at 2.8.

So I think this -- again, I'm sure Dr. Levenson, with his really good presentation yesterday didn't have enough chance to put in all of these things. But this really goes along with the questions that we've had. Does the use of ICS protect against these events? And the answer appears to be no. And then Dr. Salpeter and the new analysis she showed us this morning of with and without ICS came to the same conclusion.

I'm not sure there's any reason, unless he has a different take on it than I did, for Dr. Levenson to comment on those two, but they were in the handouts. Figures 9, 10. Pages 29 and 30.

DR. LEVENSON: My only comment on that -- your discussion of the figure that talks about ICS use during the trial which includes both assigned randomized treatment and any sort

of concomitant treatment -- the information on the concomitant treatment was somewhat weak, as I mentioned. We only know if they at some point during the trial indicated that they took ICS, not whether they regularly took it or what they took. So that's my only addition to your comment.

DR. WOLFE: So that figure 30 was the baseline plus, and what you're saying is that even those people that were assigned in the trial to get it, presumably they got it but that some of the people getting it baseline may have not been taking it all the way through the trial. Is that the idea?

DR. LEVENSON: Yes, I have no information on the compliance there.

DR. SWENSON: Dr. Gardner.

DR. GARDNER: I've been experiencing a disconnect between the significant risks that we're seeing in the randomized clinical trials and the meta-analyses. And the evidence-based guidelines that were developed with -- for

stepwise therapy -- and in theory, they plan for protecting patients through managing the disease in a stepwise fashion.

And I'm frustrated by not having observational data. Yesterday, Dr. Zito asked about Medicaid data, which is heavy with children exposed. Dr. Kramer asked I think something yesterday that made me think of the HMO Research Network and its wealth of children. And I'm wondering how soon we might expect prospectively to see -- to be able to see the results of the evidence-based guidelines for asthma management with ICS required and LABA only on the second step, at least, before we can begin to see in children some of the effect of -- in usual use and customary application of the impact of the guidelines.

Does anyone know when we might expect to see -- be able to see that within these datasets?

DR. ARMSTRONG: As I mentioned

yesterday, Novartis is currently fielding a study of seven Medicaid databases. And actually, I would like to ask Dr. Alec Walker to come up to give a brief overview of that. And that data should be available next year.

DR. WALKER: This is a study which is currently under negotiation between Novartis and the University of Cincinnati. It's looking at a multi-state Medicaid database population with a large number of asthmatics, and as everybody has indicated, a fairly large number of children with asthma. The data currently go through 2007 and are potentially extendable. The specific question from Dr. Gardner was will this reflect current management guidelines. And as we all know, Medicaid data to some extent may. I think you would have to examine that and find within it the kids who actually are treated according to guidelines.

But the planned study involves looking at asthma-related mortality, ER visits, hospitalizations, and intubations,

much like previous ones. And it will give Novartis the opportunity to look both at Foradil-specific estimates, which is of particular use to it, but large numbers of young users under contemporary care and hopefully contemporary standards of care. And the chance, because of the size, to continue issuing -- looking at confounding factors.

DR. GARDNER: But presumably, Dr. Walker, then you also will be able to tell what proportion of children are treated outside of guidelines as well.

DR. WALKER: Absolutely. The question as to whether a Medicaid database gives you a usable national estimate for that, of course, is a little bit of a question.

DR. GARDNER: Of course. But perhaps with the HMO network.

DR. WALKER: There is certainly between Medicaid and commercial data the ability to look at patterns of utilization and adherence

to guidelines.

No question about that.

DR. RAPPLEY: As you described that study and its focus on one medication, is there enough use in pediatrics of that particular medication for that information then to ultimately be useful to us, aside from its -- I understand that it would be useful to the company. And is this an opportunity for there to be some collaboration among various sponsors in looking at various medications and its use?

DR. ARMSTRONG: We did select this database, because we felt that there was enough use of the free Foradil combination. But agree that it would be an opportunity to look at salmeterol as well.

DR. SWENSON: Dr. Kocis.

DR. KOCIS: Good morning.

DR. SWENSON: I'm sorry. Go ahead.

DR. ARMSTRONG: Thank you. We did have the opportunity to present some of the observational data in children yesterday that we

have. It doesn't really address whether or not they're being treated to the guidelines, or to what extent they're being treated to the guidelines. But if they are treated in accordance with asthma treatment guidelines, we did have very positive data. And if you could show the same slide I showed yesterday.

The one thing I would like to point out on this slide, as soon as it comes up, is that the top study in the analysis -- which will be appearing in just a second, I'm sure -- was a Medicaid population and does represent the largest number of patients contributing to the data. As you can see by the weighting and the point estimates, it is weighted the highest in this analysis. And it does show that when patients are treated with a long-acting beta agonist with an inhaled corticosteroid -- in this case, as Advair -- there were decreased asthma-related emergency department visits and hospitalizations in children. And we also

compared to an alternative treatment regimen, which was Advair versus inhaled corticosteroids plus monoleukasts, and as a similar significant reduction in emergency department visits and hospitalizations.

So we have looked at these outcomes in children. And in this case, there were about 43,000 children represented here, with about 16,000 on Advair.

DR. RAPPLEY: And the dates on those?

DR. ARMSTRONG: I'm sorry?

DR. RAPPLEY: The dates?

DR. ARMSTRONG: The dates of these studies?

DR. RAPPLEY: Would they reflect the newer guidelines?

DR. ARMSTRONG: Yes, they would. They're all relatively recent. They're all post-2000. All of these studies are.

The other thing I just wanted to clarify was in the adjudication process for the asthma-related hospitalizations and

asthma-related deaths, I just wanted to correct something. In our adjudication process, there was no adjudication as to whether patients were taking their inhaled corticosteroids. They were assigned a treatment, and if an event occurred on that assigned treatment, it was, as I said, assigned to that treatment. We don't know if those patients were actually taking those medicines at the time.

DR. SWENSON: Dr. Knobil, Dr. Martinez has a question for you.

DR. MARTINEZ: Yes, I think that guidelines, sponsors, the FDA have agreed that the first step in treatment of asthma -- this was for you, Dr. Knobil -- that the first step in the treatment of asthma is to use inhaled corticosteroids alone. And if we start from that premise and put as a second premise that epidemiological data -- and I'm a pediatrician and epidemiologist -- show that 60 -- perhaps two-thirds of all asthma is relatively mild and

should respond well to inhaled corticosteroids alone, we should expect that if these medicines are being used correctly, two-thirds of sales of your products should be fluticasone and one-third should be Advair.

So would you please give us information as to what proportion of the sales today are of Advair and fluticasone in the pediatric and adult populations.

DR. KNOBIL: Yes, I don't have the fluticasone numbers available to me right this moment, but I could probably get those to you before the end of the meeting. But what you said is completely correct and is consistent with the Advair label -- that children should be symptomatic on an inhaled steroid before stepping up to adding the long-acting beta agonist in Advair.

So the observational studies that we did would have been in children already on inhaled corticosteroids, and comparing the two different add-on medications.

DR. MARTINEZ: But what I'm asking is an issue that regards the way in which these medicines are being used out there. It's not what we have said, but what the reality and the practice is. And the impression that I have on the data I have seen is that it is exactly the opposite. Two-thirds of the inhaled corticosteroids that are being used today in pediatric practice are probably Advair or combination therapy, and one-third is single inhaler.

And I think this has to do with an issue that I will address later, which is the way in which we are in a certain sense influencing the public and physicians as to how these medicines should be used.

It is very important that we get a commitment -- if we're going to decide that these medicines are going to stay on the market -- from the sponsors, that they're going to solidly foster the use of these medicines in the way the guidelines say.

My conclusion from the information that I have, which is that two-thirds of the sales of inhaled corticosteroids in children -- and their data from Denmark, by the way, that have been produced by Hans Peskar, (?) showing that 60 percent of the sales in Denmark of inhaled corticosteroids in children are in the form of combination.

Well, that does not correspond to the epidemiology of the disease and to the practice of physicians every day, including myself, who see patients with asthma every day.

So I think what we have to obtain from industry is the commitment to foster the use of these medicines in the way you say we should use them and in the way guidelines say we should use them. And the result that we're obtaining is not that if more than 50 percent of the sales of inhaled corticosteroids are in the form of combination therapy.

DR. KNOBIL: I don't have the fluticasone numbers to hand right now, but for Advair -- to partly answer your question, there are about 2.1 million children who are receiving prescription medications for asthma in the United States. And there are about 290,000 children on Advair.

DR. SWENSON: Dr. Mosholder.

DR. MOSHOLDER: Yes. We have actually from last year's Pediatric Advisory Committee -- I have some drug use data that might address some of Dr. Martinez's questions, if I may. This is total dispensed prescriptions according to Verispan. And for the 12-month period ending in March 2007 -- so this is a little bit older data -- but there were 10.5 -- let's see, 10.5 million prescriptions for inhaled bronchosteroids, and for combination products, namely Advair, 18.2 million.

SPEAKER: Is this for asthma?

DR. MOSHOLDER: Well, no, this actually would be for asthma or COPD. All uses.

So unfortunately, I don't have it broken down by indication.

DR. SWENSON: Dr. Kocis.

DR. KOCIS: Good morning. I want to make a brief comment and then ask some specific questions based on the information that was presented to us yesterday.

I'm a pediatrician who trained just down the street in Washington, D.C., in an inner-city hospital in the late '80s when we were using dioflin (?) and steroids to treat children. We had a room called the asthma room, and kids poured in day and night there. I then trained in critical care in Baltimore, where I took care of critically ill children who failed their asthma treatment and came to the ICU.

In fact, I worked in the ICU at Sinai, where Jessie -- Julian Dorsey was hospitalized. I've been a member of the PAC Committee, which is a great privilege to me, over the last three years, and I was at the

Advisory Committee in November that began to look at the data regarding Serevent one year post-exclusivity.

And I need to comment about a frustration that I personally have, and I believe other members of the PAC, in how we're asked to review data after it's been approved by committees, one year after pediatric exclusivity, with extremely limited amounts of data, and then a database of adverse events -- the AERS database -- and try to make some conclusions when the data coming to us is woefully inadequate for pediatric patients in general.

And so that committee asked for more data, and that apparently led to this Committee. And we're here today, and I'd still have to say that I don't have the data from industry on several of the topics that we've asked for, which is pediatric safety data broken down by age, by indication, so that we can make a proper assessment of the

risk/benefit analysis today.

The PAC committee -- okay, the final comment was on Dr. Chowdhury's slides yesterday, which I think were unfortunate at least, and I believe set back the ability of us to evaluate medication safety in children in an open-minded fashion today, I think, to come to conclusions that we already know about the safety of these drugs in children, at least in my mind, is not true.

When we look at outcomes in pediatric patients, one thing I need to reflect on is the change in practice -- in a similar fashion to the change in practice in the use of inhaled steroids as a mild therapy in the earlier studies to combine therapy, critical care medicine in the treatment of severely ill asthmatics has also changed.

It is an extremely rate event for children to die once they come into a health care center, as Julian's experience showed us. That if these patients can come to a

health care center that's expert at caring for children, they can be salvaged.

In the eight years that I've been at the University of North Carolina, I have not had a single asthma death. We had one death in the community recently of a football player, age 17, who died. When he called EMS, they evaluated him and decided not to bring him to the hospital. He was found dead at home.

So when we look at outcomes of death, they are there; they are real. Whether they're related to the underlying disease, the drug, genomics, or a combination of factors, I think we certainly don't know. Hospitalization certainly is a good surrogate for loss of control, and ICU admission is another important factor in looking at outcomes. Intubation, though, of note is something that is rarely done today. Given equal levels of respiratory failure in children for different diseases, our current

practice is to not intubate children. The reason for that is the intubation process itself can lead to their demise, and likewise, the asthma makes it extremely difficult to ventilate children. And so when children come to my ICU, intubated often from an outside hospital, one of the first things we try to do is to extubate them immediately. Or if they come to our emergency room and we evaluate them there, that intubation is an extremely rare event, and one that we go to a great extent to avoid.

Now, moving on to the specific questions, we've heard a lot of comment about -- and I'm confused in looking at all the studies about the concomitant use of inhaled steroids and explaining away some of the negative effects. Certainly, when we're having adverse events -- deaths, hospitalizations, the combination scores -- certainly, that confounder has come up.

And as we've heard, that is the recommendation in the way it is to be used. And yet in many of these studies, we are talking about -- we don't know if they used concomitant inhaled steroids or not -- is there -- and this is to the manufacturers who are advocating or explaining away the results or those adverse outcomes -- is there data to show that there was not compliance in that? Or is it only assumed that's possible -- that they feel better with the bronchodilator, and therefore they stopped taking the inhaled steroids? That's question one.

The second one is the two manufacturers -- the formoterol products. I got confused yesterday in particular as in regard to the meta-analysis, when you decided to add or not add the higher dose, non-approved dose of formoterol. Because apparently from that dataset -- at least we can glean from that -- is that the higher dose is more effective than the lower dose.

And yet in the other formoterol studies in children, the non-approved dose being the higher dose is where the greater adverse events were noted. I want to say that this is of importance to children, and certainly when we look at breakdowns of children by age, because of the fact that if we just take the 50th percentile for children's weight, for a 5-year-old that would be 18 kilos. For a 12-year-old, that would be 40 kilos, or nearly twice the weight of a 5-year-old. And if we take an 18-year-old, that would be 67 kilos, or nearly 50 percent greater -- greater than 50 percent greater than a 12-year-old.

So when we look at these bands that we've described and sort of broken down for this drug -- less than 4, 5 to 12, 12 to 18 -- it's important for me to understand, and particularly with the formoterol and the dosing -- about the high dose being more or less effective and/or having greater side

effects. And then -- I had one last question.

DR. SWENSON: Dr. Kocis, you have a lot of questions. Perhaps I could ask each of the sponsors to step up, and if you have -- in some cases, you may only be able to respond to one of his questions. And then those that can respond to two, please do so.

So let's have GSK first.

DR. KOCIS: Can I just make one other thing that I slipped over, and this is going back to the issues at the PAC committee that we are commonly faced with. So we were given the patient inserts for Advair. And I want to actually congratulate Advair for doing most of the studies that we've seen. They've done a lot of pediatric studies, and we've gleaned a lot of information from that, and that should be rewarded.

If we look at the Advair Diskus pediatric use label, the first line says use of Advair Diskus in patients 4 to 11 is

supported by extrapolation of efficacy data from older patients, and by safety and efficacy from a study of Advair Diskus in children with asthma age 4 to 11.

If we go to the next label, it says for pediatric use, 38 patients 12 to 17 years were treated with Advair HFA in U.S. pivotal studies. My only point to this is in the PAC committee, this is what we're facing. We're facing drugs being approved in children by extrapolation from adults -- whether that's appropriate or not -- and then also the number of patients enrolled in these pivotal studies are very small.

Often too small to really show efficacy, but certainly unable to show safety signals. And therefore, we look at and need meta-analysis that pool data in children to begin to make important decisions about risk and benefit.

Thank you.

DR. ARMSTRONG: That was a lot of

questions. I'll try to remember all of them. I'll start with the last question first, about the labeling. I think that Dr. Seymour described in some detail yesterday about how some of the approvals for pediatrics do occur. They do bridge from adult studies, because the safety and efficacy of medications are proven in adults and adolescents first before going to the pediatric population. There are fewer studies in pediatrics, and we have shown you the safety data from all of the studies that we have, which comprises about 1,200 children receiving Advair.

So from our perspective and apparently from the FDA's perspective, we believe that's a substantial amount of data to be able to observe safety and efficacy in children. However, we have continued to study children, and those studies do not necessarily get into the package insets. So we have a lot more data than may be represented in the package inserts.

Your first question is do we have

any measure of compliance to inhaled corticosteroids. And if the patients were reporting a background inhaled corticosteroid, meaning a steroid that they were taking prior to entry into the study and it was not part of the study protocol, then we did not collect compliance data on the background inhaled corticosteroid. If patients were receiving ICS as a study drug, then yes, we did measure compliance.

So it is an hypothesis. I think it's a plausible explanation that adherence goes down during the studies, and I did show you data yesterday that showed that there was an increased risk of hospitalization and death when we compared ICS use as background medication versus ICS use as study drug, which I'll show you again with one more bit of information.

So the bottom two lines here are what I showed you yesterday. ICS's background had about a fivefold increase in

asthma-related hospitalizations when we compared that with ICS given as a study medication.

One thing I didn't point out yesterday was that there was also increased risk of hospitalization versus patients receiving placebo, which is also what we've seen with salmeterol. So I think what's going on here, and I think a very plausible explanation is that poor outcomes occur when patients stop taking their inhaled corticosteroid.

And we do know that in clinical trials -- either when they receive another medicine or whether they just feel better because they're in a clinical trial or feel like they don't need to take their inhaled corticosteroid anymore -- we see worse asthma-related outcomes, even versus placebo.

So this is the basis for our plausible mechanism for why we're seeing increased asthma-related outcomes in patients

on background ICS.

We also know -- one more point -- that patients who have been given an ICS by their physician are likely more severe than patients who have not been given an ICS by their physician. And so discontinuation of an ICS in that more severe patient population may result in more severe outcomes. Again, it is a theory, but one that seems to be supported by these data.

DR. SWENSON: Dr. Bonuccelli.

DR. BONUCCELLI: Thank you very much. Yes, you had several questions, and one thing I want to start with is just to make sure that all the Committee members do understand that the analysis that AstraZeneca showed you was based on every trial that met the FDA criteria laid out. We did not cherrypick that analysis at all. That was a comprehensive analysis of everything we actually thought the FDA would also look at.

So if I could have from our primary

presentation yesterday the first slide.

Your first comment was a bit of confusion about the sort of slicing and dicing of background use versus randomized use, versus free combination, versus -- you know, fixed combination. And I just wanted to point out to you that for our analysis in our 23,510 patients, when we did try to look at that rich dataset, we really were not doing that in order to make a risk signal go away.

Our relative risk estimates were all to the left of one. So whether you looked at it overall -- all formoterol versus non-LABA -- or you looked at it with background, randomized, or if you looked at it in the combination product, no matter how you looked at it, it still landed with a relative risk at point estimate lower than one. And for our 18 micrograms -- our approved U.S. dose or higher -- again, the estimate was the same.

So I do believe we've had validation in the room. And we agree with Dr. Salpeter. You want to start with as rich a dataset as you can, because then you can query it for specific questions. And that's what we tried to do for you yesterday. But the 18 micrograms or higher, in particular, for something you think might be a drug-related effect, you'd want to see if there was an increase. We did not see that.

That specific analysis is just for your information shown here. So just to give you that picture again. You had me land right on the line -- right at a point estimate of 1.01.

With regard to children, I would point out to you that we also had -- our dataset in children under the age of 12 was equal in size to the complete dataset evaluated in the FDA's analysis. So we do not currently have an approval for children under 12, but we did want to provide that

data to this Committee because of the paucity of data that you're looking at, and tried to make that assessment.

And we did show you that yesterday. I'll show you that again.

This again is in the 3,400 -- more than 3,400 patients overall. And this is all of our randomized controlled clinical trials in that age group. And again, we have a point estimate that lies just to the right of one. It does disfavor formoterol in this overall analysis. But I hope you also caught in our briefing materials and in Dr. Carroll's presentation that included in this analysis is one trial where we had an under-treated arm.

That under-treated arm -- that's one of the problems with hospitalizations. If you're under-treated, you have them. If you have a drug effect that causes it, you have them. But if you take out that under-treated arm, which had seven

hospitalizations, that moves this estimate to below one. Very consistent with what we saw in our overall population.

So I hope that answers some of your questions.

DR. SWENSON: Dr. Armstrong.

DR. ARMSTRONG: To start with your question on corticosteroid use, most of the Foradil studies, including the studies with the largest number of events, were conducted prior to 1998. Patients were permitted to use inhaled corticosteroids but it was not required.

And -- you know, the use was not stratified. And we did not collect the compliance with that medication. We had two studies in which the sponsor did provide inhaled corticosteroids, and in those studies, compliance with the inhaled corticosteroid was high, and the events did not occur in the LABA ICS group.

To get to your question about the higher doses, we did the post-marketing

commitment study. D2307 was done specifically to address that question. And in this study, we matched the inclusion-exclusion criteria to the earlier pivotal trials.

And these were patients 13 in age and older. We did have 300 adolescents. In this, we compared Foradil 12 twice a day to 12 twice a day plus PRN -- that was an open label arm -- to 24 twice daily and placebo. And even though it was powered to see a threefold difference based on the event rates that we'd seen in the earlier trials, overall, there were fewer events. But they seemed to be relative -- yes?

DR. KOCIS: So this, though, the data you're showing on the bottom, you talk about there being 300 adolescent patients of the 2,000 in the study, this is combined data.

DR. ARMSTRONG: No, there were 300 patients in the study. Yes, so this is all the patients. I can tell you that none of the

events --

DR. KOCIS: Not children.

DR. ARMSTRONG: None of the 300 adolescents had events in any of the treatment arms in this study.

