DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS

ADVISORY COMMITTEE

Wednesday, July 13, 2005

8:00 a.m.

Gaithersburg Hilton
The Ballrooms
620 Perry Parkway
Gaithersburg Maryland

PARTICIPANTS

Erik R. Swenson, MD, Chairman
Teresa Watkins, R.Ph., Executive Secretary

MEMBERS:

Mark L. Brantly, M.D.
Steven E. Gay, M.D., M.S.
Carolyn M. Kercsmar, M.D.
Fernando D. Martinez, M.D.
I. Marc Moss, M.D.
Lee S. Newman, M.D.
Calman P. Prussin, M.D.
Michael Schatz, M.D.
David A. Schoenfeld, Ph.D.

CONSULTANTS AND GUESTS (VOTING):

Karen Schell, RRT, Consumer Representative
Jacqueline S. Gardner
Nancy J. Sander, Patient Representative

GUEST SPEAKER (NON-VOTING):

Christine Sorkness, Pharm.D.

FDA STAFF:

Robert Meyer, M.D.
Badrul Chowdhury, M.D.
Ann Trontell, M.D., M.P.H.
Sally Seymour, M.D.
J. Harry Gunkel, M.D.
Eugene J. Sullivan, M.D., FCCP

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

DR. SWENSON: Good morning, everyone. I am Dr. Erik Swenson. I am the Chairman of this Pulmonary-Allergy Drug Advisory Committee meeting, meeting today here to discuss the implications of recently available information and data related to the safety of long-acting beta agonist bronchodilators.

Before we go around and introduce the members of the panel, I would like to ask them to remember that we have microphones here that have dual functions. One is to show that you wish to raise a question. That is the "request" option there; then to speak is on the right-hand side. So, in raising questions, would you please first hit the "request" button. We will be monitoring and call you in turn. Please do remember to use the "speak" button when you do speak since transcribers will need to hear you on the tapes.

With that having been said, I would like to have members of the panel here go around and introduce themslves. We will start with Bob Meyer

and have you introduce yourself in turn.

Introductions

DR. MEYER: I am Bob Meyer. I am the Director of the Office of Drug Evaluation II in the Center for Drugs.

DR. CHOWDHURY: I am Badrul Chowdhury, the Division Director, Division of Pulmonary and Allergy Drug Products.

DR. TRONTELL: Ann Trontell, the Deputy Director of the Office of Drug Safety.

DR. SULLIVAN: My name is Gene Sullivan. I am the Deputy Director of the Division of Pulmonary and Allergy Drug Products.

DR. SEYMOUR: I am Sally Seymour, medical officer in the Division of Pulmonary and Allergy Drug Products.

DR. GUNKEL: Harry Gunkel, medical officer in the Division of Pulmonary and Allergy Drug Products.

MS. SANDER: Nancy Sander, President, Allergy and Asthma Network, Mothers of Asthmatics.

DR. GARDNER: Jacqueline Gardner,

Professor of Pharmacy at the University of Washington, and a member of the Drug Safety and Risk Management Advisory Committee to FDA.

DR. SCHATZ: Michael Schatz. I am an allergist/immunologist from Kaiser Permanente San Diego.

MS. WATKINS: I am Teresa Watkins, executive secretary for this committee.

DR. GAY: I am Steven Gay. I am medical director of critical care support services, assistant professor at the University of Michigan.

DR. MOSS: Marc Moss, associate professor of medicine, Emory University in Atlanta.

DR. NEWMAN: Lee Newman, professor of medicine, National Jewish Medical and Research Center and University of Colorado Denver.

DR. BRANTLY: Mark Brantly, professor of medicine, University of Florida.

DR. MARTINEZ: I am Fernando Martinez, professor of pediatrics at the University of Arizona.

DR. KERCSMAR: Carolyn Kercsmar, professor

of pediatrics, Rainbow Babies and Children's Hospital, Cleveland, Ohio.

MS. SCHELL: I am Karen Schell. I am the consumer representative. I am a respiratory therapist from Emporia, Kansas.

DR. PRUSSIN: Calman Prussin. I am senior clinical investigator in the Laboratory of Allergic Diseases, NIAID, NIH.

DR. SCHOENFELD: David Schoenfeld, professor of medicine at the Harvard Medical School and professor of statistics at the Harvard School of Public Health.

DR. SWENSON: Thank you. I would like now to call Maryanne Killian, of the FDA. She has a statement on conflict of interest to read.

Conflict of Interest Statement

MS. KILLIAN: Good morning, everybody. The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act. With the exception of the industry representative, all members of this

committee are special government employees or regular federal employees from either agencies, subject to the conflict of interest laws and regulations.

FDA has determined that the members of this advisory committee are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC Section 208 and 21 USC Section 355(n)(4) which applies to FDA people. Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them including those of their employers, spouse or minor child related to the

discussions on July 13, 2005 regarding implications of recently available data related to the safety of long-acting beta agonist bronchodilators, and on July 14, 2005 regarding the continued need for the essential use designation of prescription drugs for the treatment of asthma and chronic obstructive pulmonary disease under 21 CFR 2.125. These interests may include investments, consulting, expert witness testimony, contracts, grants, CREDAs, teaching, speaking, writing, patents and royalties and primary employment.