DR. KOCIS: I guess that's a summary of 2,000 patients, not 300 pediatric patients. Is that correct?

DR. ARMSTRONG: This is a single study of 2,000 patients, in which there were 300 adolescents enrolled.

DR. KOCIS: But you don't have it broken down by ages is my point.

DR. ARMSTRONG: So there were no events in the study in that age group, in the 13 to 18s.

DR. SWENSON: We now will take a 15-minute break and we'll reconvene at 11:00.

(Recess)

DR. CHOWDHURY: Despite progress in the understanding of asthma, the choice of medications is quite small. And most

medications have limitations, that you heard yesterday. The main medications for treating asthma are albuterol, inhaled corticosteroids, and inhaled long-acting beta agonists. As we discuss the possibility of removal of long-acting beta agonists from the U.S. market as recommended by OSC colleagues, keep in mind the choices that are left, and the consequence of use of alternate medications, such as albuterol at high dose, and chronically, systemic corticosteroids, and theophylline.

The consequence of removal of the asthma indication will not only reduce choices, but may also have a negative consequence of inappropriate use because the actual LABA products would remain on the market for the EIB and the COPD indication, and the label warnings and directions of appropriate use will be gone with removal of the asthma indication.

It was reassuring to hear from industry and others yesterday and today that

at present, most use of LABAs are with other controller medications, which in most cases are with inhaled corticosteroids. We also heard very good arguments why single ingredient LABA products should remain on the market. Another reason to have single ingredient inhaled LABAs, every label is for patients with EIB who do not routinely need concomitant use of another controller drug.

We continue to believe that symptomatic benefit that inhaled long-acting beta agonists provide to many patients outweigh the serious risk to a small number. The LABAs should remain on the market, but the safety risk needs to be managed. We certainly would consider more efforts to ensure that the safety risk is communicated and managed adequately.

Thank you.

DR. SWENSON: Thank you, Dr. Chowdhury. Now, Dr. McMahon has a few comments.

DR. McMAHON: Thank you.

I'm going to make just a few comments this morning summarizing briefly our purpose here today, and then we'll go into reading the questions that are going to be before the Committee and that we'll be discussing and that you'll be voting on.

Why are we here? This is a large advisory committee, and has many very important members, and was requested by a Pediatric Advisory Committee meeting in 2007 that convened to address -- and they asked that this meeting be convened to address benefits and risks regarding LABA use in children, and in the context of that, to talk about LABA use in adults.

In preparation for this meeting, the FDA did a meta-analysis of both pediatric data, but also pediatric data in the context of adult data. The framing of the data that was used for this meta-analysis were done before the meta-analysis began, as was

mentioned yesterday by Dr. Levenson. The data that were included in the meta-analysis were patient-level and trial-level data on LABA trials from the sponsors of LABAs. It included patients that had the asthma indication, and included parallel placebo and/or active controlled trials with and without ICS use. Only approved doses and products were included. Now, to change the parameters of this analysis, the analysis would need to be completely redone. So I just wanted to make that point.

To summarize the findings of the FDA meta-analysis were that the risks of LABAs were quantified, and we've been discussing those numbers, both including data from the SMART study and excluding data from the SMART study. The analysis found an overall age trend, with younger age being associated with higher risk, and found that we could not draw distinctions regarding individual LABAs and how they might differ

with respect to risk, in part due to sample size issues.

I wanted to mention this morning another concern that was brought up was whether all events may be in data that are currently published on LABA risk. And I can't speak to that, but that was something that was of concern that Dr. Salpeter and others mentioned.

So the benefit data I wanted to mention that were analyzed for the FDA talk were derived from review of simply the pivotal trials for drug approval. I want to mention that spirometric -- interpretation of spirometric endpoints were consistent with analyses of others that have spoken.

OSE focused only on pivotal trials for drug approval, and interpretation of secondary endpoints may vary. Generally, trials were not powered to assess the quality of life data; therefore, it was a little bit uncertain in many instances, since the trials

were not powered to study these endpoints.

Given these findings, what is the age-specific risk/benefit profile for LABAs for the asthma indication? And more specifically, I want to read the questions to the Advisory Committee on long-acting beta-2 agonists.

We would like you to discuss and answer the questions below. We have structured questions one through four by active LABA ingredient and by age group. If there are issues that you believe are relevant to the entire LABA class, please state so in your discussion.

Note that questions five through eight, which concern individual LABA-containing products, require voting. I would just say parenthetically the reason that we included specific LABAs was that some of the data were laid out by specific LABA.

Question one: discuss the benefits 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 greater than or equal to 18 years of age; in adolescents 12 to 17 years of age; and in children 4 to 11 years of age.

Two, discuss the benefits of using formoterol 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: Adults greater than or equal to 18 years of age; adolescents 12 to 17 years of age; and children 4 to 11 years of age.

The next two questions, I'll read

again.

Number three is discuss the risks 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: Again, adults greater than or equal to 18 years of age; adolescents 12 to 17 years of age; and children 4 to 11 years of age.

And number four, discuss the risks of using formoterol for the treatment of asthma in patients not adequately controlled on other asthma controller medications, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies in each of the following age groups: In adults greater than or equal to 18 years of age; in adolescents 12 to 17

years of age; and in children 5 to 11 years of age. Note that Symbicort is not indicated in this age group.

Five -- and these are voting questions -- do the benefits of Serevent salmeterol xinafoate outweigh its risks for the maintenance 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 the following age groups: In adults greater than or equal to 18 years of age -- although I said a voting question; in adolescents 12 to 17 years of age -- another voting question; and in children 4 to 11 years of age -- a voting question.

So the next question, number six, is regarding Foradil. Does formoterol fumarate outweigh its risks? Do the benefits of Foradil formoterol fumarate 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 corticosteroids, or whose disease clearly warrants initiation of treatment with two maintenance therapies in the following age groups: In adults greater than or equal to 18 years of age -- a voting question; in adolescents 12 to 17 years of -- a voting question; and in children 5 to 11 years of age -- a voting question.

Number seven, do the benefits of Advair fluticasone propionate and 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, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies in the following age groups: In adults greater than 18 years of age -- a voting

questions; in adolescents 12 to 17 years of age -- a voting question; and in children 4 to 11 years of age -- a voting question.

And number eight, do the benefits of Symbicort budesonide and formoterol fumarate outweigh the risks of the maintenance treatment for 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 the following age groups: In adults 18 or older years of age -- a voting question; and in adolescents 12 to 17 years of age -- a voting question.

Then there are two additional questions at the end -- number 9 and 10 -- that are not voting questions but discussion questions.

Number nine is, based on your discussion and votes above, are there further

labeling changes or risk mitigation strategies for individual LABA products or the class as a whole that would be advisable?

And 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?

DR. SWENSON: Thank you, Dr. McMahon.

Dr. Jenkins will have a few points to make.

DR. JENKINS: Actually, I wanted to follow up on the discussion we were having before the break. I had a point I wanted to hear more discussion on that we didn't get to, so if that's okay, I'd like to raise it now.

I'd like to hear more discussion about the available data on what is the risk when inhaled corticosteroid -- excuse me -- when the LABAs are added onto a background of inhaled corticosteroid therapy? I don't think there's any disagreement around

the table, or maybe even in the room, that LABAs increase the risk of asthma death and serious asthma exacerbations. I think there's also pretty broad agreement that the standard of care in 2008 for treating patients with asthma is that for maintenance therapy, they should be on a controller medication -- the primary controller medication being inhaled corticosteroids.

So as I'm thinking about what's the risk for a patient in 2008 who is getting appropriate therapy with inhaled corticosteroids -- what's their risk if they get a LABA added on top of that background of inhaled corticosteroids? And we've seen a variety of data from Dr. Levenson, Dr. Salpeter, and from the companies that in some ways are similar, and in other ways are showing different results.

I thought it would be useful if we could have further discussion about given a background of appropriate anti-inflammatory

therapy with inhaled corticosteroids and you get to that step two, step three decision, what's the added risk by adding LABA in those situations? Dr. Levenson had some analyses of that, Dr. Salpeter had some analyses, and the companies as well.

Because that's fundamentally the question we face in trying to manage the risk of these drugs.

I think we can all agree patients should not be on single-ingredient LABAs alone, except maybe in the rare circumstances, as Dr. Chowdhury said, where they have EIB, exercise induced bronchospasm, and don't need a controller therapy but maybe want a longer duration of protective effect than they would get with albuterol pre-exercise. But I think there's pretty broad agreement that patients should not be on LABAs alone; they should be on LABAs only if they're also on a background of controller therapy and failing.

So if we could have some discussion maybe from Dr. Levenson and Dr. Salpeter, and the companies about -- you know, what are the data we have available to address that? It struck me yesterday in Glaxo's presentation -- they kind of walked through a hierarchy. They had studies where ICSs were background, but they weren't part of the randomized therapy. That had one risk estimate.

They then went onto studies where ICS was part of the study drugs, and that was a different risk estimate. And then they had the Advair data where if you were getting the LABA, you knew you were also getting the corticosteroid in the combination. And that gave a different risk estimate. So I'd like to hear some more discussion and exploration of those data.

DR. SWENSON: Well, Dr. Jenkins, we have quite a bit still on the plate here, and what I'd ask is we have a few more comments to

be made, and then before lunch perhaps we could open it up for some brief discussion to your comments and thoughts here, if that would be all right.

I'd like to ask Dr. Rappley here to make a few comments that she thinks are clearly important for the pediatric issues.

DR. RAPPLEY: So speaking now as chair of the Pediatric Advisory Committee, I think that some of what you're hearing today is some frustration that the overall time has not been spent enough in discussion of pediatric-relevant questions and issues. And so I think that we are hoping to focus that as we move into the discussion.

I think what I have heard from the Office of Surveillance and Epidemiology is that they have -- their stand is that evidence for benefit from LABAs is slim, and that evidence for risk with LABAs is so strong that the burden of proof should shift, such that it must be proved that LABAs are

safe, and approval should be withdrawn until that proof is provided of the safety of LABAs.

What we heard from the Division of Pulmonary and Allergy Products is different. It's that the evidence is that most patients do derive benefit from LABAs, and that evidence is clear that there is risk and that this risk can be managed through informing prescribers, patients, and the public through labeling, med guides, and other communications that would lead to informed treatment decisions.

We heard from industry that the benefits outweigh the risks. And we've heard six presentations from the public. Five urged us to continue use of LABAs, and one further emphasized the risk. The FDA meta-analysis showed us that there was an increase in risk with younger age groups, which is our particular concern. And in all of this, the risk of not treating was alluded

to or described in a qualitative or historical sense. And I think Dr. Jenkins then asks us to focus on the really relevant question -- the question that is relevant today in this point in time and the question that really is relevant to children.

So as we continue our discussion into the rest of the morning and afternoon, it's my hope that we focus on evidence that is relevant to children. There is evidence today that has been presented -- yesterday and today -- that we acknowledge that, and we deal with that primarily. And that when we talk about the need to extrapolate and go to evidence that comes from work with adults, we do that because in pediatrics, we do that in order to take treatments out to children.

But we acknowledge that we do that because in acknowledging that, we do that, then we can answer that last question, which is what are still the gaps? What are the gaps that continue to frustrate us in

pediatrics in terms of lack of information that's relevant to children, particularly in a diagnosis that represents perhaps 10 percent of the pediatric population. And medications that are among those most commonly used in children is really not acceptable to no longer have data that's relevant to children. We really need to change this. And we won't do that unless we consciously acknowledge when we pull from adult data and when we deal with pediatric.

Thanks.

DR. SWENSON: Dr. Chowdhury, you had just one clarification you wished to make.

DR. CHOWDHURY: Thank you, Chair. The question about extrapolation for some of these products both for safety and efficacy is coming up, and I just want to give an explanation of that so that we don't get too much distracted in a way which I did not intend and I think is not correct.

First of all, you have to keep in

mind that the products we're talking about are indicated for patients ages 4 and above or 12 and above. They're not really for very young children. As far as the disease asthma goes, it's generally accepted that it is still asthma. It is called asthma in a 4-year-old or a 50-year-old. And looking at Geno documents (?) and (inaudible) documents and others when the percentage of asthma is talked about, they're talked about in the same context across generally ages.

We do understand the responses to drugs may vary, and they do vary. And we, of course, acknowledge that. As far as different aspects of the disease, such as bronchial inflammation, they go on in all ages. Of course, the differences are prominently size and category. And looking at these documents, for example, the diagnosis and treatment of asthma in childhood, a (inaudible) report which is the allergy consensus report, it talks about

similarities and differences. And just reading it here, a responsiveness to non-specific stimuli is higher in normal infants and young children than in older children or adults. So there are differences. We acknowledge that.

But for developing drugs or for asthma, the assumption that is made that the drug is first of all shown to be effective in adults, and then the children studies are done, and for long-acting beta agonists the beta receptors are there in adults and in children. The differences may be there but not necessarily that prominent. But again, the important thing is -- the expectation is the long-acting beta agonists will be effective in children as in adults, but that is where the drug development does not stop.

Specific efficacy and safety studies are conducted, and they're conducted by the companies to actually show that they are safe and they're effective. So they are

pediatric studies.

And one thing to keep in mind, these are orally inhaled, locally acting drugs. They act locally in the lungs. So even if you actually want -- there's not really any clean mechanism of extrapolating for local effects. There's no way of finding any markers as a surrogate as opposed to (inaudible) drug. You can look at the PT in the blood. For a locally active drug, you actually cannot even do extrapolation. So extrapolation to that context is really not done.

And another point I just want to make and explain a bit further again so that we do not lose context about the combination products -- the combination products are combinations of convenience. And in many situations, there's actually combinations of products which already has been studied as individual products. For example, Advair Diskus contains fluticasone salmeterol. And

salmeterol has been studied as a diskus formulation.

Fluticasone is there as Flovent Diskus. And there are many studies which were done for these products which I eluded to and gave numbers of the studies and patients in the studies. I will not repeat it here.

So when these two products, fluticasone, which is approved as Flovent Diskus, salmeterol as Serevent Diskus, and other formulations are put together, the burden here is to show competence as to the present. (Inaudible) competence are known to have studies prior to putting them together. So the (inaudible) program for these combination products as Dr. Seymour explained yesterday is from the clinical standpoint showing contribution that Flovent which you have put combination product is still there, the same as fluticasone, and so is salmeterol.

And to get to that, there are a lot of in vitro studies and other studies that are done to make that fluticasone was there and salmeterol was there. So therefore, when we look at combination products, the paradigm shift in that is not to say that (inaudible) and there's no studies to back it up.

So with that I would just like to stop and see if there is any questions on this. Thanks.

DR. SWENSON: All right. We have about half an hour before lunch break and I thought that we should pick up the questioning. And I would hope that the Committee members in their comments could focus on particularly the issues that Dr. Jenkins and Dr. Rappley have addressed. So I'm going to pick up the questions in the list from the previous and start with Dr. Schneeweiss.

DR. SCHNEEWEISS: Sure. This is a leftover question, but it's still relevant for me. I appreciate that there is little or no

information on adherence to background ICS in the trials. But such data must be available outside the trial setting. The adherence, particularly in children, where the intention is to treat with both ICS and LABA in separate monopreparations. What is the adherence differentially for those two products? Which one gets dropped earlier -- the ICS or the LABA? And I would be very surprised in that information is not out there.

The second is just a comment to Dr. Chowdhury, who puts quite some faith into label changes translating into utilization changes and clinical practice. And what we have heard from Dr. Martinez today, that might not really be the case in practice.

DR. SWENSON: Anybody wish to speak to those points either from sponsors or panel members?

DR. STOLOFF: I'm Dr. Stoloff. I gave you a talk yesterday and I'm on the Guidelines Group. But I will speak to a paper concerning

adherence. I was the leadoff of a paper a couple of years ago that was published in the Journal of Allergy and Clinical Immunology on adherence rates of the medications, including combination medication or monocomponent medication, including inhaled corticosteroids, leukotriene receptor, antagonists, and the combination of fluticasone and salmeterol in the diskus device known as Advair.

When we looked at all that data and we looked in a large managed care, multiple managed care companies -- this was published in 2004 -- this was a couple of million lives. When you look at fluticasone alone, the number of claims data per patient for a 12-month period -- so that should be 12 canisters or 12 delivery devices -- the average refill rate -- and this is really important for all of us.

It's important for this meeting. Co-payments in this is $10 or less a month, okay, for these products. The average refill

rate was 2.27 canisters per year for an inhaled corticosteroid. The molecule was fluticasone -- 2.27. So approximately nine months a year, there was no product.

Number two, if you looked at monoleukasts, monoleukasts averaged -- which is -- and I still believe I am correct -- the number one prescribed medication in the United States for mild persistent asthma in the pediatric population -- the average refill rate was three. Three 30-day supplies. It's actually 3.68, 3.7. A little less than four. Four.

If you want to round it off to four. So eight months a year, they're without medication.

Three. If you looked at the combination of fluticasone and monoleukasts, you still didn't get much better. And then if you looked at the combination of fluticasone plus salmeterol -- and this was an end of only 224 individuals this

time -- this was 2004, but we put out the update in 2002 -- the refill rate actually for each canister -- so we're giving them exactly -- to answer your question, you get the separate salmeterol and the separate fluticasone.

For salmeterol, it was 2.44 and for fluticasone it was 2.35 when given as individually prescribed as mono components to be used together. For the combination of Advair, which was 563 patients looking at a 12-month calendar year, it was 4.06 canisters. So even where you're giving the combination eight months out of a calendar year, zero, with a $10 or less co-pay in a very, very large multiple managed care view.

DR. RAPPLEY: I want to speak to the question about actual practice and what is our responsibility perhaps as a large committee here now, both pediatrics, pulmonary specialists, and risk specialists in terms of medication.

You know, we always come down to

this issue in pediatrics, because it is often a public health issue. The question I think distills down to do we use the FDA approval decision -- our recommendation about the approval decision -- do we use that mechanism to send a message to physicians across the country that they need to follow standard of care?

Or is our recommendation about the approval decision reflecting our best assessment of the risk and benefit of these medications, and that we need to find an additional, and many additional perhaps ways to send a strong message to physicians to follow the standard of care?

I put it out there for us to think about.

DR. SWENSON: Dr. Henderson?

DR. HENDERSON: I just wanted to remind you of some of the data that we showed yesterday regarding the concomitant prescription of inhaled corticosteroid and particularly in

children 5 to 12.

And this was data from a large PBM, 60 million lives, in which it looked at the timing of a Foradil prescription with a timing of an inhaled corticosteroid and found that three-quarters of the patients had inhaled corticosteroid prescription filled within 90 days of their Foradil prescription.

Thanks.

DR. RAPPLEY: Thank you.

DR. SWENSON: Our next question is from Dr. Burlington.

DR. BURLINGTON: This is a question for Dr. McMahon of the Office of Safety and Epidemiology.

Like companies, FDA usually looks at all the safety data, not just selected parts of it. And I'm sure you're doing that here. And of course you weigh that look by the strength of the evidence. But when the randomized trial data begins to get a little thin then you have to rely more on the other

sorts of data. And I didn't hear comments from the Office of Safety and Epidemiology about their assessment of the AERS data, which at least to my look seems somewhat reassuring, as thin as it might be, with the possible concern about the uptick recently in childhood deaths.

At the second level of data, in terms of the epidemiologic data, we heard that it was not looked at because of the complications of confounding by indication. And yet the analysis on the epidemiology studies that we saw from GSK seem to suggest that the exact opposite conclusion was applicable here -- that is that the patient is getting two drugs, and presumably if they were confounded by indication, the worst patients were doing better. And I'd like if the OSE would comment on that.

Third, or fourth, actually, kind of data we are looking at here is the ecologic data. And we were cautioned yesterday that

it's a basic problem to look at the ecologic data that is the secular tend in death rates, and yet we heard an attempt by Dr. Schoenfeld to quickly reconcile some of the odds ratios and hazard rates we'd heard with the trend in death rates, and which conclusion if you use a very low odds ratio or hazard rate, that there might be room to fit that within what's been observed.

And yet I'd like to know whether there's any comment on the ecological data with some of the very high estimates of the hazard rate that we've heard -- the seven or the nine that we heard from Dr. Salpeter this morning. Or do we have to reach a conclusion that those hazard rates are estimated from very atypical subsets of the patients at risk.

Next, I would like to ask a question about unintended consequences. Dr. Mosholder presented data from a managed care organization, presumably one that

strongly discourages fixed dose combination prescribing in which he showed a rather surprising 48 percent of the patients were getting single-entity LABA prescriptions without concomitant ICS. If we were to remove the asthma indication from the fixed dose combinations, why do we not think that we would end up with more single entity prescribing with LABA rather than combined use?

DR. SWENSON: Dr. Burlington, you've asked a number of questions, so I see that Dr. McMahon is there, and Dr. Graham, so why don't we start with you, Dr. McMahon.

DR. McMAHON: Yes. I was just going to ask Dr. Graham to comment for a minute on these questions.

DR. GRAHAM: Bruce, I tried to jot down the questions, and if I didn't get them right, please clarify for me.