In accordance with 18 USC Section 208(b)(3), four waivers have been granted to the following participants. Please note that all interests are in firms that could be potentially affected by the committee's deliberations. With regard to the July 13th meeting, Dr. Carolyn Kercsmar for activities on a speaker's bureau. She receives less than $10,001 per year for a grant which is valued at less than $100,000 per year, and for a grant for which the firm supplies products worth approximately less than $100,000 per year;

Ms. Nancy Sander for ownership of stock currently valued at between $25,001 and $50,000, and for unrelated advisory board activities for which she receives less than $10,001 per year; Dr. Steven Gay for speaker bureau activities with four firms, from three of which he receives less than $10,001 per firm per year, and one for which he receives from between $10,001 to $50,000 per firm per year. We would also like to disclose that Dr. Erik Swenson owns stock worth less than $5,001. A waiver under USC 208(b)(3) is not required because the de minimis exemption under 5 CFR 2640.202 applies.

With regard to the July 14th discussions, Dr. Carolyn Kercsmar for activities on a speakers bureau. She receives less than $10,001 per year for two grants which are valued at less than $100,000 per year, and for a grant for which the firm supplies products worth approximately less than $100,000 per year. She also owns stock less than $5,001. A waiver under the USC 208(b)(3) is not required because the de minimis exemption under 5 CFR 2640.202 applies. Dr. Fernando Martinez for

his membership on a speakers bureau. He has not lectured or received remuneration in the past 12 months, and for membership on a related advisory board. He has not participated or received any remuneration to date. Dr. Michael Schatz for his activities on a speakers bureau. He receives less than $10,001 per year, and for a grant for which the firm supplies product worth approximately less than $100,000 per year. Miss Nancy Sander for ownership of stock currently valued between $25,001 and $50,000, and for unrelated advisory board activities for which she receives less than $10,001 per year. Miss Sander also owns stock worth less than $5,001, again a de minimis waiver is not required because 5 CFR 2640.202 applies. Dr. Steven Gay for speakers bureau activities with five firms, from three of which he receives less than $10,001 per year, and two of which he receives from $10,001 to $50,000 per firm per year.

We would also like to disclose that Dr. Marc Moss' spouse owns stock less than $5,001. A waiver under 18 USC 208(b)(3) is not required

because the de minimis exemption under 5 CFR 2640.202 applies.

A copy of the written waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building, 5600 Fishers Lane, Rockville, Maryland.

In addition, Dr. Christine Sorkness is participating as FDA's invited guest speaker on July 13th. She would like to disclose that she is a researcher with regards to GlaxoSmithKline's Advair and Novartis' formoterol. She also lectures for GlaxoSmithKline concerning Advair and receives less than $10,000 per year.

Lastly, Dr. Theodore Reiss is the industry representative on the committee at the meeting. He is acting on behalf of all related industry. He is employed by Merck. Thank you. I am done.

DR. SWENSON: Thank you, Miss Killian. I would like now to turn the microphone over to Dr. Robert Meyer of the FDA.

DR. MEYER: Thank you. Prior to more formal introduction by Dr. Chowdhury, I wanted to, first off, thank the advisory committee in advance for your attendance today and for what I am sure will be a very careful deliberation.

One of the things I wanted to mention was that there was some speculation in the trade press yesterday that there was a very specific purpose and outcome hoped for by the agency in holding this meeting today. I just wanted to be clear that the FDA looks forward to a very open discussion of the data available on the safety experience with the long-acting beta agonists and any potential future regulatory actions that might be recommended coming out of this committee. So, thank you very much for your attendance today.

DR. SWENSON: Thank you, Dr. Meyer. Now Dr. Chowdhury, from the FDA, is going to give us some introductory remarks pertinent to our discussion today.

FDA Introductory Remarks

DR. CHOWDHURY: Good morning. Honorable

Chairperson, members of the Pulmonary-Allergy Drugs Advisory Committee, representatives from GSK and Novartis and others in the audience, I welcome you to this meeting.

In this brief presentation I will introduce you to the subject matter of this advisory committee meeting. Members of the committee, the objective of this meeting is to discuss the implications of the available data related to the safety of long-acting beta agonist bronchodilators. There are two long-acting bronchodilators marketed in the United States that will be discussed in this meeting. These are salmeterol from GSK and formoterol from Novartis. Products containing salmeterol and formoterol are indicated for use as bronchodilators in patients with asthma and COPD as maintenance treatments.

These are effective drugs and form important components of the treatment options available for patients with asthma and COPD. But an important array of adverse effects that has been observed with these drugs is the occurrence of

severe asthma exacerbation. The intent of this advisory committee meeting is to discuss this specific finding of severe asthma exacerbation related to these two drugs. Since the available data pertain to asthma, the focus of this meeting is on asthma and not COPD.