Regarding the AERS data, AERS spontaneous reporting is notoriously

unpredictable. And so we know there's lots of under-reporting. And the older a product is, the lower the reporting for things becomes, especially when things -- once they're labeled and sort of enter into common knowledge. So we never use AERS as a means of monitoring the effects of an intervention because it is so unpredictable and doesn't correlate with anything.

So unfortunately, the only thing that AERS tells us is that there are episodes of asthma death with the product. It tells us nothing about whether it's going up, it's going up, whether something we've done has had an effect or not had an effect.

Now, regarding observational studies, asthma is a very complex disease. There are many factors that can influence the severity of the disease. How do you define that severity within the context of the observational data you have available in your database? And then there's problems sort of

validating that.

All of these factors together -- generally, what happens -- well, there are two problems. There's a problem of confounding by indication, which here is sort of intractable. So the question is is it the disease severity or is it the drug, because it's not randomized. And no amount of adjusting for confounders can necessarily deal with that.

The second is that -- and this is probably the bigger problem -- is that with mis-classification in terms of adherence, compliance, and the like, you can take an association and make it evaporate. And so when we review epidemiologic studies that are submitted to us from industry or that appear in the literature, that's probably the single greatest problem that we have in one dimension or another, is that there is mis-classification that drives the observed endpoint -- the odds ratio, the relative

risk, the hazard ratio -- towards the no effect level. And so then that makes it difficult to deal with it. So our view regarding asthma, and specifically the questions of the LABAs, are that really they can only be resolved by large, randomized controlled trials.

Now, I think your third question related to the ecologic data that shows that over time, there has been a decline in reported asthma mortality. Well, a couple of things. One, there's no relationship between the people who died and whose deaths are recorded in national statistics and who is taking what drugs. So we've got two parallel lines. We've got two lines -- a line that shows drug use going up, and another line that shows mortality going down. But those aren't related in terms of relating to the same people. So that's where the ecologic element comes in.

Fifty percent of the decrease that

we have in asthma mortality is due to changing and coding from ICD-9 to ICD-10. The remainder of that difference I would submit is probably due more to changes in practice of care than it is to the medications themselves.

We just heard data presented that I was unaware of, and I appreciate being told about it, is that on average, people who use these various LABA products or combination products are only on them for three or four months out of the year. So it's really very difficult for me to imagine that the decline in mortality is due to such episodic and inconsistent use of LABA products, especially if we want to posit that stopping to take them would drive things up.

So I think there's a real disconnect, and I think ecologic data -- you know, might be chapter 2 or chapter 3 of any epidemiologic textbook -- is you can be fooled and usually are fooled. And you

shouldn't rely upon it. So I know it's very tempting and very tantalizing, but I would beg this committee not to pay attention to it because it's really not supported with any evidence.

Now, the fourth question I guess related to unintended consequences. And I've got several different answers or aspects of an answer to that question. One really relates to what do you think the magnitude of the health benefit is. Now, the information that we reviewed looking at the pivotal clinical trials that led to the approval of the drugs suggested to us that there really wasn't a whole lot of juice for the squeeze. And yes, it's a bronchodilator, but what did that translate into?

And as I showed in my talk yesterday, there was 90 percent statistical power, to show a 0.5 score change in asthma quality of life, and yet the adverse studies weren't able to make that. So they had

90 percent power to show that effect if it was really there and they didn't see it.

Now, this other data that's been presented -- we saw a lot of clinical trials presented by Dr. Lemanske yesterday, and those are not things that we reviewed. But based on the things that we did review where things were carefully measured and carefully calibrated, we drew the conclusion that there didn't seem to be a whole lot of translation between FEV1 and benefit. So if you believe that the benefits aren't all that great, it's hard to imagine that the consequences of removal of these drugs would be all that catastrophic.

If you have a different assessment of what the benefits of these drugs are, then you might arrive at a different conclusion about what the unintended consequences would be. But based also on the information we just heard about the very low compliance with these products, again, it's very hard for me

to imagine. People are doing this all the time, it appears. People are withdrawing the drug from their market, and it's happening across the country. And we're not seeing the catastrophe that people say will happen if the drugs come off the market.

So I think it's a really tough argument to make that the catastrophe will result. There's no question that for some patients, that these drugs, I'm sure, are lifesaving and life-changing. I have no doubt about that in my mind. But if you look at a population level, the question is what are we getting? So it's really -- it's this eternal struggle between what do we do at the individual level and what do we do at a population level.

So I'm not sure if I've addressed all your questions.

Andy, Dr. Mosholder is here and he may have a few other remarks.

DR. BURLINGTON: Well, before we turn

it over to Andy, David, yesterday you gave us an estimate of 5,100-and-some deaths per year attributable --

DR. GRAHAM: No, it wasn't per year.

DR. BURLINGTON: Over three years.

DR. GRAHAM: It was over three years.

DR. BURLINGTON: Which would be about 1,700 per year.

DR. GRAHAM: Right.

DR. BURLINGTON: So somewhat more than 45 percent of the deaths in the last year would have been attributable to LABAs by that analysis. And if we use the point estimate that Dr. Salpeter gave us earlier this morning, one would have to reach an even higher conclusion.

Is that really credible?

DR. GRAHAM: I think it's open to questioning and to investigation. If you recall also yesterday in my remarks, what I said was that if the -- that that was predicated on the assumption that the risks of asthma mortality for the combination products were the same as

the single entity products, and also that the background rate for asthma mortality was the same as the background rates that were reported in the SNS and the SMART studies. Now, if there has been a change because of improvements in the quality of health care and the like, that would reduce the background rate. So let's say that the background rate, instead of being 6 per 10,000 per year -- that was the control groups in SMART and SNS -- that it's 3 per 10,000 per year.

Then the projections that I placed on the slide yesterday would be cut in half.

So I think that for the data from 1994 to 2004, where we were focusing on Serevent, I think that's pretty hard-and-fast data. And I think you look at how many thousands of people probably died as a result. That was 10 percent of all asthma deaths during the time period covered by that. In the more recent time, where it is very well possible that the background rates

have reduced for a variety of reasons having nothing to do with LABAs themselves, that that would change the actual number of deaths that have occurred.

DR. MOSHOLDER: Andy Mosholder. Just to address your questions about the observational studies, actually in the OSE review document, we do have a brief summary of some of the studies I mentioned yesterday in my talk. The reason we didn't emphasize them yesterday or in the document is because of the limitations that David just described, in particular confounding by indication is very hard to handle in non-randomized data.

Certainly, we in OSE could have pursued an observational study using our own epidemiologic contractor resource if we thought that that would have provided -- you know, data of high inferential quality. But we did not. That's why we pursued the meta-analysis of clinical trial data.

The most recent observational study

I'm aware of was only available in abstract form, but it was from Kaiser Permanente. It actually showed an increase in asthma mortality with LABAs both with and without inhaled corticosteroids. But unfortunately, it's only available as an abstract to date. But the results have been mixed, and that's why we feel that that's not where the answer is.

Regarding the HMO data that I presented showing -- you know, close to half of the patients getting the single entity inhalers with never receiving a concomitant ICS, that was done at a time when the 2002 guidelines were in place, which would have recommended against that for asthma treatment.

So I guess I'm not -- I wasn't clear on your point that there would be an increase if the label indication were removed for those products.

DR. SWENSON: Dr. Notterman.

DR. NOTTERMAN: Thank you. So I just want to continue the theme of this discussion. I've come to the conclusion based on what I've heard today, and also based on having been involved in patient care in this area, that we can't be sure when looking at studies whether or not ICS were or were not used in combination with LABA. I think that all of us understand that physicians don't always follow guidelines, and that patients don't always listen to their physicians.

So I'd like to just focus for a moment on the two products where -- in which we know that an ICS was prescribed in conjunction with a LABA, and that is Advair and Symbicort. And I'm sure this data has already been presented, but I'd like to try to refocus on it. And I'd like to ask each of the sponsors, and I'd also like FDA to comment on the number of adverse events, including death and hospitalization, in children and in adults for the two

combination products. That's the first question.

The second question -- well, let me stop there just so we have some clarity on that.

Thank you.

DR. SWENSON: Let's go to the FDA first and then the sponsors.

DR. LEVENSON: Well, perhaps I can get my slides from yesterday. Slide 29.

Okay, as I said yesterday, there were no deaths or intubation from Advair. The same is true for the Symbicort data I looked at, so naturally, there wouldn't be any in the pediatric population as well. I don't have the hospitalizations broken down handy by the age group.

DR. NOTTERMAN: Am I correct, Dr. Levenson, there is no difference with respect to hospitalizations?

DR. LEVENSON: For Advair?

DR. NOTTERMAN: Yes.

DR. LEVENSON: Well, the best answer to that question would actually be looked at the estimate of the confidence interval on slide 35. The confidence interval goes from -2 to 1.7. So any value in there might be a reasonable estimate for the risk difference for hospitalization, which is the only events we see in Advair here.

DR. NOTTERMAN: And you think the same is true of Symbicort?

DR. LEVENSON: Symbicort, I have very limited data on. And you can see the confidence interval is extremely wide from -1.47 to 16. So Symbicort data is very limited.

DR. SWENSON: Do the sponsors wish to handle these questions?

DR. KNOBIL: You can show the slide. These are the same data that I showed yesterday and is quite similar to what you've just seen. In our analysis, we included over 11,000 patients on Advair and over 11,000 on ICS. If you remember, the FDA's analysis had about 6,600

patients per treatment group. But still, we had no asthma-related deaths on Advair and you can see the risk difference was essentially zero per 10,000 patients. So it would be, I guess, even lower per 1,000 patients to make it comparable to the FDA analysis.

This was the overall population. If we go to the next slide, this shows the pediatric population. Again, there were no asthma-related deaths, and for hospitalizations, there was one on Advair and two on ICS alone. So the risk difference was -5. These two patients were in the 12 to 17 age group.

DR. BONUCCELLI: So as I understand the question, it's the number of intubations and asthma-related deaths by age group. So this is our overall trial data. This was shown in our primary presentation. And it shows you that we had one intubation and no asthma-related deaths.

SPEAKER: I'm sorry. Just for Symbicort?

DR. BONUCCELLI: This is Symbicort. I'm sorry, my apologies. Cathy Bonuccelli from AstraZeneca.

Can we have the pediatric data, please?

This is the same information -- deaths and asthma-related intubations in pediatric patients. This was 3,400 pediatric patients under the age of 12 years. And we have no deaths and no intubations in that population.

For hospitalizations --

DR. MARTINEZ: Sorry. I want to just -- since you were there, I wanted to ask a question, because I have here in front of me the paper by Dr. Sears, which is in the online repository for the European Respiratory Journal. And here, the numbers seem different from those that you have showed us. Here, it says that there were eight asthma-related deaths among 49,000 patients taking formoterol, and two among 8,000 patients not randomized to formoterol in

their analysis, which was made with a database provided by AstraZeneca. And the risk ratio uncorrected for the fact that there were more patients taking inhaled corticosteroids in the formoterol than in the non-formoterol, was 1.57. So would you please explain to us what's the difference between these, because this is a third database from the formoterol data different from the FDA, different from yours, in which there are deaths, and the deaths are more in the group that is using formoterol.

DR. BONUCCELLI: So the Sears manuscript is referenced in our briefing document. That information is presented in the briefing document. The difference is these are the randomized controlled parallel group trials with an appropriate comparator arm. The additional patients that were included in the Sears database were from additional studies, open label studies, uncontrolled studies, and studies that were LABA versus LABA, so it didn't have a comparator arm that was included in the

FDA dataset. That's the difference you're seeing.

DR. MARTINEZ: Well, let me just --

SPEAKER: Let me just -- I'm sorry, sir. I just want to make sure that I'm not getting confused by this. For a moment, I just want to look at the Symbicort data with respect to formoterol because that's the only case in which I can be absolutely sure an ICS was administered in conjunction with the LABA. So I just want -- before we get to that other issue I want to hear a clear unequivocal statement from the manufacturer as to -- if you have that slide, if you can just put it up again -- how many adverse events, including deaths were there with Symbicort in the studies you wish to present?

DR. BONUCCELLI: So in the 23,510 patient dataset, we had no asthma-related deaths. And this might help you a little bit, too. For hospitalizations -- asthma-related hospitalizations, Dr. Carroll had shown this

slide previously -- the line that would be specifically Symbicort -- so both components in the same inhaler -- is that very last bucket. The very last line on there.

SPEAKER: And is that children?

DR. BONUCCELLI: This is all of Symbicort in that last one.

SPEAKER: Can you show the children's data?

DR. BONUCCELLI: Yes, can we get some pediatric -- a picture of pediatric data? I don't know if we have pediatric Symbicort only. I'm not sure we have that picture.

SPEAKER: Thank you. And Dr. Martinez, I'm sorry for having interrupted you. I just wanted to make sure --

DR. MARTINEZ: No, it's okay. It's okay.

SPEAKER: I was clear.

DR. MARTINEZ: I understand your point.

DR. BONUCCELLI: Can we show -- we can

show you the pediatric. The other thing about that -- if I could have that slide back again that was just up. Did we lose it?

Just one other point on this slide that I don't want to lose is just that in our hands the free combination and the -- and the fixed combination -- the Symbicort inhaler do, in fact, look the same from a risk perspective in our dataset.

DR. MARTINEZ: So if I may again -- so we're in the face of choices with respect to what you include or what you do not include. I think in the same way that you criticize the choice of only including four studies, I could criticize the choice of not including all the data that is available, as Dr. Sears did in his study. And in fact, when he divided in his study those who were taking concomitant ICS or were thought to be taking concomitant ICS, the risk is 2.32 for those who are taking formoterol. So the fact that some of the studies were not included because of the reasons

that you have stated give the appearance that there is absolutely no risk which in fact is not the case if we in some detail analyze Dr. Sears' data. The discussion could be long with respect to what should be or should not be included. And I'm not saying that any of the criteria used is good or bad. It's just that it is highly dependent on what you choose to include or not what kind of data is shown to us.

DR. BONUCCELLI: So Dr. Sears is with us today, and I'll let him comment on his manuscript.

DR. SEARS: Thank you, Fernando, for your question.

My name is Malcolm Sears. I'm professor of medicine at McMaster University. My accent tells you that I don't originate in Canada. I came from New Zealand. I started practice in 1966, which if you remember, was the midst of the first epidemic. And I was very involved with the New Zealand Medical Research Council investigation of the second

epidemic, and authored most of the papers that arose from that. So I've been involved in the beta agonist controversy, short-acting and more recently the long-acting, for many years, and have practiced over 40 years and treat many patients with the whole range of asthma, including children, although I am not a pediatrician.

When I was asked to look at the AstraZeneca dataset -- and I should declare as the chairman has asked conflicts of interest. I have worked with asthma, as I said, for 40 years. So I've worked with every company that has asthma-related molecules. I have offended almost every company that has asthma-related drugs.

But my visit -- my participation here was at the request of AstraZeneca to be an external advisory, and they have paid my -- well, I hope they will be paying my accommodations and travel costs.

And are also paying me an hourly

rate for my loss of time from my practice.

So with that upfront, when I was asked by AstraZeneca to look at their complete dataset to see -- following the issues of the salmeterol study -- were there similar signals in the formoterol data, my initial hesitation was will this align me so much with the company that I will be an incredible witness?

And so there were three stipulations I made which the company agreed to immediately. One, that if we publish this, that it's not written by the company but that I wrote the paper, which is why my name is first author. Secondly, that I have access to every available piece of data and anything I want to see, I can see. And thirdly, that I can bring in an independent person to assist in this whole process. And if you've seen the paper you'll note that Sammy Sweesa (?) is a co-author.

I invited Sammy to work with us on

this dataset. And if you know Sammy, he is very rigorous and very tough in looking at the questions and the appropriate analyses.

And I think what we have done here and showed, it is a different dataset but it's the most complete at all. In the publication, we've focused on trials between three months and 12 months duration because that's -- we expected to see the magnitude of the signal if there is any. But in the supplementary data, we've included every single patient from dose ranging studies through to longer term studies. The whole is there.

So in the online supplement you've got even more trials than any that you've seen. But in those that we published in the main print paper which is coming out next month in print form, we focused on the 68,000 patients in three to 12 month trials. As Fernando has said, the numbers of deaths, eight versus two, put in context of

denominators, it's not a fourfold. It's a 1.5 difference. And the differences are very small because the numbers are small. And if you go to those who are on inhaled steroids, we are now comparing seven versus one. That number is so unstable that if you have one more death here, one more death here, the odds ratios will be up and down.

So my conclusion from that data is that while it needs to be out there to be seen, you cannot interpret on such limited data for deaths. You've got to put it in the context of the whole. And in the context of the whole you have many more events in terms of the serious adverse events which were almost all hospitalizations. Over 90 percent of the serious adverse events were hospitalizations.

And there the use of formoterol with or without steroids, but particularly with steroids, reduced adverse events. The relative risk for a serious adverse event in

the whole formoterol database is .91, with a confidence that goes from 0.5 to 1.5. So no signal. But if you look at the use of formoterol with inhaled steroids as you have in Symbicort, the odds ratio for a serious adverse event, mainly hospitalization, was 0.63, with a confidence of .52 to.76. Clearly, clinically and significantly -- statistically significantly reduced risk.

So my conclusion from the whole of the dataset is that the use of combination of this particular LABA, formoterol with ICS, is not only safe, it increases the safety as compared with non-LABA treatments.

And my final comment would be, having lived through asthma treatment for 40 years, I have no wish to go back to how we treated asthma in the '70s and '80s, even in the early '90s. We have very good effective treatments. The message is patients with asthma, as Bob Lemanske suggested, are

individuals, need to be assessed properly, need to have education and environmental issues addressed, need appropriate treatment specific for the individual, and need to be followed up and reassessed to make sure that you've got the appropriate management in place.

That applies to children as well as adults, because as Fernando and I share an interest in the epidemiology of asthma -- and one of the articles which we published from our New Zealand study in the New England Journal about five years ago shows very clearly that childhood asthma tracks to adulthood. The pattern of adult asthma is set in childhood, and we need to be very sure that we treat childhood asthma seriously and adequately.

Thank you.

DR. SWENSON: Thank you, Dr. Sears. I think there are a couple of questions to you. So if you would remain. We're already a little

bit behind time. The panel has a lot of questions, but I suspect you want to have some lunch, too. So please make these questions brief.

I think we'll take two. Dr. Schoenfeld.

DR. SCHOENFELD: Yes, I was just wondering if you had an estimate of the risk difference for mortality from your studies.

DR. SEARS: In the total dataset, the odds ratio given was eight to two, with different denominators.

DR. MARTINEZ: No, but seven to one with ICS.

DR. SEARS: With the ICS was a relative risk of 2.3, but a confidence interval that's very wide because you have seven and one.

DR. MARTINEZ: It is seven out of -- sorry, I have it in front of me. Sorry, Dr. Sears.

It is seven out of 46,000 and one out of 13,000. So you can go through your

math there.

DR. SCHOENFELD: But I thought that you actually had -- the seven one was a different subset. You had several different --

DR. MARTINEZ: The ones taking ICS.

DR. SEARS: These are the ones where they know they were taking ICS.

DR. SCHOENFELD: So it was 7 out of 46,000.

DR. SEARS: Seven out of 46,003 and 1 out of 13,905. I also have it with me.

DR. SCHOENFELD: So 7 out of 46,000 and 1 out of 13,000.

DR. SEARS: Yes. But if that one was zero or two, those numbers change readily.

DR. SCHOENFELD: Of course. Of course, yes. No, the problem is that it is very hard to do absolute risk estimation. I mean, I was doing a little back of the envelope thing, and to actually rule out a risk of 1 in 8,000, which would be the kind of risk we might like to rule out, we'd need probably a clinical trial of

210,000 patients. You know, I'd appreciate if I'm wrong, please correct me.

But something like that -- you know, which is, of course, there are that many patients out there but it would be kind of a daunting task.

DR. MARTINEZ: But what is important to stress here is that the comparisons we heard before using the fixed combination that Dr. Notterman was telling us about, 1 in 6,000 patients approximately -- 6,000 and 6,000. And because the outcome is so infrequent there were no deaths in either of the two groups. When you increase the number to 46,000 and 13,000, you have an increase in the number of deaths which is only to 1 in the case of patients not taking formoterol and ICS, and 7 in those taking formoterol and ICS, which tells me that we don't have enough power to say practically anything about the comparisons between fixed combination and inhaled corticosteroid.

DR. SWENSON: I think at this point

and on that humble note, we should take a break, and we will reconvene at 1:00.

(Whereupon, at 12:11 p.m., a luncheon recess was taken.)

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

(1:09 p.m.)

DR. SWENSON: Good afternoon, everyone. We've got a very tight timetable here and yet much to discuss, so I'd like to begin. And the organization of this: as you know, we have 10 questions -- or rather, 10 points, some of them which will be voting questions. The first four are discussions, and we're going to spend about 40 minutes.

I thought that it would be best to just make this a general discussion about both the risks and benefits of the two long-acting beta agonists, so we'll -- rather than go one-by-one, we're going to just open up questions, because I think everyone is mostly of the opinion that largely this is a class effect, and I think will predicate the discussion on that.

And then we'll spend 25 minutes or so on each of the voting questions. Each of those questions, I will first repeat. We'll

have a brief discussion, open, and then we'll have a vote.

The voting will be done by all of the members of the Committees simultaneously, and then the vote will be projected, and then we will go through all of the panel members and asking you to very briefly state why you voted as you did. And then the last portion of the meeting, then, will be to questions 9 and 10, which would be more advice to the FDA in their future deliberations and how to proceed.

So I'll open up this first portion here. Essentially what we're doing is discussing the benefits and also the risks of using salmeterol or formoterol for the treatment of asthma in patients not adequately controlled on other asthma controller medications -- that means either low or medium dose inhaled corticosteroids, or whose disease severity warrants the initiation of treatment with two maintenance

therapies. I want people to weigh in as best we can equally on the adult question as well as the pediatric question.

And so at this point, why don't we just open up to questions on this broad issue? I know much of this has been touched on in our earlier sessions, so I would ask any members not to repeat things unless you feel that it really has a special compulsion to have to be repeated. We have to keep to the clock.

So I see Dr. Wolfe -- we'll start with Dr. Wolfe.

DR. WOLFE: This is --

DR. SWENSON: Doctor, could I just interrupt? I want to just -- a point I didn't make here is that the way these questions are listed, I believe they are following the FDA's labeling of a product, which is congruent and tightly coupled to the guidelines that we've been talking about, so we're not talking about the sole use of these long-acting beta agonists,

we're talking about them being used as the way they're labeled and as the way the guidelines dictate.

Dr. Wolfe?

DR. WOLFE: Dr. Jenkins' question really applies to one of two areas. What is the evidence once someone -- adult or child -- has been treated properly, stabilized as much as possible, with ICS, of getting an additional benefit from salmeterol or formoterol? And I think one of the problems is that the data we have include a lot of people who sort of jumped to a combined product before necessarily being adequately treated with the ICS.

Dr. Martinez knows more about this than I, but I think that is a major problem here, because we don't have a great body of data that says everyone has gone through the proper pre-steps, whether they're adults or children, and then and only then do we give them something else.

I mean, Dr. Martinez's statement

this morning was that the benefits of ICS are more in the reduction of severe exacerbations and hospitalizations, whereas the benefits of LABA are obviously on FEV1 and things like that, so you're getting different kinds of benefit packages, measurable, and I think that we do not have an adequate database on people who have really been tried up to then to answer this question.

You could clearly answer it for the FEV1, you could answer it for fewer puffs per day of a rescue medicine, and so forth, but I don't think you can answer in terms of really important health benefits.

DR. SWENSON: Fernando?

DR. MARTINEZ: I think -- there is one study in which that was done systematically which was presented yesterday. I think -- I don't know who presented it and it doesn't really matter -- which is the so-called Gold study -- oh, I think it was Dr. Chowdhury. The Gold Study was adequately done for the purpose

that you just said; in other words, the patients were first put on inhaled corticosteroids and then if they were not controlled where either corticosteroids or long-acting beta agonists were added.

In general, the addition to the same dose of inhaled corticosteroids of long-acting beta agonists increased control, but if -- but then -- the data could also be re-analyzed as looking at the comparison between adding long-acting beta agonists or increasing the dose of inhaled corticosteroids in the different drug arms, and the conclusion has to be first that there is increased control if you add inhaled corticosteroids to the same dose of -- sorry, if you add long-acting beta agonists to the same dose of inhaled corticosteroids, and you get approximately the same degree of control in the Gold data, if you compare the subjects who are not-well controlled and whom inhaled corticosteroids was added to those and whom

LABA was added.

So I think in part this was some of the criteria that were used for the guideline committee, of which I, by the way, was one of the members, to decide equal weight to these two, although the discussion was lengthy and other data in which this was not done in the way I have described, have shown that they may be better controlled if you add a long-acting beta agonist than if you add inhaled corticosteroids.

DR. WOLFE: There's very little data, is what you're saying. That one study is it?

DR. MARTINEZ: Most of the data is in the sense you just said, which is you start the patients on that, and you only use historical use of inhaled corticosteroids to separate them, not during the trial. In that sense, the Gold Trial is the most important.

Sorry if I took too long.

DR. SWENSON: Quite all right.

Dr. Wolfe, did that answer your

question as best as possible?

DR. WOLFE: It does. Again, I point out that on the benefit side, the most objective things we have are FEV1, fewer use of rescue medicines. We don't really have evidence of a serious benefit, we have just the opposite -- increased asthma hospitalizations and increased death, so the seriousness of the benefit is much less than the seriousness of the risk. We'll get into the risk discussion, but that's, I guess, my assessment of one and two.

DR. SWENSON: All right. Dr. Knoell?

DR. KNOELL: So related to questions three and four, and with implications to question ten, we have talked about this, but I wanted to get more clarification, and it's about the issue of using, or continuing to use LABAs as a single agent, and compliance issues.

And we saw data from Dr. Mosholder which we talked about earlier this morning where up to 48 percent of patients on a LABA were not concomitantly using an ICS. We saw

industry data suggesting only 1 percent of the time does that happen in their data sets that they reviewed, and the concern I have is do we really have a good sense of the non-compliance issue? How many patients are really vulnerable to using a single agent and taking themselves off the ICS? Do we have a reliable data source that we can use for our decision-making today? If not, is that maybe a study that we need to pursue in the future?

DR. SWENSON: Should we have Dr. Mosholder just make a comment?

DR. MOSHOLDER: Yes. As I recall, the slide from GSK, I believe, was looking at the total use of LABAs, including Advair, and since most of the use is of Advair, and that's automatically with an ICS, that was the 90-some percent, then of the remainder, I think it was maybe one percent of the total, was being administered without an ICS, but the data I showed was eliminating the Advair product, just drilling down on the single-entity inhalers and

if you look at it that way then it's about 50-50, so if that clarifies.

DR. McMAHON: So Dr. Knoell, can I restate what I think I heard you say? As we consider whether or not we should change approval for the single agent, we need to consider the consequences of the single agent being approved for use, the consequences in inappropriate use, and that if in fact we think the risk is stronger for the single agent, then that should drive that decision, rather than the evidence that applies to the combined agents?

DR. KNOELL: Yes.

DR. SWENSON: Okay.

DR. KRAMER: I had two questions, and the first one relates to question number three. It was a question I had remaining from earlier, and it has to do with the fact that several times both yesterday and today, statements were made -- actually, by several of the FDA presenters -- of the increase in the African-American subgroup, and I was concerned

that the public record hadn't really emphasized what was in our packet -- our packet that we reviewed in advance, and I'd like to point out that the actual SMART publication was in there, and on page 18 of the SMART manuscript, it states that African-Americans in SMART had lower baseline inhaled corticosteroids, lower peak flows, more emergency department visits, hospitalizations, and nocturnal symptoms, and I just didn't hear that qualification being stated, so I think if we're considering the risks of salmeterol in that subgroup, we should clearly state that at least that was said.

And then I noticed that in the statistical appendix that was included in the FDA analysis by Dr. Levenson, that there is an analysis in Advair, I believe, of the composite -- let me just see if I have the right one in front of me. It is -- where they had African-Americans -- they had a subgroup analysis in which the estimated risk difference for African-Americans was .38, but

there were 4 events in LABA and 4 events in a very similar denominator 4 out of 548 and 4 out of 568, so I just think that, at least from what I saw, if I've got a mistaken impression that perhaps we've got an unreliable risk signal in the African-Americans, I'd like someone to correct me on that because that was what I took away from these descriptions.

And I do have one other question.

DR. SWENSON: Ann? Do you have a comment?

DR. McMAHON: I just wanted to mention that we don't -- as far as the FDA meta-analysis is concerned, we don't have baseline risk data disease severity data for the different subgroups, so your comment is well-taken in that sense, that we don't really have those data for the meta-analysis. And it was described in SMART.

DR. KRAMER: So can I ask my second question? The other -- actually, it has to do

with talking about the benefit aspect for both these drugs, and I'm not a pulmonologist so I'd like to hear from the other people on the Committee who are, but I'm concerned about the assumed hierarchy of benefit, where we have this great concern about death, obviously, and of severe exacerbations, but when I hear patients talk and the testimonials we heard from patient advocates, there's a lot of concern about dates of school missed, and what their daily life is like, the nocturnal awakenings, the anxiety over attacks, all these things that are subjective and may not be captured well in an overall quality of life scale.

So what concerns me is for us to talk about risk and only pay attention to life threatening risk, if the patient population is really concerned also about these more subjective things, so could we have some comment from the experts on this one?

DR. SWENSON: Yeah, I think that's a

very good point, and we haven't touched on that, is that we have this global apparent, very large signal of quality of life improvement, and one can argue about the sensitivity of the instruments, but feeling from many is that patient's lives are improved and then yet we do have this obvious, worrisome signal of a greater mortality, and it then is a parallel issue about extensive drugs and how do we draw the line for quality versus cost.

Those things, we have to just make some judgments, but it hasn't been emphasized enough, and I don't know that we have any real good tools for that, but maybe we could get some people to opine.

DR. KRAMER: What concerns me is that there have been statements made that there is not a counterbalancing benefit to these risks, and it all depends on what you consider to be a benefit.

DR. SWENSON: Dr. Martinez, I know you've made this point once before --

DR. MARTINEZ: I will make it again because I think it's a very important point. There is no doubt that the advent of long-acting beta agonists has improved the lives of the majority of patients with asthma, and it would be, in my opinion, irresponsible to withdraw this medicine, because I even feel that when this is assessed, in real life, the impression that the great majority of clinicians get is that the improvement is even better than the one that is seen in clinical trials; and therefore, from that point of view, there's little doubt that this has been a very important new tool that we have.

The reason why I have stressed during these discussions the risk part is because I think often, it is not as stressed as the reward part, but I think there's no doubt that what you're saying is perfectly true. With respect to everyday symptoms, this is a medicine that is even more efficacious than what it appears to be

affecting.

DR. SWENSON: Anybody else which to speak to that particular point? Dr. Goldstein?

DR. GOLDSTEIN: Yeah, I wanted to follow up on that and maybe ask OSE to expand on this, because what we're starting to now hear is a discussion on the benefit/risk ratio of LABAs, and to further that, what I haven't heard is this benefit/risk ratio for this particular class of drugs and asthmatics put into context with other drugs and other conditions.

In other words, there clearly are, basically for every drug -- for vaccines, for Digoxin, for Tylenol, that was mentioned the other day, there are rare significant safety concerns, but there is much greater, overall, benefit.

So I was wondering if somebody from OSE, maybe Dr. Graham, who was so vociferous about the risks, could help us understand where the benefit/risk ratio for this particular class of drug lies in comparison

to other drugs.

DR. GRAHAM: I'll take your adjective to describe my presentation yesterday as a compliment.

DR. GOLDSTEIN: It was absolutely meant that way. Passion is good.

DR. GRAHAM: A couple things. It depends -- well, John Jenkins yesterday mentioned NCEDs as an example, that we accept NCEDs for the relief of pain. It isn't necessarily severe pain, it could be a mild ache, and we accept the risk of gastrointestinal bleeding, and there's a lot of NCED use, but the actual, if you would -- what's the attributable risk death rate from NCED use in the overall population, it's pretty, pretty low. It's much lower than what we're talking about as possible here with the LABAs.

DR. GOLDSTEIN: Let's take a more apples-to-apples comparison.

DR. GRAHAM: Okay.

DR. GOLDSTEIN: NCEDs for GI distress

is different than LABAs for a potentially fatal disease.

DR. GRAHAM: Okay.

DR. GOLDSTEIN: So maybe Digoxin or an anti-arrhythmic may be a more appropriate comparator.

DR. GRAHAM: I think probably patients risk of death from arrhythmia or heart failure is greater than the risk of death from asthma of probably 80 or 90 percent of the people who are getting treated with the LABAs, because LABA use, as we've heard is -- what have we heard at this meeting -- a couple things we've heard at this meeting, we heard today that the average duration of LABA use seems to be somewhere around three months, so three out of 12 months on average, you've got LABA use, so there's nine months where they're not.

Now, is that three continuous months or are they taking a month here, a month there, a week here, a week there. Then we heard that this question of risk, if the

drug is abruptly stopped, that that might actually be worse than the risk of the drug itself. Well, if you've got non-compliant use, then we have people who are withdrawing themselves all the time.

Then, we have the -- I had a third point to make on this -- oh, we heard also that -- and this may have been yesterday and it may have been in Dr. Mosholder's presentation -- that at least as far as the single entity products went, that the lion's share of the prescriptions were for a single prescription. Now, I don't know what the corresponding data are for Advair, that if you look at Advair, what percentage of the prescriptions are for patients who say, let's get more than one prescription.

I can tell you anecdotally, and it's just an anecdote, but sometimes if an anecdote becomes really common, it's saying something, that in our LABA investigation team of four people, that three of us in the

last year have had the experience of a family member being prescribed Advair inappropriately.

In my situation, my daughter had bronchitis, she was wheezing, the doctor gave her Advair. That happened with another member, and then the third, it was with the wife for the same thing, so if you want to talk benefit/risk, and you want to talk risk of death, then you really also have to identify the entire -- it's not everybody who gets Advair who's at risk of death from asthma.

DR. GOLDSTEIN: With all due respect, you really didn't answer my question.

DR. GRAHAM: Well --

DR. SWENSON: I think that maybe we need to move on in the conversation, because we've moved into anecdotal discussion which we've all agreed is not going to be useful for us, so I'd like to hear -- I'd in particular like to hear from members of the Pediatric

Advisory Committee.

Dr. Joad?

DR. JOAD: Thanks. I did want to speak to the benefit. As a pediatric pulmonologist, my idea of the improvement that you can even see in the studies is significant clinically and I would agree with Dr. Martinez that it has felt like a revolution to be able to have these long-acting beta agonists to add to the armamentarium in what we were doing before, so I do not consider the benefit trivial at all.

I personally think that the individual -- the individual agents should not be used as indications for treating asthma, because I don't believe that people really look at those black box warnings the way they should.

And I think there is an alternative in the combined products, so it's not that these people will be out of nothing to do, I think the argument that we need a choice of inhaled corticosteroids is a weak argument.

I'm told, pretty much, by my insurers of my patients which inhale corticosteroids, I'm going to use, so it's not like I'm looking at this big menu that I get to pick from all the time, and also the argument that all drugs have side effects doesn't go over well with me with the side effect of death and hospitalization, because usually when I think of a side effect, I think it's something that's side -- you know, that you're trying to take care of pain with the NCED and then you get some GI irritation as a side effect, but if you give a drug that you know makes the disease you're treating worse, then that's a big concern to me.

I don't want to be giving a drug, and I wouldn't recommend anybody else give a drug, that is making the disease you're treating worse. So then that takes me to these combination drugs which I was very happy to see, which I hadn't seen before, the -- I was convinced that Advair is a safe

drug in children and adults, so I felt like we can use this drug that has made a huge difference and the company was able to convince me that Symbicort in adults seems to be also safe although I didn't think they had evidence that it was in kids which leaves me a little bit uncomfortable with adolescents for which it's approved.

Thank you.

DR. SWENSON: Dr. Jenkins?

DR. JENKINS: Just a couple points I wanted to make. There's been comments about the three months of use of the LABAs. We have to keep in mind that asthma, in many patients, is an episodic disease, so it may not be totally surprising that they don't use the drug 12 months in a row, because they may not be symptomatic all months of the year, and there's a difference between looking at patients who, for whatever reason, come off the drug and then have a reason to go back on the drug.

That's pretty different from

saying, it's okay to come off the drug and take the drug off the market because there's no harm when people come off and go back on. You've taken away that therapeutic option.

As far as the NCED comparison, and I brought this up yesterday, there are a lot of drugs for symptomatic conditions that carry a serious and sometimes life-threatening risk. The more appropriate comparison for the NCEDs would be chronic use for osteoarthritis. You're not modifying the disease, you're treating pain, but you have people who are using those on a regular daily basis, and we're not just talking about GI irritation, we're talking about potentially life-threatening, fatal, GI bleeds.

So in a patient with osteoarthritis, the doctor and the patient judge the benefits of that pain relief that they're going to use chronically, versus their potential risk for a GI bleed.

I think that's more analogous to

the salmeterol/formoterol than just looking at NCEDs in general that you might use for a day or two for a headache. It's really chronic, symptomatic conditions where the disease is not being modified by the drug, you're only creating the symptoms of the disease, and how much is it valued to you and the patient to have relief of those symptoms, even knowing that there's a small risk that you could have a fatal event from the drug as well. So I think that's the comparison and there's any number of those comparisons you could make.

Basically any of the pain drugs that would be used chronically fall into the same category. You're relieving symptoms and you're carrying with that a risk of serious potentially fatal adverse effects.

DR. SWENSON: I'd like to ask my pediatric colleagues, because it's not an issue that I have to worry about in adult patients, but the question of the higher dose inhaled

corticosteroids as an option against adding a LABA and the extent of growth minimization and all of that. We haven't heard enough of that. I think it's got to be put into this equation. Any -- oh, Dr. Joad.

Please.

DR. JOAD: Well, I guess I have to refer to the Camp Study. I don't know if there's a better study than that, but they followed a group of children between five and twelve for three or four -- three years, I think, and one arm of the study got inhaled corticosteroids, another one didn't, and the difference in height was about one inch per year in the first year, and for the next one to two centimeters per year -- one centimeter per year for the first year, and then after that, there was no difference in growth velocity.

And there are other studies that take siblings, one of whom has asthma, and the other doesn't, and the one with asthma takes inhaled corticosteroids their entire

childhood, and then you look at their eventual height and it's the same.

So I think -- and please, other people in this area may want to comment, too -- that we think that there may be some small growth suppression, but it's small if at all.

DR. SWENSON: Okay. Dr. Newman?

DR. NEWMAN: I was in queue here just to -- as an adult pulmonologist respond to Dr. Kramer's question about the qualitative aspects of benefit, and yeah, I was on the Committee in 2005. At that time, I guess we considered that the efficacy was sufficient. I don't think that my view has changed.

I was informed at that time by having a pulmonary career of treating adult asthmatics that startled the LABA era, the pre- and post-era, and it's just been very clear to me that two things -- one, I have a little trouble reconciling my qualitative experience, which has been very positive in

the post-LABA era, since introducing the LABAs, with the quantitative data that had been used to basically qualify these drugs for FDA.

As practicing pulmonologists, when they hear that this discussion is going on say to me, why are you having that discussion? We know this stuff is really good for our patients and it's improved the care that we deliver, and then you try to explain, well, it's because there's somewhat of a disconnect between the quantitative data and what we have qualitatively experienced.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I'm wondering if we could get a restatement, again, just for clarity because I know it was presented before, and it would be fine from FDA, of the single use of salmeterol and formoterol in the United States for the indication of asthma as a percentage of the total use of the drug. In other words, I'm asking what percent of the total use of

salmeterol is single use and approximately now?

DR. MOSHOLDER: Let's see -- I have to return to my slides. Andy Mosholder, for the record -- return to my slides from yesterday. I don't know if we can do that or not, but roughly 50 percent of the formoterol and salmeterol use was for asthma. I think maybe 50, 60 percent. If that was the answer to the -- that's for the single-entity products.

DR. NOTTERMAN: I think what I'm asking -- you're halfway there -- is of the total use of these drugs, single agents and in combination for the indication asthma, what proportion is dispensed as a single agent?

SPEAKER: (inaudible)

DR. NOTTERMAN: Right, I thought I saw that yesterday a couple of times. That's slide number 27 for Dr. Mosholder.

SPEAKER: Are you including Advair in there or without Advair?

SPEAKER: I'm including all combination use.

DR. MOSHOLDER: Let's see -- advance slide, please. Actually, I'm sorry, that would have the data. Yeah, you see that the Advair combination product is dominating and a much smaller -- now that's for all indications, but even if one takes away about half for a COPD, it would still be the case. If that's a partial answer.

MR. NOTTERMAN: That's a good answer, so I guess my question is, and my challenge is, we've heard from several people that it would be very difficult for the most precise tailoring of therapy to change the label or remove the label for the single agents for asthma because many patients require titration with respect to the specific dosage form and type of corticosteroid.

And this data, to me, belies that statement and suggests to me that at least for the treatment of asthma, physicians and other providers don't see a major advantage in the ability to mix and match.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I just wanted to bring up one other potential benefit that I've heard mentioned a few times in discussion of these drugs, and that is the benefit of not having to use other drugs. We've heard from several people that some of the other drugs that have been used in the past to treat asthma and that might very well need to be used in addition to controller medication if these drugs were removed from the market, have their own risks.

So one of the benefits of having these drugs around may be avoidance of risks of other drugs, whether that's chronic use of a short acting beta agonist or whether that's the use of a drug which I can remember from my residence, like theophylline.

DR. SWENSON: Dr. Zito?