Surrogates of short-acting beta agonist bronchodilators, such as albuterol, is not a subject of this meeting. As you discuss and deliberate on the safety of thee two drugs, keep in mind the well-established efficacy of these drugs because the use of these drugs, like any other drug, is dependent on the risk/benefit ratio.

As you can see in the agenda, the first presentation will be by Dr. Christine Sorkness. Dr. Sorkness is a professor of pharmacy and medicine in the University of Wisconsin. She will give an overview of long-acting beta agonist bronchodilators. We are very fortunate that Dr. Sorkness, and expert in pharmacological drugs used in the treatment of asthma, has agreed to speak at this meeting. I thank her on behalf of the agency.

Following Dr. Sorkness, GSK and Novartis will make presentations on salmeterol and formoterol respectively, followed by FDA presentations on these two drugs. This will be followed by an open public hearing and committee discussion.

As you hear these presentations you will note that the safety signal of severe asthma exacerbation with salmeterol was seen in postmarketing studies, specifically the recently halted large controlled study called the salmeterol multicenter asthma research trial, acronym SMART, conducted by GSK. In contrast, the safety signal of severe asthma exacerbation with formoterol was seen in the studies conducted by Novartis to support registration of formoterol in the United States. Novartis also conducted a Phase 4 study with formoterol that did not show a clear signal of severe asthma exacerbation, but the formoterol Phase 4 study was much smaller compared to the SMART study.

We are choosing to have this meeting now

because all pertinent data on salmeterol and formoterol have only become recently available. We also decided that it would be fruitful to discuss these two related drugs together in one meeting. Although salmeterol has been approved for marketing in the United States since 1994, the study relevant to this meeting, the SMART study, was halted by GSK in January of 2003 and the data has been recently fully analyzed.

Formoterol was approved for marketing in the United States in 2001. The Phase 4 study for formoterol was completed in March, 2004 and the data from the study also has been recently analyzed.

The significant regulatory actions that the FDA has taken so far pertaining to these two drugs, based on the available data, are in cooperation of the results of the SMART study in all salmeterol-containing product labels, including the addition of a boxed warning, and not approving formoterol 25 mcg twice daily dose for marketing in the United States. Formoterol is currently

approved at a dose of 12 mcg twice daily. Please note that the formoterol drug label does not currently have warnings similar to salmeterol because of lack of specific data related to the marketed formoterol 12 mcg twice daily dose.

In the presentations from the industry and the FDA you will see the data that led to the agency regulatory actions. As you hear the presentations, I request that you keep in mind the questions that are in the FDA briefing book and also attached to the agenda since you will discuss and deliberate on these questions later in the day.

Here are the four questions that you will be asked to discuss and deliberate later in the day today. Question one, the product labels of salmeterol-containing products have been modified to include warnings related outcome the SMART study. Based on currently available information, what further actions, if any, do you recommend that the agency take to communicate or otherwise manage the risks of severe asthma exacerbations seen in the SMART study?

Based on the currently available information, do you agree that salmeterol should continue to be marketed in the United States?

Question two, the label of the formoterol-containing product does not include warnings comparable to the warnings that are present in the salmeterol-containing products. Based on the currently available information, should the label of formoterol-containing products include warnings similar to those in the salmeterol label?

Based on the currently available information, do you agree that formoterol should continue to be marketed in the United States?

Question three, what further investigation, if any, do you recommend to be performed by GSK that can improve the understanding of the nature and magnitude of the risk of salmeterol?

Question four, what further investigation, if any, do you recommend to be performed by Novartis that can improve the understanding of the

nature and magnitude of the risk of formoterol?

These are the four questions. We look forward to an interesting meeting and, again, I thank you for your time, effort and commitment to this important public health service. Thank you.

DR. SWENSON: Thank you, Dr. Chowdhury. At this point we would like to invite Dr. Christine Sorkness who was just introduced. She has been kind enough to give us a broad overview of these drugs and I would like to turn the podium over to her.

An Overview of Long-Acting Beta Agonists

DR. SORKNESS: Good morning. I would first like to thank Dr. Chowdhury and Dr. Sullivan for inviting me to speak this morning, and most of all, for gathering this group of both clinicians, researchers, industry colleagues and the committee to review what I believe to be an incredibly important topic. The risk versus benefit considerations for the long-acting beta agonists are the topic at hand and the committee has been asked to discuss the implications of the available

data related to the safety of long-acting beta agonists, as Dr. Chowdhury articulated.

It is a little bit awesome to review this topic because of its breadth and depth, and also because I know many of the committee members and would acknowledge that they probably know more than I do about this particular topic. So with that caveat, I am going to indicate that I am just going to review and try to set a tone for the discussions and in particular anchor some of the available data, at least as I see it as a researcher and a clinician, that you might use to answer the questions that you have been charged with.

The specific objectives that I have been asked to address are to provide an overview of the clinical pharmacology of the long-acting beta agonists; to discuss the selection of therapeutic outcomes which I believe are relevant for the assessment of risks versus benefits of the long-acting beta agonists; to review selected clinical trials, selected because there are so many which provide insight into the risk/benefit of the

long-acting beta agonists; and to outline the controversies and the remaining questions which I believe are related to the role.