DR. ZITO: I think it would be useful to get beyond just prescription sales and to be able to look within populations, particularly within the pediatric population, and particularly to look at new onset use of these

meds that does not have any -- for the combination products that we're talking about in which the stepped approach is not being followed, so we don't necessarily have -- can take too much confidence that people are really improving just looking at those very gross figures.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Actually, this is a question for Dr. Martinez. So Dr. Martinez, when you were speaking earlier, you had mentioned that the flexibility of having a LABA plus a number of the different single agent inhaled corticosteroids was important in your practice. I wanted to explore with you why that's necessary. Is it driven by a failure to control asthma or by side effects or both?

DR. MARTINEZ: The main issue in asthma is control. It's the issue that we stress in the guidelines. There are children -- and I'm a pediatrician, I only see children -- who even if they're taking regularly

their inhaled corticosteroid, are still having symptoms or as was, for example, described yesterday by Dr. Stoloff or J.C. -- C.J., who can't do their normal activities. So the main -- for me, the main issue is symptoms. I don't treat lung function, I treat symptoms and that's the most important parameter, and of course I also control children for their lung function and many times they're not having the symptoms. So I know that your question next is the flexibility.

For me, in pediatrics, this is a non-issue. If a child is on inhaled corticosteroids and meets the addition of a long-acting beta agonists, I don't think I have prescribed in the last 10 years -- 5 years, I would say -- I have prescribed a long-acting beta agonist by itself in any child. I have always prescribed it together with an inhaled corticosteroid.

DR. KRENZELOCK: As a clinical toxicologist and director of a poison center, I

can tell you that I had Theofolin poisoning prior to the advent of (inaudible) was significant and on a daily basis, we would see poisoning, we'd see intentional poisoning as well, but seizure activity and a variety of other debilitating sort of outcomes from Theofolin poisoning, so it was significant, and I can tell you now that where we would see these every day, we don't see them every month now. It's very, very rare for us to ever encounter Theofolin poisoning unless it's intentional, in an older person who's been on Theofolin therapy for perhaps years and not using an alternative therapy.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Sorry, I just wanted to go back again because I -- what I was really trying to drill down is the pediatric community that treats asthma, could they live with fixed dose? In other words, not having the flexibility to have a LABA plus, of various forms of inhaled corticosteroids -- could they

live without that? In other words, that there be essentially no availability of LABAs not combined with an inhaled corticosteroid?

DR. SWENSON: Dr. Joad?

DR. JOAD: Yeah, well first of all, Advair comes in three different strengths of inhaled corticosteroids, so that pretty much -- getting an inhaled corticosteroid right is not a precise thing anyway, so it certainly worked fine with me. If I ever needed to do something, assuming that they're step three anyway, you can start with the lowest dose of inhaled corticosteroid that comes in Advair and then if you want to do something in between, you can add an inhaled steroid if you want to and you still have only two drugs. So you can titrate all you want to, if you want to go to two drugs, but there's really no reason, I don't think, I haven't felt like I needed to.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I actually have a question to the adult pulmonologists, and that has to do

with the African-American population. Except for the kids, the only other strong signal that was differential, was in the African-American population. The statements about the symptoms and the benefits that we've heard, they feel that these drugs are really, really good. Is that also true for the African-American population? And you would also feel the same way relative to their risks that we saw in the data?

DR. RAPPLEY: And would people speak to that as single agent or combined. Be clear about how that's being answered.

DR. SWENSON: Any members of our pulmonary group want to weigh in? Dr. Newman? Or are you pointing to me?

Okay. It's been my impression as I -- and we did struggle with that SMART study in 2005, was that there were so many issues about imprecision on background use and compliance with inhaled corticosteroids, and then added additions about unfortunate

aspects of the American health care system that often leave minority groups sometimes with less than best care. I think there were enough questions in there that it wasn't necessarily such a drug effect, but it was a combination of many other things and certainly in treating a number of minority patients since then, I don't feel that it's really borne out, I don't think we've seen any further data to make us concerned that sponsors, in some cases have shown us, that this has -- and I think even the FDA -- so it doesn't necessarily concern me in combination, I think still.

As a sole use for asthma in adults, I probably should be prescribed.

Dr. Hoidal?

DR. HOIDAL: I just wanted a little discussion or clarification on what I sense is a tension between the question, I think, the way you posed it with regard to the use of LABAs as its presented in the package insert, and

that -- and the information we find that 50 percent -- roughly 50 percent don't use it as indicated, as we move towards a vote.

DR. RAPPLEY: So you would like more discussion about -- you'd like us to consider how these meds are used in unrecommended ways as we think about approval or disapproval recommendations for the single agents? I think that was what I heard also raised as a concern by Dr. Knoell.

DR. ZITO: As a related comment, I've been trying to study Dr. Shelly's data, and tried to understand it, and when I read it, LABA plus variable ICS versus LABA plus concomitant, we see a great -- a twofold greater risk with concomitant use, and if it relates to this issue that it's really only 50 percent concomitant use that's really happening, then it does raise, I think, the question that you were just asking which is, in practice -- and also reflecting on Dr. Lemaske yesterday saying that there seems to be a change in the behavior or expectation of

patients and families, that maybe we can get off -- you know, maybe we can stop using inhaled corticosteroids, so it sounds like there's a dilemma in here of whether the people will actually follow the practices that would be safer.

Am I understanding that properly?

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I was just going to follow up with that. My perspective was through my years of experience working with asthma patients and somebody brought this up earlier. The patient that comes to you, and in our case, we're a specialty clinic so they're referred patients from the outside, and you sit down and you talk to them and one of the first things they tell you when they become honest with you is -- you know, I use my beta agonist whether it's short or long-acting, because I take a puff and it works. This thing I use sporadically because I puff on it, puff on it, and I'm not convinced that it works.

I think that's a real central issue around what we're talking about here, despite the best of intentions of physicians and other health care practitioners involved in the educational process. Or what we haven't talked about with this 50 percent single use of LABAs without ICS subpopulations -- you know, are we talking about, is that generally applicable to adults, pediatrics, and different subpopulation groups? I don't think we have a handle on that.

DR. SWENSON: Well, I don't think we're going to be able to answer these very important questions and we need to move on now to the voting of the specific questions posed to us, that's questions five through eight, and so if we could have question five put on the screen -- I'll just read it as well, and that is then, do the benefits of Serevent outweigh its risk for the maintenance therapy of asthma in patients not adequately controlled on other asthma controlling medications, either low dose,

medium dose inhaled corticosteroids, or whose disease warrants an initiation of treatment with two maintenance therapies in the following age groups?

And I think we should probably vote on these, and then the procedure here will be that we have this new voting system here and as you see in front of you, each of you can vote yes, no, or abstain, and once we begin the vote, you'll be asked -- we'll ask you to press the button that corresponds to your vote and then when we have all the votes in tally here, they'll be locked in and then they'll be displayed on the screen.

And then at that point, with the results there, we will work through the Committee members and ask you to justify and give us grounds for your vote. Obviously, at some point we'll have heard all the same things, so if you are in agreement with other people and everything's been stated, you can do so.

Okay, we just have a couple questions here, maybe procedural --

DR. WOLFE: I just have a clarification on a question. Five and six are single ingredient. Does it justify adding salmeterol or Serevent as a single ingredient or Foradil/formoterol, whereas six and seven are the combination. Now, the assumption underlined that we're only using Serevent or Foradil when everything else has been tried turns out not to be correct because a lot of these people are getting these drugs without the inhaled corticosteroids.

So I'm just trying to distinguish if that's what was meant by the questioners between the five/six pair and the seven/eight pair, because when you reach a decision on whether Advair or Symbicort merit use, you're talking about two drugs in someone that may or may not have been taking either of them, whereas with Serevent, part of the implication here, because of the way it's

used in the real world is, that do we recommend Serevent alone because that's what the drug is, or Foradil alone.

So I'm just -- is this a correct interpretation of why you have paired these questions this way?

DR. SWENSON: That's important, and we'll get Dr. Jenkins to weigh in. As I understand it, these questions are posed in the sense of using the labeling indications as they are and the guidelines, and I'll ask Dr. Jenkins then to clarify that any further.

DR. JENKINS: Yeah, the questions are posed for the individual agents because this is what their current approval -- their indications state in the approved labeling. So again, for the single ingredient products, the current indication is for the maintenance treatment of asthma in patients not adequately controlled on other asthma controller medications.

We give the example of low to medium dose inhaled corticosteroids, but that

definition could also include something like a leukotreine receptor antagonist as a controller, but it also has four whose disease severity clearly warrants initiation of treatment with two maintenance therapies, so we were asking the question exactly the way the current indication is listed in the labeling to get your input on, is this an appropriate -- does this remain an appropriate use of these drugs.

You could vote no and say, it could be appropriate it you changed the labeling to say X, Y, or Z, but when you start going down that pathway, you get all these hypotheticals about what the labeling could say so we find it cleaner to ask you yes or no based on what the labeling currently says, and if you don't feel that the benefits exceed the risk given the current labeling, you should vote no, and then you can later tell us in your answer, but it could exceed the risk if you changed it to say such and such.

It just gets too confusing to ask everyone to hypothesize what the label could say that they could vote yes or no for, so we ask based -- this is what the label currently says.

So this is how they're currently marketed, do you agree that this continues to be an appropriate indication statement for these products.

DR. NOTTERMAN: So just to make sure I and my colleagues understand, it is logical to vote one way for the Serevent question and another way for the Advair question, and that would have to do with one's evaluation of the appropriateness of the label rather than the use of that drug for any purpose in asthma?

Am I correct?

DR. JENKINS: If I understand your point, I think it is correct. Now, the individual ingredient questions I think are getting to some of the issues people have been raising for the last two days about choice so

that you're not forced to use one inhaled corticosteroid when you might prefer a different one. It gets to the issue about, don't forget these are also indicated for exercise-induced bronchospasm. There might be situations where patients just need a single ingredient, but the real question here is about maintenance treatment of asthma in people who are not adequately controlled on controller therapy.

DR. NOTTERMAN: So someone who thought that, for example, for Serevent, the label should be changed to at most contra-indicate its use, in asthma as mono-therapy, or to somehow more subtly change it but did think that LABAs in fixed dose -- or I should say in fixed device combination with a corticosteroid, should continue to be marketed in this way would vote no and then yes for the Advair?

DR. JENKINS: Yes.

DR. NOTTERMAN: Thank you.

DR. KRAMER: I apologize for having to step out of the room when I was coughing, but

there's one thing I really need to get answered from the pulmonologist before I feel comfortable voting.

I heard Dr. Joad that explained that she wasn't -- she was comfortable with the single agents being removed from the market because she thought that the issue about other alternative ICSs is not a big issue.

But I'd like an understanding about what the operational implications would be given that these drugs themselves would still be on the market for COPD, for instance, and therefore we'd have a situation where we'd have a drug on the market, there'd be no indication for asthma, and no, therefore, warnings with all of what we've learned about the risk of single agent, and there could be off label uses great as the current use is.

So I want to know if I've made that scenario up. I know it was commented upon in one of the packets we received, but I'd just

like to know what the pulmonologist thinks about the reality of that and the need -- is there a need because of the economic consequences of managed care organizations limiting to single agent inhalers rather than a combined. Is that a problem? And is there a problem with needing to up the dose of steroids more than you can do in the fixed dose combination?

DR. SWENSON: Well, if I could take a stab at that, I think that we do have the single agent inhaled corticosteroids so there's a little bit of flexibility in terms of adding on to possibly more than what the combinations might provide. That's one possibility. I think Dr. Jenkins, we -- for time's sake, I mean, we just have a lot of imponderables here, I think, and --

DR. JENKINS: I do want to clarify one point about what you just stated. If we were to decide, based on the Committee's advice and our internal deliberations, to remove the asthma

indication from one or more of these drugs, that does not mean that we would take off every piece of information about the risk of these drugs in treating asthma from the labeling. Now, it doesn't mean you lose the indication and you're going to lose all information from the labeling about serious adverse effects.

There are situations where we comment on safety issues for off label use of drugs if we think it's significant enough and has been demonstrated, so I don't think you should have the presumption that if you vote and we agree to remove the asthma indication from any of these products, that there would be nothing left in the labeling about asthma and we would strip away all the warnings about the risk in asthma. We would have to work through that internally, but we do have situations where we comment on safety issues for off label uses.

DR. SWENSON: We've been asked if the industry could make one point -- please, make it

very brief. We need to move to voting.

DR. ARMSTRONG: Absolutely. I'm sorry. I just wanted to clarify one point and it is something that I've brought up before. Just regarding the flexibility of various ICS and also in our analysis, I know that the OSE quoted an 11 percent concomitant ICS, but we did, again, do an analysis of a 60 million PMB and found that 84 percent of the 5 to 12s, had a concomitant ICS script and three quarters of the -- within 30 days of getting their LABA script, so I think that's an important number to remember in thinking about these single agents and also, again, that the single agents do give a flexibility of stepping up and stepping down as recommended by the guidelines.

DR. SWENSON: Dr. Bonuccelli, just very brief.

DR. BONUCCELLI: Brief. So this is just to Dr. Joad's earlier comment about adolescents for Symbicort. I just wanted to make sure the Committee was aware, that is in

your briefing document on page, I think, 78. There's an analysis of 12 to 18 year olds. We had more than 2,000 patients in that category and our relative risk was.77.

DR. SWENSON: One question.

DR. MARTINEZ: Long-acting beta agonists are also indicated for exercised-induced bronchospasm. Based on what I read here, if the decision would be made to eliminate the indication, would that indication also be eliminated?

DR. JENKINS: I don't think that necessarily would be the case because the use for EIB can be very different, very sporadic, so no, we're specifically asking you to focus on maintenance treatment of asthma as we say in the labeling -- we didn't ask you about the EIB indication.

Based on how you vote and make your recommendations, we would have to think about how to apply that to the EIB indication as Dr. Chowdhury has mentioned, some patients

don't require controller therapy, but get a beta agonist as prophylaxis for exercise and so they're not directly linked necessarily.

DR. SWENSON: All right, at this stage we'll begin voting and you have before you the three age groups for these different agents and we'll vote in turn with each sub group and then ask for your reasons for voting. I think the children are more important than the adults, but the way they've set it up, we'll vote on the adults first.

So at this point, we need to have the voting members of the Committees vote on the question number five for adults, that is greater than 18 years of age. So if you will key in your vote now. We're told the votes are coming up. All right, so we had a very heterogeneous vote here, and I'll start down at this end of the table.

Oh, okay, I've been asked to put this in the record by my voice here. So the voting result on this question in adults for

question number 5, we had 10 yes votes, 17 no votes, and no abstentions.

So if we could begin, then, on the right hand side of the room as I look at it, Dr. Kramer.

DR. KRAMER: So you want my reasoning?

DR. SWENSON: Yes, please.

DR. KRAMER: Okay, I voted yes because I feel that with the extensive guidelines we have and the professional societies education and the patient education, that it's -- and the labeling that we've made very clear about the need to use inhaled corticosteroids, and I'm concerned about taking away the option of if somebody happens to have been stabilized on a different steroid than what is available.

There's only two steroids available in the combined agents, that that would be difficult and adding another steroid inhaler to a combined agent would be unrealistic in terms of getting people to use it and I'm concerned about cost of the combined inhalers

being more expensive than perhaps the single agents alone.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted no, and I voted no mostly on a quibble that Dr. Jenkins allowed me to make, which is that I'm not sure that the language in the label is strong enough about the importance of these drugs being used specifically with a steroid rather than some other controller medication, and I could be fairly easily convinced to vote yes if the label were different.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: Sure, I voted yes. I basically agree with everything Dr. Kramer said. Also having once been an internist, I feel if it's still available for COPD, it's still going to be used for asthma in adults.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted no because I think that long-acting beta agonists are dangerous without inhaled corticosteroid use,

concomitant and that there will be single agent use without inhaled corticosteroids if the drug is indicated for asthma as a solo agent.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted no for the same reasons.

DR. SWENSON: Ms. Celento?

MS. CELENTO: As the patient representative, I voted yes, and I'm in agreement with Dr. Kramer's line of thinking.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted no, mainly because of issues related to the label. I think the label should be greatly strengthened to make it much clearer that mono-therapy for asthma should basically be contraindicated.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes for the issues also addressed by Dr. Kramer and in particular, for the ability for clinicians to have flexibility in prescribing -- and the label could direct its appropriate use.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes for many of the same reasons that were stated. I think I'm also sensitive to the quality of life issues that have been described and I think it's important to give practitioners the opportunity to titrate therapy for their patients.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I voted no for reasons already stated.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted yes because I think that there's probably more data to support the adult versus the children.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I voted no, in agreement with prior statements, but in addition, in hearing how these medications are used actually in practice, that -- and the fact that labeling would stay on the product for other uses given the results that we have now, that I think that would cover the issues.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted no on the cumulative effect of everything that was stated. I don't have more to add to that.

DR. SWENSON: Dr. Martinez? I'm sorry, Dr. Rosenthal, forgive me.

DR. ROSENTHAL: I voted yes, but I completely agree with the statements that have been made regarding the need to strengthen the label.

DR. JENKINS: Dr. Swenson, could I just ask one thing. As the people who voted no, they're saying, I agree with what was previously stated, could you specifically say if you agree that the labeling should be strengthened or -- we heard a couple people say, I voted no because we don't think the current labeling is adequate, but if you changed it to contraindicate monotherapy, it would be different. It would be useful for us to hear that as you go around as well. I'm not sure if you're agreeing -- with which part to what

people said.

DR. SWENSON: Are you asking, then, should we backtrack to those people that voted no and said simply that it was already stated and have them declare so?

DR. JENKINS: If they would like to. It's just useful for us to hear the comments about whether you would have voted yes. Someone suggested a contraindication, would that be something you would think would be an appropriate step forward? When you say I agree with the previous statements, it's not clear if you're agreeing with those statements or other statements.

DR. SWENSON: I didn't keep track of where that first started, but is it Dr. Notterman? Would you put yourself on record then as to why you voted no?

DR. NOTTERMAN: I did already, but I'll do it again.

DR. SWENSON: I'm sorry, we just didn't record it.

DR. NOTTERMAN: I voted no because I think the label is ambiguous, it should be greatly strengthened, and it should indicate that the use of these agents as monotherapy for asthma is contraindicated.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I voted no, and actually I'm not convinced that a change in labeling is going to change what we currently see happening.

DR. SHATIN: Dr. Shatin. I had voted no -- I think earlier Dr. Hennessy had mentioned the importance of having the LABAs with the corticosteroids, so I agree with that part of the no. Also, the issue with labeling.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted no because the first paragraph of the indication does not mention ICSs and many people do not read beyond that first paragraph so I have serious concerns with the label and the data about the inappropriate usage supports that even more.

DR. SWENSON: Okay, Dr. Martinez, I

guess we pick up with you now.

DR. MARTINEZ: I voted yes because I don't think there's any clear and unmistakable demonstration that inhaled corticosteroids prevent the effect and therefore would be contradictory, at least from my point of view, to vote yes to keeping the combined therapy and to vote no to the single agent.

DR. SWENSON: Dr. Rappley?

DR. RAPPLEY: I voted no. I think the risks outweigh the benefit. I would like an opportunity to consider label changes that would strengthen and that might result in a different vote.

DR. SWENSON: I voted yes with some hesitation. I think that I want to see that box warning there, and I feel that the data just aren't overwhelmingly significant to rule out their benefits against risks, and I think that we as a profession and we as a health care group can do a better job of teaching to fill in the gap.

Dr. Shoenfeld?

DR. SHOENFELD: I voted no, and for three reasons and only the first is really from data, the other two are from comments here. The data use is that I -- is that single use is dangerous. The two that are based on comments here is that the choice of ICS does not appear to be a crucial part of therapy and that compliance to a two inhaler therapy appears to be difficult.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted no. I do not think that the -- I think the labeling needs to be substantially strengthened. I think the evidence presented is that as used now there's a lot of -- there's substantial monotherapy and I'm not convinced by the flexibility argument presented.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I voted no for reasons stated, and I think that the labeling has to be targeted to what it is we're trying to say, but

also because we were focused here on issues relating to children. And if we're going to make significant changes in managing risk of these drugs in adults, I'd like to have a different conversation that has to do with how you would manage risk with adult patients as differentiated from how you would manage it with children. I think they're different questions. We have understandably not been focused on that here and shouldn't have been.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted no for the reasons I described before, and for the many other reasons that have been mentioned here, and I don't think fixing the label would fix it.

DR. SWENSON: Ms. Holka?

MS. HOLKA: I voted yes because I do think it's important to -- for physicians to have the options. I am not opposed to labeling changes and I think there are a lot of labeling changes that need to be made.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I voted no, and I believe that label changes should include a contraindication to asthma when this drug is used solely and I don't believe labeling changes can protect the public.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no, and yesterday Dr. Chowdhury said, at the end of his talk, "safety should be managed through labeling." And I think that there are different kinds of labeling. One labeling is essentially saying, this drug is not approved anymore for asthma, and I think that the effectiveness of that as a de facto labeling change would be infinitely greater than the effectiveness of what is more or less there now. I mean, I am all for educating patients and doctors and everything, but the fact is that it's still being prescribed as a single entity drug.

I think that since the meta-analysis was dominated by a lot of studies in which it was used as a single

evidence drug, even though I agree that you can't state that the ICS can overwhelm or neutralize the damaging effects of the LABAs, it looks as though the use of LABAs alone is more dangerous and I think that the only way of taking care of that realistically based on the way doctors practice medicine and everything is to essentially counter indicate it by -- I mean, I'm not -- I'm using counter indicate very loosely. I'm saying it should not longer be approved for asthma. That's the safest way of changing the labeling.

DR. SWENSON: Dr. Newman-- oh, I'm sorry, Dr. Zito. Please, forgive me.

DR. ZITO: I voted no, and I concur with the previous statements.

DR. SWENSON: Do you want to state exactly?

DR. ZITO: For the reasons that I'm not confident that re-education will produce the desired effect in terms of practice. So contraindication is, to me, a wise idea.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted no. I'm convinced of the danger signal that's real for the LABA monotherapy. I am not convinced that the safety risk of the LABAs can be managed through labeling, and I hate to sound cynical about that but having been on the 2005 committee, and seeing the labeling changes and not being presented with any evidence to show that it's really changed, that part of practice worries me about what labeling can do.

And I don't think it's crucial to have the mono -- you know, LABA, as an option for purposes of adult practice.

DR. SWENSON: Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted no because I see an increased risk, and I don't think that label change alone will translate into better practice, and this is in compliance with the actual treatment guidelines that ask for combination products, not for single products.

DR. SWENSON: We'll now then move to

the age group of adolescents, those 12 to 17 years of age. And again, you can vote yes, no, or abstain.

Has everyone voted? One more. Should we re-vote here or is it -- oh, okay, Dr. Martinez, you have to vote.

Okay, so the voting result on question five as it relates to the adolescent age range is six yes and 21 no, with no abstentions. And in this case, what we'll do is we'll start on the other side and move around, so if I could ask Dr. Schneeweiss to give us his justification.

DR. SCHNEEWEISS: I voted no, for the same reasons as before.

DR. SWENSON: Dr. Schneeweiss? I'm sorry, I didn't hear you. I was --

DR. SCHNEEWEISS: I voted no, for the same reasons as for the other age group, 5A.

DR. SWENSON: Dr. Jenkins, is that satisfactory here or do you want a --

DR. JENKINS: Yes, I think that's

fine.

DR. SWENSON: Good. Dr. Newman?

DR. NEWMAN: I voted no, for the same reasons.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted no, for the same reasons.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no, for the same reasons. Just to point out that in the meta-analysis, there was a very sharp, significant worsening as you got to younger, so whatever the vote was before, it gets worse as we get to the younger age group.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I voted no, for the same reason.

DR. SWENSON: Ms. Holka?

MS. HOLKA: Thank you, I voted yes, for many of the same reasons. I did struggle a little bit with the age group, but thought it was worthwhile keeping that as an option.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted no, for the same reasons.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: No, for the same reasons, and for the additional reason that Dr. Wolfe points out.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: No, for the same reasons.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: No, for the same reasons.

DR. SWENSON: I voted yes, in consistency with my adult vote. I think that adolescents are likely closer and I still want this flexibility.

DR. RAPPLEY: I voted no, for the same reasons.

DR. MARTINEZ: I voted yes, for the same reason.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I switched my vote

from yes to no because of the sense that the risks are increasing as the age goes down, and the benefits are no better demonstrated in the younger age groups.

DR. SWENSON: Dr. Shatin? Oh, I'm sorry, Dr. Cnaan.

DR. CNAAN: I voted no, for the same reasons, plus the paucity of the data in adolescents and the inability to separate between the adolescents and the adults for some of the data we saw.

DR. SHATIN: I voted no, for the same reasons, and I also agree with Dr. Wolfe about the even worse outcomes for this age group.

DR. SWENSON: Ms. Vining?

MS. VINING: I did change my vote as well because of the data, or lack of data, for the pediatric populations.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: No, for the same reasons.

DR. SWENSON: Dr. Hudson? I'm sorry, Dr. Krenzelock. My eyes are jumping.

DR. KRENZELOCK: I'm so used to hitting the yes button now that I voted yes, and to maintain the status quo -- until there are more data out there to really support changing it the way it is right now, I think Dr. Lemanske stated yesterday that there's a BATGER study coming out, there's a study coming out. Dr. Armstrong indicated from Novartis that there's a large medicated study coming out and so I'd like to see those data before reconsidering that.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I changed my vote to yes because of the more limited data in the adolescent age group, and the data suggesting that perhaps there was an increased risk of that in that group compared to other age groups.

DR. SWENSON: Did you mean --

DR. HUDSON: I changed my vote to no, from yes to no.

DR. SWENSON: So her vote is no.

Dr. Notterman?

DR. NOTTERMAN: I remained at no, basically for the same reason, but felt even more strongly in adolescents. I think in addition to the data we have, we also have the known behavioral issues related to at least some adolescents in compliance. So that was a factor for me, and frankly, I think FDA should consider placing an age contraindication on the use of these drugs for individuals less than 18 years of age as monotherapy.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I changed my vote to no. I have concerns about the data as well as compliance concerns in that age group.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted no, for the same reasons I voted no for adults.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted no, because long-acting beta agonists are too dangerous to use without an inhaled corticosteroid to allow their availability as a single agent that's

indicated for asthma in any age group.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, for the same previous reasons.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted no, because of the need for labeling change, and I agree with everyone who said more data are needed in these kids. I'm not sure that -- unfortunately, since that confidence interval is so wide, it didn't help the confidence interval of my vote at all.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: I voted yes, and that was assuming that we could clearly have the label change that would contraindicate monotherapy and the expectation that we would have that, and I would like to provide flexibility for practitioners and patients, but I'd also like to point out people use the meta-analysis signal in the younger age groups as their reason for voting no and I was very worried that that meta-analysis was driven heavily by single agent

use, the FDA meta-analysis.

And I was really struck that there was absolutely age signal for Advair which is the combination use, so I just -- I'm not completely convinced we have enough data to say that adolescents shouldn't have this available as an option.

DR. SWENSON: Okay. We'll now move to vote on the youngest age group of children 4 to 11 years. So please place your vote. Okay, on this vote for the question 5 in children 4 to 11 years old, there was 1 yes vote, 26 no, and no abstentions. So we will now proceed then from the right hand side and Dr. Kramer?

DR. KRAMER: I changed my vote to no on this one, and I think I was convinced by some of the data that was presented yesterday -- was it Dr. Lemaske -- showing that it wasn't really clear that in this age group that there was the added benefit above the ICS LABA.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted no, for the same

reasons that I did for the 12 to 17 year olds.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: Yeah, I changed my vote to no, for the reasons I don't think there's adequate safety data for this age group.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted no, because long-acting beta agonists are dangerous when used without corticosteroids, and I don't think they should be available indicated for asthma without a corticosteroid.

DR. BRANTLY: I voted no, for the same reason.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted no, for the same reasons I voted no in the previous age range.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted no, for the same reasons.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted no, for the same reasons.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted no, because of the safety issues.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: No, for the same reasons.

DR. SWENSON: Ms. Vining?

MS. VINING: No, for the same reasons.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: No, for the same reasons.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: No, for the same reasons.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: No, because of the safety issues in this age group.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted no, in this case differently from before, because I don't think we have enough clear and unmistakable data of benefit in this age group. I hope we will come out from the BATGER study.

DR. SWENSON: Dr. Rappley?

DR. RAPPLEY: I voted no, and note

that the risk is even stronger in this age group.

DR. SWENSON: I voted no, simply because I think the signal now is so much more dominant for an adverse problem.

Dr. Schoenfeld?

DR. SCHOENFELD: I voted no, for the same reasons previously.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted no, for the same reasons previously.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: No, for safety reasons.

DR. SWENSON: Dr. Joad?

DR. JOAD: No, for the same reasons.

DR. SWENSON: Ms. Holka?

MS. HOLKA: I voted yes, and I have to say I don't know how that happened -- but anyway, I did actually end up voting yes --

DR. SWENSON: Do you feel it was a mistake?

MS. HOLKA: Yes, I absolutely feel it

was a mistake.

DR. SWENSON: So you wish to enter a vote of no?

MS. HOLKA: I would like to enter a vote of no, and I do believe that it would be a safety signal between the ages of 4 through 11, so I apologize for that mistake.

DR. SWENSON: I just asked Dr. Jenkins, do we need to do the mechanical vote again, or can this serve as a change in her vote?

DR. JENKINS: I think that's fine.

DR. SWENSON: Okay. Good.

DR. JENKINS: It's kind of like Palm Beach County.

DR. SWENSON: Kocis?

DR. KOCIS: I voted no, for the same reasons.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no, just to give the numbers here, it was 2 -- the risk difference was 2 in 18 to 64, 5.57, and in this

age group the risk difference was 14.83, so I think that this is a very sharp gradient that merits even more that's necessary voting no for this age group.

DR. SWENSON: I need to read into the record that Ms. Holka has changed her vote to no.

Dr. Zito?

DR. ZITO: I voted no, for the same reasons as before.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted no, for the same reasons, and concur with Dr. Wolfe.

DR. SWENSON: And Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted no, for the same reasons I stated before.

DR. SWENSON: We'll then move to question six and I think this should go a bit faster here, since we now have the swing of things. So question six then is, do the benefits of Foradil/formoterol outweigh its risks for the maintenance therapy of asthma in

patients not adequately controlled on other asthma controller medications, for instance, low to medium dose inhaled corticosteroids, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

And we'll again, go through the age groups as listed. So would you please now vote on the adult age group that is persons over 18 years old.

Okay, the voting results on question 6 for adults greater than 18 years of age, we had 9 yes votes, no 18 votes, and 0 votes to abstain. So we'll start the discussion here with Dr. Schneeweiss, your vote?

DR. SCHNEEWEISS: I voted no, because I'm concerned about increase risk of serious evens and the agent is still available in combination which is clinically more appropriate.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted no, and I'm

actually in agreement with what was just said, and also with what applied in question five.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted no, for the reasons previously expressed by others. It doesn't seem to change the case whether -- for me, whether we're looking at salmeterol or formoterol alone in either case.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no again, just because the only way of taking care of this more serious problem of single ingredient is to disallow its use for -- or remove its use for asthma.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I voted no, and my rationale remains the same as it was before.

DR. SWENSON: Ms. Holka?

MS. HOLKA: And I did actually vote yes, so that's good. It would be for the same reasons why I voted yes for this age group in question five. I believe there needs to be an

option for that single agent to be available.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted no, for the reasons in the previous question.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: No, for the same reasons as before.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: No, for the concerns of abuses, monotherapy, and lack of flexibility or the lack of a flexibility argument.

DR. SCHOENFELD: I voted no, for the same reasons as before, but I should add that there is a consideration here in that we don't really have data on this single agent as we do on the other so we're making the assumption that the risk is the same based on the notion that this is a class risk, and we don't have any proof of that actually but I think that that would be something that if we had proof of, we could -- we should -- would reconsider, but we don't have proof of and so I think the safest

thing is to presume that it is a class risk.

DR. SWENSON: I voted yes, as I just discussed for question five, for a risk/benefit assessment -- then I think the option should still be available for this age group.

DR. RAPPLEY: I voted no. I think it's a reasonable assumption that it's a class effect.

DR. MARTINEZ: I voted yes, for the same reason I voted yes in this age group in the previous question.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted yes, also for the same reasons as in the previous one for this age group.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted no, for the same reasons as with question five, and because there's even less data on this one.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I voted no, for the same reasons -- particularly I was concerned about

the lack of data. But I'd also like to point out something seems different for the age 65 and higher in the meta-analysis that it was more beneficial. So I just would like to say that for the record.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted no for this population. Prior, I had voted yes, but I think that the 43,000 study participants in Serevent versus the 3,700 in Foradil made a difference in terms of data.

DR. SWENSON: Dr. Krenzelock? Or Dr. Knoell, excuse me.

DR. KNOELL: I voted no, for the same reasons, but I would also like to remind everybody, we all know this, but that formoterol and Serevent are not identical in terms of their onset of effect or their agonist potential for the receptor so I would hope in the future there might be more studies, more data, to make more informed decisions.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes, for the reasons that I stated previously.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, because I think the physician should have flexibility in this age group and that the label should have a strong contra indication to using this as monotherapy.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted no, but I do want to say with considerably less zeal than I voted no with respect to salmeterol in this age group, and for the reasons that other people gave for -- just indicated, first there's less data, second the data is less compelling such as there is, and third, there were known biochemical and pharmacologic differences between the two ages.

So while it's safest to consider this as a class effect, I do want to encourage FDA and the sponsor to continue to develop more data for this indication in the

future for this drug.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted yes to preserve physician flexibility, but I too would like to request more data and that more studies be done on this substance.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted no, for the same reasons I voted no in all categories in question five.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted no, because I believe it's safe to assume that this is a class effect among the long-acting beta agonists.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, for the same reasons as question number five, but would also encourage more study.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted no, because of the need for stronger labeling, and I agree with the calls for more data for this agent.

DR. SWENSON: And Dr. Kramer?

DR. KRAMER: I voted yes, assuming that there would be contraindication to monotherapy in the label and that the guidelines in the physician's -- the guidelines in -- the physician education should help to ensure that it's used with ICS, and also I'd like to add one additional comment for this as well as for the Serevent.

I'm concerned about the psychological impact on patients to actually contraindicate the individual agent for asthma and then prescribe a drug that has that as one of the two components in terms of what they'd think if they read those labels -- and there are people smart enough to realize those are the same drugs, so I think you need to think about whether you have patients who would be afraid to take a lifesaving therapy.

DR. SWENSON: We'll now move to vote on the adolescent age group, 12 to 17 on

question six, so please place your vote.

DR. SWENSON: The results on this age group and the adolescents, there were 6 yes votes, 21 no votes, and no abstentions. Okay, so we'll start then with Dr. Kramer.

DR. KRAMER: I voted yes, for the same reason I voted yes in this age group for Serevent.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted no, for the same reason that I voted no, for the same age group for Serevent.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, for those previous reasons stated.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted no, for the same reason that I voted no on the previous question.

DR. SWENSON: Dr. Brantly?

DR. BRANTLEY: I voted no, for the same reason I voted no in the previous question.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted no, for the same reason I voted no for this age group in the previous question.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted no, for the same reasons I voted no previously.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I changed my vote to no, for the same reasons that I did in the previous group.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes, for the reasons I stated previously, but I'd like to also state for the record that I'm very uncomfortable with the lack of evidence that exists, or the evidence that doesn't exist that really gives us a good cause/effect relationship for this malady that we're discussing today, and I'd really like to see some research conducted to explain why this occurs.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: No, as previously stated.
DR. SWENSON: Ms. Vining?
DR. VINING: No, as previously stated in the last question.
DR. SWENSON: Dr. Shatin?
DR. SHATIN: No, for the same reasons stated previously.
DR. SWENSON: Dr. Cnaan?
DR. CNAAN: No, for the same reasons as in question five for that age group.
DR. SWENSON: Dr. Rosenthal?
DR. ROSENTHAL: Also no, assuming that there's a class effect, and so for the same reasons, I said no for this age group -- for the previous age.
DR. SWENSON: Dr. Martinez?
DR. MARTINEZ: Yes, as previously stated.
DR. SWENSON: Dr. Rappley?
DR. RAPPLEY: No, as previously stated.
DR. SWENSON: I voted yes, for the

reasons I voted yes for salmeterol. Dr. Schoenfeld?

DR. SCHOENFELD: No, for the reasons previously stated.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: No, for the reasons previously stated.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: No, as previously stated.

DR. SWENSON: Dr. Joad?

DR. JOAD: No, for the same reasons.

DR. SWENSON: Ms. Holka?

MS. HOLKA: Yes, for the same reasons.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: No, for the same reasons.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: No, for the same reasons.

DR. SWENSON: Dr. Zito?

DR. ZITO: No, for the reasons in the previous question.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: No, for the same reasons as the previous question, same age group.

DR. SWENSON: And Dr. Schneeweiss?

DR. SCHNEEWEISS: No, for the same reasons.

DR. SWENSON: We will now then move on to the last age group here, children 5 to 11 years old. And please place your vote.

So the voting results here for this age group of children 5 to 11 years old in question 6 is a unanimous no, 27 no's and no abstentions. So let's begin then with Dr. Schneeweiss.

DR. SCHNEEWEISS: No, for the same reason as before.

DR. SWENSON: Okay. Dr. Newman?

DR. NEWMAN: No, for the same reasons as previous.

DR. SWENSON: Dr. Zito?

DR. ZITO: No, for the same reasons as previously stated.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: No, for the same reasons.
DR. SWENSON: Dr. Kocis?
DR. KOCIS: No, for the same reasons.
DR. SWENSON: Ms. Holka?
MS. HOLKA: No, for the same reasons.
DR. SWENSON: Dr. Joad?
DR. JOAD: No, for the same reasons.
DR. SWENSON: Dr. Gardner?
DR. GARDNER: No, same reason.
DR. SWENSON: Dr. Hoidal?
DR. HOIDAL: No, for the same reasons.
DR. SWENSON: Dr. Schoenfeld?
DR. SCHOENFELD: No, same reasons.
DR. SWENSON: Dr. Swenson here. I voted no, for the same reasons I voted with question five.
Dr. Rappley?
DR. RAPPLEY: No, for the same reasons.
DR. SWENSON: Dr. Martinez?
DR. MARTINEZ: No, same reasons.
DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: No, for the same reasons.
DR. SWENSON: Dr. Cnnan?
DR. CNAAN: No, for the same reasons.
DR. SWENSON: Dr. Shatin?
DR. SHATIN: No, for the same reasons.
DR. SWENSON: Ms. Vining?
MS. VINING: No, for the same reasons.
DR. SWENSON: Dr. Knoell?
DR. KNOELL: No, as previously stated.
DR. SWENSON: Dr. Krenzelock?
DR. KRENZELOCK: No, same reasons.
DR. SWENSON: Dr. Hudson?
DR. HUDSON: No, same reasons.
DR. SWENSON: Dr. Notterman?
DR. NOTTERMAN: No, for the same reasons.
DR. SWENSON: Ms. Celento?
MS. CELENTO: No, for the same reasons.
DR. SWENSON: Dr. Brantly?
DR. BRANTLY: No, for the same

reasons.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: No, same reason.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: No, for the same reasons.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: No, for the same reasons as for question five, this age group.

DR. SWENSON: And Dr. Kramer?

DR. KRAMER: No, for the same reasons.

DR. SWENSON: Okay. We'll now then move to question seven, and I'll read that just for the record. Do the benefits of Advair, the fluticasone propionate, salmeterol xinafoate combination, outweigh its risk for the maintenance treatment of asthma in patients not adequately controlled on other asthma controller medications, either the low dose or medium dose, inhaled corticosteroids and whose disease severity clearly warrants initiation of treatment with two maintenance therapies?

Again, in these following age groups, so we'll first have the vote for adults, those 18 years or older.

Okay, the voting results for question 7 on Advair in adults greater than 18 years of age is a unanimous 27 yes votes, no votes to abstain or vote no.

So Dr. Kramer, we'll ask you to start.

DR. KRAMER: I voted yes, because I felt that the data was clear, and that it's a fixed dose combination with ICS, and I think the sponsor should be congratulated for studying the number of patients they've studied.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted yes, because although there is likely to be with any long-acting beta agonists some risk of a catastrophic poor outcome, the benefits to the majority of patients outweigh those risks.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, because I

think it has been demonstrated a higher degree of safety and I think the benefits are significant and I think this is also consistent with treatment recommendations.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted yes, but I would like to see randomized safety trial evaluating serious asthma outcomes.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted yes, I am convinced by the data that it's both safe and effective.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted yes in support of the treatment recommendations and the recommendation of safety.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted yes, because I thought that there was clear and compelling evidence of safety and efficacy in this age group. I did want to comment that I thought that studies that were presented today and

yesterday that purported to show continued problems with the use of LABAs and corticosteroids were fatally flawed and not assuring that the ICS were actually used as described.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, because I think that the evidence presented show the benefits outweigh the risk.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes, because I thought it was proven to be safe and effective.

DR. SWENSON: Ms. Vining -- oh, Dr. Knoell, sorry.

DR. KNOELL: I voted yes. I feel the societal benefits far outweigh the risks, and as previously mentioned, I agree. In the future, I would like to see re-visitation of redesign of trials that would better define what the risks of these are, kind of in the spirit of Dr. Graham's talk yesterday.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted yes also. I think it's consistent with the treatment recommendations, but I would urge the medical groups to redouble their efforts to educate their membership on the importance of using LABAs in conjunction with ICS.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I voted as well to be consistent with the other votes, but also that the benefit definitely outweighed the risk in this instance.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted yes, because the combination of the data presented and expert opinion convinced me that the benefits outweighed the risk. I would strongly urge an education push both for the health care providers and the community because of the big issue of adherence.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted yes, because I

believe that this is a safer formulation than the monotherapy.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted yes, because I think the benefits clearly outweigh the risks, but I still think that the burden of proof is still on the fact that this combination needs to be demonstrated as being safe and I don't think it has.