First an overview of the clinical pharmacology of albuterol, salmeterol and formoterol. We have come a long way from ephedra from China and its pharmacologic properties many, many years ago to, certainly ephedrine and epinephrine and isoproterenol. The three major drugs that we use in our therapeutic armamentarium for asthma right now are albuterol, salmeterol and formoterol. You can see in common that they all have a simple catecholamine ring, and there has been great novelty from the industry of adding a variety of different side chains to these products to affect their oral versus inhalation efficacy and, in particular, if you look at salmeterol and formoterol you see that there are very large side chains that have been attached to the basic molecule of albuterol. This has allowed these two products to have an extended duration of action.

Both salmeterol and formoterol are highly

lipophilic products, which may explain some of their long duration of action, salmeterol more than formoterol. We know that salmeterol binds within the ligand binding cleft of the receptor which probably allows sensitivity stimulation of the receptor and its long duration, and there are other speculated mechanisms of action for the long duration of formoterol. Formoterol is a raceme and only the RR and N tumor is active.

If you were to compare very globally the beta adrenergic agents, this table is probably relevant. Most of the pharmacologic studies relate molar potency of these products to isoproterenol, which is designated as a potency of 1. You can see that both formoterol and salmeterol are more potent products than isoproterenol. The pharmacologic profile of the drugs is illustrated, with isoproterenol an formoterol classified as full agonists and albuterol and salmeterol as partial agonists.

You can see that in comparison to isoproterenol as its comparator, albuterol,

formoterol and salmeterol all have the luxury or beta2 selectivity which is acknowledged to allow these drugs to have primarily effects on the lung versus the cardioselective effects that we see primarily with activation of the beta 1 receptors.

The duration of action clearly is different in these agents and, because of the long side chains and mechanisms of action of formoterol and salmeterol, we have known that these are the longest acting inhaled bronchodilators on the market today, with durations of action of at least 12 hours after a dose, and the bronchoprotective effects, which specifically in this slide refer to the prevention of bronchoconstriction induced by exercise or non-specific bronchial challenges such as methacholine, have, indeed, a long bronchoprotective effect.

If you were to look at a more direct clinical comparison of formoterol and salmeterol based specifically on information in the package inserts, it is believed that equipotent bronchodilating doses of formoterol and salmeterol

are listed as above, based specifically on the dosage form by which they are delivered. So we believe, at least in clinical practice, that 12 mcg of Foradil aerolizer is clinically bronchodilating equipotent to 50 mcg delivered by Serevent Diskus. In order to deliver these equipotent doses, the recommended inspiratory flow rate is acknowledged to be about 60 L/min for both products over a time course of 2-3 seconds. As you might expect, particularly because these drugs have been FDA approved for individuals with much more severe broncho-obstruction such as in COPD, probably an inspiratory flow rate much below that can get adequate delivery of drugs.

Both of these drugs are classified as pregnancy category C and, indeed, enjoy the same FDA approved indications based on the package of information submitted to the FDA, the only distinction being that salmeterol is approved for the treatment of asthma and prevention of bronchospasm for children over 4 years of age and 5 years on formoterol. Both of these agents have

been approved for EIB prevention and for maintenance treatment of COPD, which is not part of the agenda today.

Now, the differentiation of formoterol and salmeterol, by and large, comes down to its acknowledged difference in onset of action. You can find many, many studies that would classify different pharmacologic profiles. In summary, formoterol probably achieves 80 percent of the maximum bronchodilation within 5-10 minutes. It is thought to have an onset of action quite comparable to albuterol and acts within 3 minutes. For salmeterol most of the data suggests that 90 percent maximum bronchodilation occurs after one hour, with a median time to significant bronchodilation of 30-40 minutes, and an onset certainly at a time point of about 10 minutes.

This is a simple cartoon that segues to the issue of the long-acting beta agonists themselves in combination with clucocorticoids. This is a cartoon that suggests the proposed molecular interaction between the long-acting beta

agonists and the inhaled corticosteroids. The long-acting beta agonist, through their activation of the beta adrenergic receptor with adenylyl cyclase, cyclic AMP, protein kinase A and mitogen activated protein kinase may actually prime the glucocorticoid receptor for greater nuclear translocation and affinity for the binding to the glucocorticoid regulatory element, which is designated in this slide as GRE. Therefore, it has been speculated by a variety of pharmacologic models--Ikleburg[?] and others who have done very elegant work--that actually the anti-inflammatory effect of glucocorticoids can be enhanced with the combination of long-acting beta agonist and, clearly, that is certainly the rationale that brought the combination products to the marketplace.

Now, when we talk about risks versus benefits of any agent, it is best to talk about the outcomes of interest. I am going to preface my remarks by the fact that I think the medical community and patients have all been led to hope

for a 100 percent active and effective drug with absolutely no side effects. I quite honestly believe that to not be realistic. Therefore, when we talk about risk/benefits we need to put in perspective and weigh those issues, and I think it is important to recognize that we may have very safe medications that really have very poor clinical efficacy, and I would suggest that they have a distinct risk in their own right by their inability to treat the disease at hand.

So, I am going to try to illustrate some issues about what I believe to be important outcomes and talk about some of the clinical trials to date that teach us lessons about this as applying this drug class to asthma.

We traditionally have used lung function measures for management of asthma, both from the perspective of clinical decision-making and clinical research. There are many longitudinal studies of lung health that have been enhanced by measurements of lung function, particularly FEV

1

and FEV 1/FEC ratio. Clearly, it has been

acknowledged that the gold standard for trial entry for the pivotal trials reviewed by the FDA have been traditional FEV
1's of 60-80 percent predicted with 15 percent reversibility. Therefore, there have been very uniform population groups that have been studied in our clinical trials. I would actually conjecture now, and will come back to it, that we may need to broaden that a bit to capture a more generalizable population.

Clearly, lung function measures have been primary outcomes to measure efficacy because we can standardize those procedures both on site and with home measurements, and we have grown to believe that we can minimize variability around the measurements and can really get a handle and our arms around what outcomes are important. Please recognize as I talk about different outcomes in asthma, I am not dispelling at all the value of lung function measurements. I think they are still critical but I don't believe that they are enough.

Let's start talking about what I believe to be illustrative studies. This is a study

published by the Asthma Clinical Research Network in which I am one of the investigators, and it was affectionately called the SOCS trial. This is a study that was intended to ask the question that in a patient who was well stabilized on an inhaled steroid and representative triamcinolone, and that had pretty stable FEV
1's and peak flow variability, could this patient basically be transferred to placebo and do equally well; be converted to a salmeterol product and do equally well; or did they need to maintain continuance on an inhaled steroid as represented by triamcinolone?

This is a study that enrolled individuals whose mean FEV1 was 93 percent predicted, had very low peak variability of about 10 percent, and during the run-in period showed very good asthma stability. The primary outcome of this study was morning peak flow. That was selected because of experience that the Asthma Clinical Research Network had with what we believe to be an effect size that we could power our study of a difference of about 25 L/min, and because that effect size

correlated with other more clinically robust endpoints in a variety of trials.

I think you can see that if you look at the primary outcome of this trial of AM peak flow you wee in the run-in period that all of the patients in ultimately the three arms improved during the run-in with triamcinolone, as you would expect. You see the placebo group, once it was randomized at six weeks, had deterioration in that outcome; whereas, the triamcinolone and salmeterol groups both had maintenance and actually improvement in the primary outcome of peak flow, and there was not statistically significant difference between those two arms in this particular outcome.

Now, there was obviously a variety of secondary outcomes in this trial. You can see that on the basis, in particular, of some markers of inflammation that there was both a clinically and statistically significant difference in favor of the inhaled corticosteroids. Because of the multiple comparisons used by the statistician, a p

value of 0.016 was that which was deemed to be of statistical significance.

This is important in that it translates to another very important secondary outcome of this trial, that being defined as treatment failure rates, on the left, and asthma exacerbation rates, on the right. First, asthma exacerbation rates were defined as increases in albuterol use, decrease in peak flow, and the need for oral corticosteroids. You can see with this particular outcome that triamcinolone is the only one by the Kaplan-Meier survival curve that, in essence, did not have significant asthma exacerbations. Very similarly, if you looked at treatment failure rates, which was defined as an FEV1 less than 50 percent predicted, at least one course of prednisone, the occurrence of emergency room or urgent care visits or hospitalization, the same trend could be seen. The triamcinolone was very effective in preventing treatment failure rates but salmeterol was quite comparable to placebo.

The summary for the ACRN investigators was

that patients with persistent asthma, well controlled by low doses of an inhaled steroid cannot be switched to salmeterol monotherapy without risk of clinically significant loss of asthma control. I think this is one of the studies that clearly the asthma community has endorsed to support the fact that long-acting beta agonists in asthma should not be used as monotherapy, and I don't believe that there is particular debate on this issue and I think there are many studies that illustrate similar outcomes.

This study is also important in that it shows clear disparity between lung function measures and other outcome measures, and leads us to the conclusion from this study that multiple measurements and dimensions of control are needed to adequately assess therapies.

Therefore, I think, whether we broach studies that are industry sponsored or NIH sponsored, we are beginning to endorse more composite measures of asthma control. This would include days of asthma control; treatment failure

and asthma exacerbation criteria, as I have shown in this study and many others. I would make as a caveat that it becomes oftentimes very difficult to compare trials because the specific definitions for treatment failure versus asthma exacerbations and mild, moderate and severe exacerbations may be a little bit different. So, it is important for us to anchor the definitions when we evaluate.

Other composite measurements have actually been improvements or shifts in NAEEP defined NAEEP defined asthma severity classification; the achievement of total control or well controlled status, as defined by GINA and applied to the GOAL study; and certainly a variety of more patient specific surveys of asthma control and quality of life that have become important secondary outcomes in our clinical trials.