DR. SWENSON: Dr. Rappley?

DR. RAPPLEY: I voted yes. I feel the benefits outweigh the risk, and the risk can be managed through communication such as labeling, med guides, and other agency communication.

DR. SWENSON: This is Dr. Swenson. I voted yes. This is a much more enthusiastic yes than on the single agent, because I think the data are really very, very strong, and only hope that with a bit more examination into the next several years, that we can come to a closer understanding of whether there is really this slight risk that's been raised.

Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes, but I should say that despite the fact that there haven't been any deaths on Advair, as was shown, I still feel that given the other data that we have from the whole picture that we should presume that there is a risk for the use of Advair, and I think that we should be very careful that we retain the black box warning, that we continue to warn people of the risk so that individuals can decide whether or not to use this drug based on a good understanding of the risk and a consideration of it.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: Yes, because of substantial benefits and relatively low risk.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: Yes, because the risk/benefit ratio is more compelling with this.

DR. SWENSON: Dr. Joad?

DR. JOAD: Yes, because of the benefits and low risk. I did want to point out

the 65 and up group might need more attention. It looked like maybe there were some safety issues with them and also the labeling should be changed so that it's not adequately controlled on inhaled corticosteroids not just on other controllers. I think we all agree it should be that, but I didn't want to vote no, because of my label suggestion.

DR. SWENSON: Dr. Kocis -- oh, I'm sorry, Ms. Holka?

MS. HOLKA: I voted yes, because I think this has been proven to be safe and effective with what's been presented.

DR. SWENSON: Okay, Dr. Kocis?

DR. KOCIS: I voted yes, because I believe the risk/benefit ratio far favors that use of the drug, but I don't want to say that the risk is zero and I believe strongly that further evaluation needs to be undertaken.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted yes with enormous hesitation, because in this age group, we have a

risk difference of still 2.13, and I have to say now I'm limiting this just to this age group because I think that the unanimous conclusions of the other people in the drug safety affect the other age groups.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted yes, because the data support safety and efficacy for short-term use -- or from short-term trials under ideal conditions and with the plea that we would develop substantial post-marketing information that relates to more comprehensive measures of improvement related to functional improvements.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted yes, agreeing with much of what we've heard here so far. I would add that in terms of addressing the labeling, it may be necessary to acknowledge something that Dr. Kramer said earlier, there may be a need in our educational materials to clarify this point about why we would be recommending this as a combination drug but not

as a single agent since we know the single agent drug will still be out there for other indications.

DR. SWENSON: Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted yes, because the benefits outweigh the risks.

DR. SWENSON: We'll now move to the vote in the adolescent age group, age 12 to 17.

Okay, the result of this vote for Advair in the age group of age 12 to 17, we had 23 yes votes, 3 no votes and 1 abstention. So we'll begin with Dr. Schneeweiss. Your vote?

DR. SCHNEEWEISS: I voted yes, because for the same reason as before.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted yes, for the same reason.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted no, because I'm uncertain of the benefit in the pediatric population.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no, because unanimously Drs. Mosholder, Levenson, McMahon, and Graham agreed that the asthma indication should not be any longer continued. I think this is a serious safety issue. They obviously paid attention to the data, the age related data on dangers that were alluded to before. And last spring, the head of drugs, the night before an (inaudible) oversight hearing said, we have a new problem called Safety First, so I think that this -- voting against this is essentially putting the people in the drug safety division of FDA first as they need to be, more often than they have been.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I voted yes, and I did so after spending a lot of time in balancing the risks and the benefits, and so I want to say that -- certainly the combination therapy would be the only way to offer this drug. I believe that clinical trials demonstrated numeric

improvements in spirometry, soft statistical maybe, maybe not, clinical benefit, and yet I'm overwhelmed by the clinical experience of practitioners here and around the country, and then certainly from the families about the benefit of the drug. And so I do so for those reasons, and yet I remain more concerned about a safety signal.

I do not believe we have excluded life-threatening events, and I believe very strongly that we need to follow this up, that large randomized clinical trial would be wonderful but would take forever as we've described and I'd like to advocate the initiation of a registry to begin to look at a whole host of factors that may contribute to asthma deaths such that 10 people per day do not continue to die in the U.S.A.

DR. SWENSON: Ms. Holka?

MS. HOLKA: I voted yes, for the same reasons stated prior.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted yes. I think it's safe and effective in this age group.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I voted yes. I think it's safe and effective in this age group.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted yes, but agree that the data is not as strong as in the older age group.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes. I think that there's not very much data here, so I think that the best thing to do is to extrapolate the risks from the adults and in terms of efficacy, I think the clinical trials are very hard to actually judge efficacy from, so my benefit estimate for both this and the previous one has basically come from the experience of doctors on this panel -- you know, which is --

DR. SWENSON: Dr. Swenson. I voted yes. Again, I think that there's just enough here to continue its support as in adults.

DR. RAPPLEY: I voted yes, for the same reasons.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted yes, based on my clinical experience with this medicine which has been very positive. I think there's a paucity of data in this age group. Dr. Lemaske told you yesterday that we're conducting a study to determine if adding LABAs is as effective or more effective than other alternatives. I would like to insist, however, on something that I said before, is that we need the cooperation of industry to make increasingly more clear that the first line of treatment for asthma in children is inhaled corticosteroids, because I haven't seen, in the last two or three years, a single ad for Flovent, and I have seen many for Advair.

So what needs to happen is that we need to cooperate, industry, and those of us who are in the trenches, into making it increasingly more clear for patients that the

first line of treatment for childhood asthma is inhaled corticosteroids.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted no, for many of the reasons Dr. Martinez just gave, although he voted yes. But there were a few things that were concerning for me. One was that the data were pretty thin in this age group, and the other is that I'm not convinced that the combination therapy completely mitigates the risk of these agents.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted yes, because I felt that it is a little premature to vote no, that is to remove the indication given that at this point in the meta-analysis on table 12, page 42, shows a risk difference confidence interval that includes 0 and only 1 LABA event in 3,000 patients included in the meta-analysis, so I think it has to be researched more. I hesitated, but right now, it felt like it's premature to vote no.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I abstained, and it's for similar reasons, really. I think it's important to have the combination of therapy available for this age group but I also believe that we don't have sufficient data and information to make a clear decision on yes.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted yes, with similar concerns to Dr. Cnaan.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I voted yes, for the same reasons previously stated.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes, just to maintain the status quo until there are data to support changing it.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, acknowledging that the data is more limited in this area, but I still think the benefits outweigh the risk.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted yes, even though there's a paucity of data, because I was willing to extrapolate to a certain extent into this age group from the adults, not necessarily the case with other age groups.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted yes, because I was also willing to extrapolate from the adult age group but I would like to echo Dr. Martinez's comments about ICS being the first line of defense and that that should be promoted and reinforced and I agree that industry has a role there.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted yes, for the same reason. And again, I would like to emphasize what Dr. Joad and Dr. Martinez said that in fact in the product labeling, I think we should indicate that this is step two therapy rather than primary therapy.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted yes, because I think the demonstrated benefits outweigh the demonstrated risks, but there are uncertain risks for which we need better data for. And in particular, I think that FDA should require a large randomized trial to quantify the risks of serious asthma related events.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, for the previous reasons, but also agree that more data is needed in reconsideration.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted yes, and you can write the same thing that you wrote for Dr. Hennessy. He expressed it very well.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: I voted yes. I'd like to echo what Dr. Martinez said about advertising ICS as the first line of therapy. I voted yes primarily because I think that it should be up to the patient and physician to decide whether the 8 in 10,000 risk of severe exacerbations or

even death is counterbalanced by the quality of life that impact that patients have to decide on an individual basis.

DR. SWENSON: Okay, then we'll move to a vote on children age 4 to 11. The results for the age group 4 to 11 for Advair, the vote is 13 yes, 11 no, and 3 abstentions. And we'll start with Dr. Kramer.

DR. KRAMER: I had a hard time with this one because I looked back and -- well, first of all, what Dr. Lemaske said yesterday really bothered me, and I was worried that there would really not be an effort to go first with ICS in this age group and when I look back at the FDA meta-analysis, it actually didn't -- if I'm looking correctly, on slide number 44, there was a blank on the 4 to 11 and I'm not sure why that is, and the -- but the company's analysis of that subgroup looked safe, so I was really uncertain, but I was swayed by Dr. Lemaske's presentation.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted yes. I think there is convincing evidence of benefit. I think that the risk data are by no means where we want them to be, and that more data are needed, that these drugs seem to be beneficial for the majority of patients that get them.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted no, because I think at this time there's insufficient data.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted yes, because I think that the demonstrated benefits outweigh the demonstrated risks, and again believe that FDA should mandate a large safety trial to look at serious asthma related events.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted yes, for the same reason I voted yes in the previous age group.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted no, because I think that ICS should be -- it should be

advocated as the first line of defense but I would like to say that -- you know, there's probably a 9- to 10-year range that -- you know, physicians should make the decision accordingly.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I abstained, because I think there's clearly a paucity of data. It's difficult to make a safety judgment based on what we know today, and notwithstanding the recommendation of CDER, I was unwilling to extrapolate data from teenagers and adults to children, particularly young children at the lowest end of this range. So I strongly wish to have industry to continue safety studies and the FDA to require these studies.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, acknowledging that there's limited information about risks in this population, but I was greatly influenced by other clinicians and experts that have presented to us about its clinical efficacy within their populations.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I voted yes, and for the same reasons that Dr. Hudson did as well.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I voted yes. I probably struggled the most with this one so far. At the end of the day, I didn't want to go back to the dark ages, so to speak, and I wanted to keep this medication available to patients with skilled physicians prescribing.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted no. I think the extrapolation in this age group is very challenging and there is insufficient data, so I think there's a need for more data and safety information.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I also voted no, for the same reasons.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I actually abstained, which is very rare for me. There was paucity of

data. The data was conflicting for what it was, and I just sort of want to use the abstain vote to make a statement that we really, really, really need to study this age group in order to come to a meaningful conclusion.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted no, and would just reiterate the points of -- that there is inadequate data to feel great about any vote in this age group, but the reason that I voted no is because one of the more compelling signals that we saw was in this age group, so I'm worried about the smaller kids.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted yes, and I have to say that for a person practicing, it's going to be very difficult if this is accepted to explain to a 10-year, 11-month, 30-day-old person that they cannot get it and a 12-year-old that they can, how these absolute numbers create tremendous difficulties for us in clinical practice. I have to say that this is a

difficult decision for me because in the previous vote I voted no when the single medicine was there, but I think in this case, there's an issue of strategy of treatment that may be effected if we go in this route. I would like to insist that further data are needed and that, I know that you have heard it before, but that the insistence should be in inhaled corticosteroids alone as a first line.

DR. SWENSON: Dr. Rappley?

DR. RAPPLEY: I voted yes. It was a difficult decision. I think that the evidence of benefit is such that risking not treating with these agents is significant. I would like to applaud members of the agency for taking a stand on both sides, for giving us their true assessment of the safety signals. I think the risk is significant, and should be so acknowledged in the labeling and in our education efforts, but in the end, my vote was to not deny these medications to children in this age group.

DR. SWENSON: This is Dr. Swenson, and I had a difficult vote. It was no. I think it's just -- in this age group, probably the lack of data and then a general trend to these drugs having a bigger problem in this age group was the reason for my no vote.

Dr. Schoenfeld?

DR. SCHOENFELD: My reasons for voting yes were the same as Dr. Rappley's.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted yes, with some concern because of the paucity of data in this age group as indicated, but the feeling that there was a need for a combination therapy in this group.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I voted no, because of the increasing risk in this age group, also recognizing that our role here is advisory and not final, and to encourage the FDA to both require more data and to find ways of communicating what these risks are and the need

for first line therapy being what it is.

And so possibly, our votes in an advisory capacity, is spurring action rather than finality.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted yes. I would like to support what Dr. Martinez said, which is, this is a group that I treat and I use this drug and it appears to be working and effective and I -- but I definitely agree that we need more research in this age group to deserve it.

DR. SWENSON: Ms. Holka?

MS. HOLKA: I did vote yes. I have to say that I definitely support what Dr. Martinez said. I think that the studies that are up and coming will be very interesting, but in doing my own study at my house with my two sons, I can tell you that having two asthmatic sons, one having failed ICS and having been put on a combination drug, it's just -- when you have someone that needs it, they do truly need it, and in three years we have not been to the ER,

so I had to vote yes.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I was most troubled by my vote. I voted yes, in this regard. I view the benefits more so weighing on the clinical experience of practitioners. The risk, though, in this group is the largest potential risk. Obviously, the risk is severe, and I'm equivocal about voting yes versus no. I weighed in on the yes side of things, and yet I believe that we need to continue to monitor this drug and this group of children, and that intervention before we get three committees together may be required if a safety signal does arise in the up and coming months and years.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no, because as I mentioned before, the risk difference is 14.83 events per 1,000 people in this age group. I would hope, and part of this is answered in the design that we heard yesterday of the study that in this age group particularly, but I would say

other age groups, that a study is done where children have been put to the maximum effective, for them, steroid, and then randomize to get either more steroid, short-acting beta agonist or long-acting one. I mean, I think that that is the way to answer some of these questions. I think there's enough concern, obviously, that all 4 of the people who worked on this issue in the drug safety division of the FDA said that it should not be allowed for any of these children under the age of 18.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted no, and my rationale is very similar to Dr. Gardner's comments.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I abstained on this one. I was nearly a yes, but for the reasons stated by the other abstainers, I -- you know, I recognize what the clinicians need and what they're saying to us in terms of benefit, but I'm not at all sanguine about the safety signal

here and we're going to need more information, so hence my abstention.

DR. SWENSON: Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted no, because for the class of agents, the risk is substantial in that age group and the data for adverse specifically is too thin.

DR. SWENSON: All right, we now move to question eight, which is, do the benefits of Symbicort Budesonide and formoterol in combination, outweigh its risk for the maintenance treatment of asthma in patients not adequately controlled on another asthma controller medications for example the low to medium inhaled dose inhaled corticosteroids, or whose disease severity clearly warrants initiation of treatment with two maintenance therapies in the following age groups?

And in this case, we only have two age groups, so we'll start with the vote in adults, those 18 years of age or older.

All right, the result then in this

age group was yes 26, no 0, and 1 abstention. And we'll start then with Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted yes, based on the entirety of evidence provided by the company meta-analysis, not the FDA meta-analysis, because I feel those data have been considered as although they might be outside the labeled doses for the United States.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I voted yes. I struggle a little bit more on this one, but I think that on the weight of evidence, I think we can support its use.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted yes, for the reasons previously stated for Advair.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted yes. Again, somewhat reluctantly, because it's not clear that in these clinical trials the benefit that accrues to the people that get in this case, Symbicort but Advair is the same thing, are from

steroid or from the LABA. I mean, I don't think they're designed in such a way to make sure that no one gets in the trial unless they've been pushed to maximum dose of the steroid, and that needs to be done.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I voted yes, in the same rationale as I did for question seven in adults.

DR. SWENSON: Ms. Holka?

MS. HOLKA: Yes. I voted yes, because I think that it's been proven safe and effective.

DR. SWENSON: Dr. Joad?

DR. JOAD: I voted yes. I didn't feel I could adjudicate the different data I was getting from different sources, but I was convinced by the industry's presentation of the data that it was safe and effective in adults.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: Yes, I concur with Dr. Joad.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted yes, based on a review of the larger data set.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes, for the similar reasons as for Advair.

DR. SWENSON: Dr. Swenson, and I voted yes for all the reasons that have been said.

Dr. Rappley?

DR. RAPPLEY: I voted yes, for reasons already stated.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted yes, for the reasons I stated for Advair.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted yes as well, but this is an agent for which I would also like to see more data.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I voted yes, for the same reasons as for Advair, but would also like more data.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I voted yes as well, and also would like to see more data.

DR. SWENSON: Ms. Vining?

MS. VINING: I voted yes, for the same reasons for Advair, and would also like to see more data.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: Yes, for the same reasons, and I'm on the more data bandwagon as well.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I abstained. Our poison center has a service contract with AstraZeneca, so I thought to avoid any conflict of interest, I would abstain, but had I not had that conflict of interest, I would have voted yes.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, for reasons previously stated.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: I voted yes, because I

think there's good evidence of benefit relative to risk.

DR. SWENSON: Ms. Celento?

MS. CELENTO: I voted yes, for the same reasons as Advair, but I'm in the more data camp as well.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I voted yes, for the same reasons as Advair.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: I voted yes, but I think the FDA should require a large trial to look at the risk of serious asthma related events.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: I voted yes, for the previously stated reasons.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I voted yes, for the same reasons I did for Advair, but I'd like to take this opportunity to join the more data camp and specifically to suggest that all the

meta-analyses be locked in the same room until they have a chance to combine their data.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: I voted yes, and I'd like to echo what was just said by Dr. D'Angio.

DR. SWENSON: Okay. We'll move now to the last group here for the use of Symbicort, and that's in adolescents, aged 12 to 17.

The results then, for this vote on Symbicort in adolescents is yes, 20 votes, no votes 5 and 2 abstentions. And we'll start with Dr. Kramer.

DR. KRAMER: Yes, for the same reasons as question seven.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: Yes, for the same reasons as I voted for the adults in this.

DR. SWENSON: Dr. Margolis?

DR. MARGOLIS: Yes, for the same reasons as previously stated.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: Yes, and as you're

probably tired of hearing, I think that FDA should require a large trial to look at asthma-related serious events.

DR. SWENSON: With even more enthusiasm, right? Dr. Brantly?

DR. BRANTLY: Yes, because of the same -- the data from the adults.

DR. SWENSON: Ms. Celento?

MS. CELENTO: Yes, because of the data from the adults as well.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: Yes, I do want to comment that this was based on extrapolation, and I also want to comment that I think it's a shame that decades after Shirley spoke about the therapeutic orphan, notwithstanding the clear intent of the Congress and others, we still have to request additional data or comment on the paucity of data in adolescents and children. I think it's a shame.

DR. SWENSON: Dr. Hudson?

DR. HUDSON: I voted yes, for

previously stated reasons.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: I abstained for the same reason, and would have voted the same way.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: Yes, as previously stated.

DR. SWENSON: Ms. Vining?

MS. VINING: Yes, and I echo Dr. Notterman's comments.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I voted no. I feel there really isn't sufficient data to make this decision.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: With much hesitation, I voted yes, because of -- I went for the extrapolation, but there is lack of data and whenever a study is done on adolescents, please, please the parents.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I voted no, and I did

so despite the lack of sufficient data and the imprecision in some of the estimates primarily because in one of the meta-analyses, the risk difference in this group for Symbicort was quite striking for the composite endpoint.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I voted yes, and with Dr. Notterman, I would like to say that it is essential that we have more data in children.

DR. SWENSON: Dr. Rappley?

DR. RAPPLEY: I voted yes, for the same reasons.

DR. SWENSON: This is Dr. Swenson. I voted yes, for the same reasons.

Dr. Schoenfeld?

DR. SCHOENFELD: I voted yes, for the same reasons.

DR. SWENSON: Dr. Hoidal?

DR. HOIDAL: I voted yes, with the plea for additional studies.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: Yes, and I concur with

what's being said about more data.

DR. SWENSON: Dr. Joad?

DR. JOAD: Yeah, I abstained because I felt like it was useful in adults -- safe and effective in adults, but in the children -- when I looked at the children's data, the young ones, from the industry, I thought it wasn't safe and effective so I didn't know what to do with the adolescents and I hate to take a drug off the market that's already been approved, so I thought I'd abstain.

DR. SWENSON: Ms. Holka?

MS. HOLKA: I voted yes, for the same reasons, but would have to echo the call for more data, especially with this drug formulation and in this age group.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I, again, reluctantly voted yes. I find it difficult still at this time that we have to ask for data broken down by age in children, and to ask specifically for indications and to demonstrate benefit and to

evaluate the risk in that group of patients.

And I think that's it.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I voted no again, because the risk difference was twice as high in this group as, for instance, the 18 to 64 group.

DR. SWENSON: Dr. Zito?

DR. ZITO: I voted no, for the same reason I did for Advair in this age group.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Mine was a very hesitant yes, for some of the same concerns that we've heard already about the risk profile here and the limited data, which continues to be, I think, very disappointing.

DR. SWENSON: Dr. Schneeweiss?

DR. SCHNEEWEISS: I voted no, for the same reasons stated by Dr. Rosenthal.

DR. SWENSON: Okay. We've passed through the voting, and the remainder of our time is to further advise the FDA on how to move forward with many of these questions that have

been raised and the concerns mentioned. So in the remaining time, I'll try to equally divide our time between question nine and question ten.

Question nine is, based on all our discussions and our votes, are there further labeling changes or risk mitigation strategies for individual LABA products or of the class as a whole that would be advisable.