Now, in reflecting upon the issue of more composite clinical outcomes, the question needs to be raised in applying an appropriate risk/benefit relationship and assessment of how much benefit can actually be achieved by the combination of inhaled

steroids and long-acting beta agonists. I am going to focus my remarks on the combination because I have told you that at least my belief is that asthma is best treated by combination and, therefore, the relevant studies are those that use that.

A fairly early study that began to address the role of inhaled steroids and long-acting beta agonists in combination is the OPTIMA trial, entitled, low dose inhaled budesonide as a representative inhaled steroid an formoterol as a representative long-acting beta agonist.

This study had both a group A and a group B. I am going to focus on group A as a representative trial of taking patients naive to being on inhaled steroids and ultimately, after a one-month run-in in which they were qualified to be in this trial, were then continued on placebo, Pulmicort or Oxis, as formoterol is called. Therefore, they continued on beta agonists alone versus being randomized to Pulmicort 100 mcg BID and Oxis placebo or Pulmicort 100 mcg BID and

active Oxis 4.5 mcg BID.

The primary outcome of this trial was severe exacerbation, designated by the arrow. This was defined as the need for oral corticosteroids or admission to a hospital or an emergency room visit or substantial decrease in peak flow. This study group enrolled patients who were 12 years of age and older, not on inhaled steroids, who had to have an FEV 1 of at least 80 percent predicted post bronchodilator, and actually enrolled a pre bronchodilator mean FEV 1 group of about 90 percent.

These are the two primary outcomes of this particular study. If you look on the left-hand side in panel A, this is the Kaplan-Meier survival curve and you can see that both the budesonide alone versus the budesonide in combination win formoterol did much better in preventing the time to the first severe asthma exacerbation as compared to the placebo group, which is the last curve that you see on the slide. When you plot this, on the right-hand side of the slide you see that actually the two active treatments were, indeed, better than

placebo but were quite comparable to each other. However, if you look at the other important outcome of pulmonary function test, the morning peak expiratory flow, you see in the top curve that the combination product is superior to both budesonide and placebo. So, whereas by one outcome the exacerbation rates of the two active products were not statistically significant, when you add in another important secondary outcome the combination, indeed, showed better outcomes.

Now, this same issue of looking at prevention of asthma exacerbations has been published by many, many authors. This is just a representative study which looked at an analysis of asthma exacerbations, looking at available studies of higher dose fluticasone versus the addition of salmeterol to low dow fluticasone.

If you look at this particular slide, which is the probability of the time to the first exacerbation, you see that the top curve, in green, is salmeterol and, in red, the combination, and the combination was clearly superior in the outcome of

time to first asthma exacerbation compared to the long-acting beta agonist alone.

The analysis in this study group culled out the different Ns of the spectrum of pulmonary function impairment at baseline. As I mentioned, typically the pivotal trials enroll patients that have baseline FEV
1's pre bronchodilator between 40-85 percent predicted. That is what you see on the left-hand side of all-comers that enrolled in those pivotal trials. If you, instead, break down patients who present with less bronchoconstriction at baseline, for example, 60-85 percent predicted versus 40-60 percent, you see that the trends are not different and that either way, depending upon the severity of obstruction in these patients, the trend of the benefit of combination certainly could be seen.

Now, the FACET trial also showed I think a very important lesson about looking at the outcome of severe exacerbations and relationships of dose-response curves with inhaled steroids, as well as the benefit of long-acting beta agonists. This

goes back to budesonide and formoterol as the representative drugs in this study, and in this study severe exacerbations were defined as a need for oral steroids or a decrease in peak flow to more than 30 percent baseline. So, severe exacerbations here are predominantly due to the need for oral beta agonists.

This is a large trial that randomized individuals to one of four arms. If you look at the far left, in green is the budesonide 200 mcg or low dose inhaled steroid group; the purple bar is budesonide 200 mcg a day plus formoterol; in yellow, a higher dose of budesonide alone versus, in the orange bar, the addition to formoterol. I think what you can see is the very logical dose-response curve that 800 mcg of budesonide fared better than 200 mcg of budesonide but, very importantly, you can see that the prevention of severe exacerbations in both groups could be enhanced by the addition of formoterol. So, again, another study that suggests to us that combination therapy can achieve the prevention of asthma

exacerbations.

Now, in brevity, rather than showing you the individual studies of exacerbations to date published, I am going to take advantage of a meta-analysis, published by Sinn and others in JAMA, in 2004 that looked at a systematic review and meta-analysis of a variety of pharmacologic therapies to reduce exacerbations.

This study clearly reviewed all of the drugs that we know that are on the marketplace but I am specifically going to look at two of the analyses. This is the effect of long-acting beta agonists alone on exacerbations and the distinct trials that the meta-analysis chose. You can see that the majority of these studies favored a long-acting beta agonist over placebo, and a pooled analysis showing a relative risk and confidence interval that favors the long-acting beta agonists.

This is the analysis that looks at many of what I believe to be the paradigm shifting trials that showed the addition of long-acting beta agonists to be better than either doubling or more

than doubling the inhaled steroids, and includes the Matz and O'Byrne studies and Pauwels studies that I shared with you earlier. I think you can see that we have at least somewhat mixed results here. Certainly the majority of trials favor the combination of inhaled steroids and long-acting beta agonists together versus favoring the high doses of steroids. Some of them are right on the line. The pooled summary obviously, here by this graph, favors the steroids and the long-acting beta agonists.

I would suggest that certainly some of the differences are certainly on the basis of study design, size of study, construct, and so forth but, again, I think the meta-analysis supports the individual trials as far as evidence that suggests benefit of the combination.

Now, in switching gears, besides asthma exacerbations, I think that the issue of the capture of asthma control, as has been defined by GINA and the NAEEP, is a very important outcome that we have begun to carefully think about and to

posture in our individual trials. The GOAL trial asked a very simple but important question, is GINA NIH guideline based control achievable, and in what proportion of patients with a salmeterol-fluticasone combination compared with fluticasone alone?

So, this is going beyond the issue of just looking at exacerbations but overall asthma control as defined by the guidelines. You can read this. There is both total control and well controlled, and it basically reflects what we, as clinicians, hope to achieve for our asthma patients. And, the question is can this be achieved by the therapies that we have at hand?

The GOAL study design was very complex. It was a year study of three strata of patients based on whether they were either corticosteroid naive or free for six months; whether they were on a modest dose of a baclomethasone equivalent or higher dose of a beclomethasone equivalent. These were individuals that had to be at least 12, not well controlled in the run-in period, and showed

reversibility of 15 percent. They were randomized to either the salmeterol-fluticasone combination or fluticasone alone via diskus, with a dose based on the stratum.

During this complex design in phase 1, the doses were either stepped up every 12 weeks until total control was achieved or a maximum dose was reached. In study phase 2 a dose of total control or a maximum study dose was continued for 52 weeks.

It is important to recognize that all the patients in this trial deserved to be on control therapy. Their FEV
1's were about 75-80 percent predicted. They had very, very obvious bronchodilator reversibility, averaging about 20 percent, and what I would call were young adults. So, whatever the stratum, these individuals deserved to be stepped up with the therapies that were used.

These are the patients who achieved well controlled status. The triangles in dark are the combination; the open circles are fluticasone alone. You can see the run-in phase versus phase 1

versus phase 2 on this graph. You can see that both study groups had a fairly brisk improvement in achievement of well-controlled status. This continued through the 52 weeks of the trial and was achieved by both study arms, but was achieved to a statistically significant greater extent with the combination therapy.

Also importantly is exacerbation rates as were studied in this trial as a secondary outcome. This exacerbation was defined in this study as either a burst of steroids or an ER or hospitalization. You can see whether it was steroid naive, the low dose inhaled steroid or the moderate dose inhaled steroid stratum. Clearly, all groups showed the trend that the combination therapy was better at achieving prevention of exacerbation rates as defined by the GOAL investigators.

The results of GOAL are very important in that significantly more patients achieved control with combination versus fluticasone in each stratum and in each stratum the time to achieve the first

individual week of well-controlled asthma was significantly lower with combination than fluticasone alone. More patients achieved control at the same or lower dose of inhaled steroid in each stratum for combination again verifying what had been previously published on the inhaled steroid-sparing effect.

I think very importantly in looking at outcomes, we know that the majority of patients who achieved well-controlled asthma in phase 1 maintained the status when assessed in the last 8 weeks of the study. But, also, there were some patients that, additionally, were able to gain control with sustained therapy. So, there may be, very importantly, subjects who initially are able to gain control but others that require longer exposure to achieve this particular outcome.

Now I am going to switch gears a little bit and talk briefly about a pediatric trial. One of the things, at least in my mind, is that most of the data that we have in looking at inhaled steroids and long-acting beta agonists, whether

they be as entry therapy or as add-on therapy in preventing the addition of inhaled steroids, has predominantly been done in adults. Even those studies which have enrolled individuals greater than 12 years in age and up in general have not had a sizeable enough cohort of the 12-18 population that really have led to what I believe is a substantive subanalysis. So, most of what we have I believe is in adult studies, and I think we will see more pediatric studies in the future.

This is a study that was recently presented at the American Thoracic Society meeting this summer, and was conducted by the CARE network of the NHLBI-sponsored network. It is a one-year prospective comparison of three control or medications for the treatment of mild or moderate persistent asthma in children.

In brief, the study schematic is a proof of study concept. All children were in a one- or two-week run-in period and then were either randomized to an inhaled steroid alone, an inhaled steroid at half the dose in combination with a

long-acting beta agonist in comparison to a leukotriene receptor antagonist. In order to achieve this particular proof of concept, the ICS group received fluticasone by morning and evening diskus and an evening capsule placebo. The middles group of combination, and what I am going to call combination in the future, received an Advair diskus in the morning, a salmeterol diskus in the evening and a placebo capsule, and the leukotriene regimen active arm received montelukast at night and two placebos.