So we'll open up and take questions in order. I saw Dr. Brantly raise his hand first.

DR. BRANTLY: I would like to go back to the issue in this class drugs, particularly combination in African-Americans. I am haunted by our decision in 2005 about putting so much weight to African-Americans in the warning that we have. As I've practiced in those days since then, my minority patients have come to me on a number of occasions saying, is this going to kill me, and I know that some of these individuals are not taking these medications which are likely very promising in this category

and given the fact that our -- the data is not clear-cut as to the stratification of severity in disease and indeed the baseline data would suggest that this group of individuals has more severe asthma.

I have some concerns about having such a strong indication about African-Americans, and would like to have that message, not necessarily softened, but put into the context of the study.

DR. SWENSON: Ms. Holka?

MS. HOLKA: Thank you. As a patient representative and, again, mother of two asthmatics, this was my first experience with all of these patient inserts. I have to tell you, we've been taking different medications for the last 10 years for asthma and I have yet to actually, embarrassedly, sit down and read an entire patient insert. What was interesting to me was that there are medication guides attached to most of these patient inserts or prescription inserts, whatever you want to call them. I did

not realize that a medication guide was specific to patients and that the other was more specific to the physician. So I found that very interesting.

I would also have to say that I found it very interesting that you could call an inhalation -- the language in these inserts is amazing, because I think there has been 15 different ways to say one particular thing and nothing is consistent. I would have to say that this inconsistency both in the prescription insert and in the medication guide really goes to the fact that there is inconsistency all over the board for physicians, for patients, in how the physicians are speaking to the patients.

I think it talks to the disconnection between physicians and patients, and further complicates and muddies the issue of all of these drugs or any of these drugs in trying to get across how they should be used to control or maintain their

disease severity.

I guess I would have to look at the one that I have open in front of me which is actually Symbicort and on one page we have puffs, we have inhalations, then we have dose -- three different terms prescribing, and then we wonder why patients don't understand the difference between all of these different things nor do they understand the difference between albuterol, rescue albuterol, rescue short acting beta agonists -- there's like 10 different ways to say this, and so many times I see them included in one document.

I would really ask for the labeling changes to look at the entire content of these documents and have them be at least consistent and correct so that the same language can be communicated throughout industry, throughout education to patients, throughout education to physicians. I just feel that that's very, very important.

Thank you.

DR. SWENSON: Dr. Notterman?

DR. NOTTERMAN: Thank you, Dr. Swenson. Since this will probably be the last time I talk, I also want to congratulate you on running a very effective meeting in a very difficult context.

DR. SWENSON: I'd like to congratulate all the rest of you for being wonderful companion committee members.

DR. NOTTERMAN: I just want to turn my attention to the label, since I imagine that's where FDA will be able to make most of the changes, and I'm hoping that the label will clearly describe information in a compelling, age-delineated way. I think it's very important for practitioners and also the medication guide, when it incorporates this information that they understand that there's a deep concern over both issues related to efficacy and particularly safety as the age of the individual is reduced at least for the time being.

I also think that the label should be very clear, very clear and stark in indicating that there is no indication for monotherapy in the pediatric age group that is less than 18. And my opinion, I don't know if the FDA shares this, that would also include for monotherapy for exercise induced asthma.

Thank you.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I think most of what I'm going to say is going to echo what Dr. Notterman just said that in at least some of the decisions about the single agents, there were several of us who voted no, because of the label and because of the risk mitigation strategy as it stands currently doesn't seem to be adequate and I think that if the FDA were to decide to try to manage that risk through labeling, that it is important -- the most important thing for me, although the data are still a little bit uncertain about it would be to make it very

clear that single agent use is not something that's recommended and that agent use with steroids is what would be needed -- is what people should be doing and if the label were that strong, I probably would have voted yes about those single agents.

DR. SWENSON: I'd just like to interject here, taking Chairman's prerogative, that in the line of that, I think that in insert, there should be not only the description of the general process, but I would like to see for those practitioners some immediate link to the guidelines that are published. I think it would be in the educational sense that should they have just time enough to take a look at those guidelines, there'd be a bit more education.

Dr. Jenkins?

DR. JENKINS: I'd like to ask the question for the members who -- several members have mentioned contraindication for monotherapy. Contraindication from a regulatory perspective

in labeling means that the benefits can never outweigh the risk. So is that what people are referring to when you say contraindication or were you thinking more in the softer contraindication mode that when you use that term -- I just wanted to get clarification on that.

DR. SWENSON: For those of you who offered an opinion -- Dr. Notterman?

DR. NOTTERMAN: So thank you for asking for that clarification. What I mean is that physicians should understand that in the context of treating individuals under 18, they should never prescribe monotherapy -- that is to say therapy in the absence of an inhaled corticosteroid.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: The reason I mention counter-indications was in the context of our vote, which was for all of the age groups not to -- to remove the asthma indication -- I think if you remove the asthma indication and say this

drug is not approved for asthma, you can also put in there, it's counter-indicated for asthma, but I'm not sure, from a regulatory standpoint, what the difference is. The question we were asked was not to put in -- whether we should put a counter-indication but whether we should -- whether we agreed or disagreed with the idea that its benefits outweigh the risk and I think the vote on all three of those groups was it does not and therefore at least our vote was it is no longer approved for asthma.

If this is repeated in the labeling, it will further strengthen it but I think that the primary thing is that we have at least voted, and hopefully the FDA will listen that these drugs not be approved for treating asthma.

DR. SWENSON: Dr. Kocis?

DR. KOCIS: I use the word contraindication, and I do mean it in the literal sense, in the label. I believe that the risk is significantly spent days trying to

understand and trying to mitigate that risk as monotherapy, and I just don't want to return to this committee in a couple of years and still try to mesh through the data and find out who or who did not get steroids.

I think that in the event that a practitioner wants to use Serevent off label or any -- excuse me, any of the monotherapies off label, that they do so with risk and obviously if there is a need, and I believe there's room for individualization of the asthma plan to add an ICS with that single therapy but they do that and the patients know that and they're aware that if they're not taking both of them, that harm comes and that's been well-documented and to just leave it neutral, I believe, misleads the public.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I didn't use the word contraindication when I was talking about this but I think the sense that I would try to convey is that these drugs -- to mitigate the risk of

using these drugs, the only strategy that we know of that may mitigate the risk and that's a "may," not "will" mitigate the risk, is using them with inhaled corticosteroids. Is it possible that another controller agent could be used with these drugs and get the same effect, maybe, but we have -- I mean, we've been dealing with little data here, but there's no data that we were presented about that and I think that to say in the label that you could use it with something else would potentially be really over reaching the data.

DR. SWENSON: Dr. Zito?

DR. ZITO: Yes, my reason for bringing up the contraindication relates to experience with the practice community and what is likely to have a serious impact to change proscribing behavior, and based on past experience, contraindications get everybody's attention and are paid attention to.

DR. SWENSON: Okay. Dr. Rosenthal?

DR. ROSENTHAL: This does not have

anything to do with contraindications in the label, but I actually have a challenge, I guess, for the sponsors of these medications to help us with today. I think we've heard a pretty consistent theme that there's concern around the table at one level or another about the safety of these medications, and I'm wondering if you had the opportunity whether you could offer us some ideas about specific elements of a risk evaluation and mitigation strategy that you might want to consider implementing to manage the risk of these long-acting beta agonists and specifically strategies that might address some of the populations of concern that have been discussed -- the pediatric population, African-Americans, other potentially vulnerable populations.

And if anyone wants to take a stab at it, I would encourage you to feel free to be creative and committal.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I'd like to raise a

subject that we haven't talked about in the last two days but came up today briefly in the public testimony, and that is the issue of inhalers that don't have any indication of what's left in them, what doses have been used.

And in thinking about risk mitigation and specifically thinking about adherence issues -- this doesn't apply to Advair and Symbicort, I realize and may others -- but if you look down a medication guide as I did before I came here and see how many of them say things like, it's important that you keep track of the number of puffs that you have taken in an inhaler that has 120 and is supposed to be taken 4 times a day. It's crazy.

It's just nuts to think that anybody's going to keep track of that and the pharmacists complain that people arrive at their doorstep in crisis because they thought they had more and then found they didn't, so my message is that I would like to see the

agency require that anything that's delivered in what should be a metered dose inhaler have some indicator of how many have been used or how many are left. Something that gives the patient a clue what's in there and I realize that's not the kind of adherence we've been talking about the last two days, but it does -- it relates to adherence and it should be an easy thing to fix since many of these inhalers do have that.

DR. SWENSON: I mistakenly cut off Dr. Rosenthal. He posed a question to the agency, so would you wish to just -- industry rather -- just quickly pose it and --

DR. ROSENTHAL: So my question was, what specific elements of risk evaluation and management strategy you would implement to address the particularly vulnerable populations that have been discussed such as the pediatric population, African-Americans and any other vulnerable populations you'd identify.

DR. SWENSON: Go ahead and

just -- time is short, if you can just give us your off the cuff here. I know you haven't had this question posed to you sooner.

MS. JONES: We'll certainly take the comments that the Committees have raised, certainly after the last Advisory Committee in 2005, we did undertake the African-American study, and we did further pediatric studies and both, again, observational and epidemiology studies. So now that we've heard the comments from the Committee, we will take those and then devise a clinical approach to some of the risk management activities. Thank you.

DR. HUKKELHOVEN: Mat Hukkelhoven from Novartis. We are certainly willing to work with the agency to update labeling if people and if the FDA believes that that is the right approach. We are already actively planning and actually executing already a large study that Dr. Stewart Walker presented to you this morning, with a lot of utilization data coming out of a database of about 800,000 people.

We are also -- we can consider expedited reporting for events of interest, serious asthma exacerbations. We can more prominently highlight obvious pediatric safety data in our prescribing information. We also can do an analysis of a large pharmaceutical benefit management organization to assess changes in prescribing behavior. We already presented some data from the METCO (?) database that shows how Foradil is used concomitantly with ICS and we can certainly expand on that and in addition, we can offer a survey of pediatric prescribers to understand better utilization patterns for Foradil.

DR. SWENSON: Dr. Bonuccelli?

DR. BONUCCELLI: In the interest of time, I won't repeat everything. We did the same as JSK in following on from 2005. We've done an African-American study and have -- a very open -- we've had the medication guide and I'm very interested in your comments about the

effectiveness of those guides. So I think there's just a lot we can do to support education. We already do some enhanced pharmacovigilance, and we'll continue that, and we look forward to discussions of other ways to have most safe and effective use.

DR. SWENSON: Okay, I hate to cut off questions here, but time pushes on and we have to move to question ten, but I hope all the Committee members, if you have further ideas, that if you could pass them to the agency I'm sure they're quite interested, by whatever means you can communicate with them.

So question 10, then, moves maybe a little further into the future here with studies and the question here is, are there further studies, if any, that would clarify the important unanswered questions of safety and efficacy for individual LABA products or the class as a whole? And we can open up questions here. I'll identify Dr. Newman.

DR. NEWMAN: Mine may sound a little

bit off center to this question, but I don't think it is. It follows up on what we were just discussing in terms of risk mitigation and I would like to suggest that in terms of future studies, it would be extremely helpful for us to know the answer to the question of whether a safety risk can be managed through labeling changes and other risk mitigation strategies.

And I would encourage the sponsors and the FDA to get together around addressing that specific issue. I feel like what we didn't see happen, at least, again, I don't think in a way that I was able to see in the data, was a significant change in practice and in use of medications since 2005 and if we're going to pay lip service to risk mitigation, that's one thing.

I hear the sponsors though saying they're sincere in their goal to bring as best we can people's use of medications and prescribing practices in line with the guidelines, and that's -- I think that merits

the time to study it and make sure that we don't end up with black boxes that are really gray boxes.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: It seems to me from everything I've heard that we really do need pediatric studies, and that there would probably be equipoise about whether or not long-acting beta agonists really add anything to baseline ICS certainly in the 4 to 11 age group. And it seems to me that a study like that that included meaningful individual endpoints, like days of school missed and asthma-free days and nighttime awakenings, the kinds of thing that have real face validity with patients and with practitioners would be even more useful than an overall quality of life scale based on what Dr. Martinez said about different aspects responding differently.

Secondly, I'd like to raise something that -- I'd at least like to raise the possibility of something that's not

typically done and that is -- well, first I want to say that we know that AYRES (?) spontaneous reporting data are not going to be particularly helpful and so it always upsets me to have at the end of these things to say, well we'll follow things in the AYRES database from the spontaneous reports. So I would like to propose an alternative which is, this is a public health issue, he safety and children of these agents and it seems to me from having looked at the regulations as I see them, this might be the type of thing where you could get a HIPAA waiver and actually require that all pediatric patients age four to eleven that start on one of these agents be added to a registry and followed with their baseline severity tracked, with their concomitant meds tracked, and the best thing would be if it were a registry of both agents, not just one company's agents, in one registry.

So I would love to see that done

because I think that then you know what people are getting. You could even follow up with them to see if they change medications over time and then follow long-term outcomes.

DR. SWENSON: Okay. Dr. Gardner?

DR. GARDNER: I would like to see the -- a comprehensive evaluation of the observational data in Medicaid and in the HMO databases, in Kaiser, wherever it makes sense and to be done for all the products and probably done with the FDA's resources. I fully appreciate the issue of compounding by indication, but they can control for it as well as they can and if Dr. Walker plans to address that in his analyses, the FDA can certainly address it in theirs, and I think that that's the best place to get data on utilization and safety in children and span the dates of changing guidelines and give us some good information on children in addition to the studies that are being proposed by Dr. Kramer and others.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: First, I would like to say that SMART was smart, and I'd like to congratulate both the FDA and the sponsors for doing that study because I think that it did -- that it did improve patient care and I think that there's a need for safety studies to be required in certain situations, that is situations where you have common diseases that have very severe symptoms and in which there's an innovator medication.

And I think we have to realize that those studies are going to be very difficult, that is, they can't be as large as you would like them to be. They're going to have to be relatively small studies given the risks that you would like to rule out -- that is, they can't be huge because if they're too large they will completely squash innovation in these diseases and these diseases are diseases in which we want innovation, so we're not going to be able to actually rule

out substantial risk, but we will be able to get a better indication of risk than maybe we can get by just looking at databases and I think that we have to consider how we could do such studies.

DR. SWENSON: Dr. Shatin?

DR. SHATIN: I'm not sure if this was addressed before, but I think as came out yesterday, the severity level at baseline hasn't been tracked in any of these studies, and I think it's very important to link what the severity level is to what the outcome is both benefit and risk, and that may have implications for the labeling if it's found that the severe asthmatics have a higher rate of these adverse outcomes, that would be important to note.

DR. SWENSON: Dr. Krenzelock?

DR. KRENZELOCK: Thank you. I was really struck by the fact that compliance with these medications is so low and so maybe we need to do some studies that look at how we enhance compliance and what are the things that impede

compliance, I think more importantly. Then the other issue that I had mentioned earlier was the fact that I'm still amazed that there wasn't any good etiology provided in terms of why this problem occurs and I'd like to see some research encouraged that would explore this in more detail. You know, is it lack of compliance, is it some pathophysiology as a result of the drug, is there a drug effect relationship? So those are the things that I would like to see from a future direction standpoint.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: This is sort of a combination of the ninth question, risk mitigation, but it's a study and it has to do -- Dr. Newman alluded to this. I mean, too often, there are risk mitigation strategies or whatever that make sense but don't work at all. I mean, the elephant in the room here is massive advertising. Dr. Martinez pointed out this morning that whereas you'd expect that two-thirds of the kids with asthma would be on

ICS, only about one-third of them are. And someone then later mentioned that you see lots of Advair ads but not too many Flovent ads.

So given that FDA has the authority to regulate drug advertising as a function of what is in the label, I would like to see an experiment which the FDA would have to initiate to figure out a way that that part of the label, the thing that we actually voted on in questions three and four that says you should only use this when there's been an adequate dose of ICS, be made much more prominent both in the doctor ads that we all see and in the direct-to-consumer advertising, just as a warning against what appears to be an inappropriate number of children, and I'm sure adults, getting bumped up to these combined drugs when they haven't in fact been tried in an adequate test of ICS.

So I think this would be an experiment the FDA could initiate and measure

whether or not it succeeded in lowering the percentage of people who were in many cases inappropriately using a combination drug when they would benefit as well or better because it would be safer from an ICS at a higher dose.

DR. SWENSON: Dr. Knoell?

DR. KNOELL: I'd like to -- I think Dr. Schoenfeld kind of addressed this but I want to take it a step further. So yesterday Dr. Graham's presentation to me was a revelation. I'm not a statistician, epidemiologist or anything, but it suggested to me that the current construct by which FDA mandates studies being done by sponsors does not take in account how to effectively determine risk and so then what I think I heard ensuing from that conversation was that to do that, we have to first predict what that risk is and then are the numbers even possible to be done. So if we reconfigure these studies to determine risk, can we manage those studies?

So it's really a question, can we do that effectively?

And the second comment I want to make is that following up on the compliance issue, it's already been stated but to state it again for question ten, I think we need to invest a lot more time into understanding compliance issues in these specific subpopulations that seem to be more adversely effected by the medications. That in conjunction with continued studies in pharmacogenomics which are ensuing, I think years from now could give us much more effective tools and be more precise in prescribing patients effectively to medications.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I'm going to echo what Dr. Kramer said about looking at multiple outcomes in view of what Dr. Martinez described to us about the heterogeneity of the population, add to that quite a few, actually baseline

characteristics, to look for that more individualized path of therapy because there's so many sub groups of patients. The adherence, I mentioned before, the other thing is that all of the clinical trials presented, were no more than a year in duration. This is a chronic disease. Let's try to have a study that's at least two years in duration while we're measuring the adherence compliance.

DR. SWENSON: Dr. Hennessy?

DR. HENNESSY: This is a situation where the safety outcome that we're interested in is essentially the same as the efficacy outcome that we're interested in that is a serious -- the frequency of serious asthma-related outcomes, and because of that, I think randomization is essential.

I'm skeptical about the value of the information that could be obtained from non randomized sources including registries. I think SMART is a good model. I think that such a study should focus on clinically

important outcomes and not measure everything as is typically done in preapproval RCTs.

I think that open label is okay and I think that innovative strategies to follow patients such as collaboration with health plans and the design and conduct of the study will make large studies feasible with the budget that could be allocated to those.

DR. SWENSON: Well, at this point, we're drawing to an end and I would like to ask my co-chair, Dr. Rappley, to summarize some of the ideas that have been stated to leave us with a final overview of the way to go.

DR. RAPPLEY: So I've been taking notes since we began voting actually about things that people have suggested need to be studied further. Probably the most often stated further need are studies that are designed to adequately address the question of safety with the long-acting beta agonist and particularly in vulnerable populations, 4 to 11, 12 to 17 and African Americans. And then beyond that,

studies that study actually the effectiveness of mitigation strategies for risk, studies that look at new onset use of what evolves as patients begin treatment with the combined products, studies that look at the differential mechanism between salmeterol and formoterol and whether or not they can be actually considered as a class; that there be not only more comprehensive measures in our studies about functional improvement in asthma but that we study these measures to bring some credibility, some validity to these as endpoints for future study; that we look at the etiology of the drug related and/or condition related deaths in asthma; that we have studies to understand and further encourage compliance; that our studies link severity level to both benefit and to risk seen in asthma outcomes; that there be a registry for asthma deaths; that there be perhaps a registry for asthma -- various asthma treatments; and that there be a comprehensive evaluation of observational datasets which we

know are widely available, Medicaid, large HMOs, primary care research networks, to understand and glean from these both long-term and short-term outcomes in asthma.

In addition to these things, people talked about the importance of our own education efforts. In some ways, this is what physicians need to do to help physicians be more effective in practice particularly around adherence to guidelines and standards of care, in particular the use of LABAs only with -- in addition to the use of inhaled corticosteroids, and that we should make a concerted effort, an explicit effort, to clarify for the public why it is that we recommend the use of combination agents and do not recommend the use of single agents.

We had a call for a visible effort from industry, so more than a commitment today, but a visible effort that a year from now we can say we have seen a significant difference in the way the industry promotes

adherence to guidelines and the combo agents as a step two and the inhaled corticosteroids as a step one.

And there has been also discussion among Committee members that we would like further updates, that we do not want to end this issue with this meeting and that we would like to have reports back from the agency to our committees and we had then the suggestion that there could even be expedited reporting of data to the agency from the sponsors as it becomes available in relevant data, and then that be tracked back to the Committees in a timely manner.

DR. SWENSON: Thank you, Dr. Rappley. So this will end, then, this meeting, and I'd like to just thank all involved -- the sponsors for their excellent presentations, committee members for all of these fantastic questions and further directions, and to the agency and to the public.

Before I finally close, I need to

make an announcement that there will be an impromptu press conference, or rather, a press gathering in the Randolph Room, which is just across the hall from this meeting room, and it's open to any interested parties.

And with that, again, my thanks to you all, and this meeting is adjourned.

(Whereupon, at approximately 3:58 p.m., the MEETING was adjourned.)

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