Because this study has not been published and there are responsibilities to editors, I am not going to be able to share with you in slide form all of the data, but I would like to summarize it for you as I did at the ATS.

Inclusion criteria for this study were children 6-14 years of age who had acknowledged mild to moderate persistent asthma, as defined by symptoms or beta agonist rescue use of peak flows in the yellow zone. They needed to demonstrate asthma by a PC20 methacholine less than 12.5 mg/ml.

Bronchodilator reversibility was collected but it was not an entry criterion because we believed it would bias the outcomes because one of the study arms contained a long-acting beta agonist. These were individuals who were naive to controller medications. The issue was to look at whether these three arms and how asthma control was achieved in individuals with mild or moderate asthma.

The percent of asthma control days during the study period of 12 months was asthma control days defined as a day without albuterol rescue, without the use of non-study asthma medications, no daytime or evening asthma symptoms, unscheduled provider visits of school absenteeism, so a day in which a parent and a physician both would be happy that the asthma was well controlled and that was the defining outcome for this trial.

In summary, I am going to focus predominantly on the two outcomes related to the full dose inhaled steroid arm and the combination arm of the half dose fluticasone in combination

with salmeterol. Both of those study arms achieved improvement in the percent of asthma control days. At baseline this group of children had about 27 percent of the days that were asthma controlled--so, very, very few. This actually almost doubled or tripled during the active they and the fluticasone group gained asthma control days of 64 percent versus the combination of 60 percent. So, both groups adequately achieved asthma control and these were not statistically different.

Treatment failure was also a secondary outcome in this trial, defined by either the third burst of prednisone or a hospitalization or ER visit due to asthma. There were only five treatment failures in the fluticasone arm and eight treatment failures in the combination arm. That was not statistically significant. Of that, there were no hospitalizations due to asthma in the fluticasone group and two hospitalizations with the combination group.

Overall, the comparison of the two groups

showed in many outcomes that the inhaled steroid alone versus the inhaled steroid at half dose in combination with salmeterol were comparable, as I mentioned, in asthma control days; the time to prednisone bursts and treatment failure status.

There were some important differences in that if you looked at secondary outcomes such as change in PC 20, the improvement and ENO as a marker of inflammation, and actually changes in maximum bronchodilator response, the full dose of inhaled steroid was actually statistically better.

I mention this study from the point of view of one study looking at children that will, hopefully, soon be published and gives us some experience, I believe, with at least efficacy and safety in a pediatric population.

Now, let's switch gears to potential safety concerns that have been raised by the use of beta agonists. That is what the committee has been asked to really put in perspective today. It has not been just in the last few years that safety concerns with beta agonists have been raised.

Studies in the early '90s suggested that the regular use of a particular beta agonist, fenoterol, might produce adverse effects. This is the number of subjects without exacerbation as a Kaplan-Meier curve and you can see those individuals treated with a regular dose of fenoterol had more asthma exacerbations than as needed. This study, by Taylor and others, raised the specter of regular use of short to intermediate beta agonists producing adverse effects.

As you well know, fenoterol never made it to the U.S. market and albuterol has become clearly the drug of choice as the intermediate rescue beta agonist. Therefore, Jeff Drazen and the Asthma Clinical Research Network felt it important as one of its missions to try to answer the question of, given that albuterol was the primary beta agonist used in the marketplace, did it matter whether patients were treated with regular beta agonists versus as needed beta agonists. To achieve this trial, patients either received two puffs of albuterol four times a day plus extra as needed, or

placebo inhaler two puffs four times a day and as needed, thus, sufficing the regularly scheduled versus as needed paradigm. The study had a run-in, a 16-week treatment trial and then a run-out of 4 weeks.

Now, whereas this group today is not here to debate the issues of safety of short and intermediate beta agonists, this trial basically has led to many of the questions that we have asked about long-acting beta agonists, and has led to what I believe is a series of trials that are in construct and will build on.

The summary from this particular study, using again peak flow as the primary outcome and power to find a difference of 25 L/min in the two study arms, suggested that whether you are on as needed albuterol or regular albuterol it really didn't make a difference in this outcome and, therefore, there was nothing evil about the use of regular beta agonists. But the authors acknowledged that clearly based on the way the asthma community was moving, PRN beta agonists was

the more rational approach.

Whereas this was a prospective trial, at the same time that this study was in the midst of being carried out, Steve Liggett's group at Cincinnati and others were working on cloning the beta receptor. This is the beta receptor as a G-coupled protein. As you well know there has been a lot of interest in single nucleotide polymorphisms at both the 27 position and the 16 position in a variety of both in vitro and in vivo studies, looking at acute bronchodilator responses as well as a variety of other asthma outcomes.

So, when this was cloned, the Asthma Clinical Research investigators went back to the BAGS trial that was still ongoing and were able to get most of the participants to come back and be genotyped. In that regard, the analysis showed that there was no effect in this primary outcome at the B27 locus. There was no effect in the B16 heterozygotes. However, there was a signal. When the B16 Arg/Arg patients were compared to the B16 Gly/Gly patients, with a difference found in the

primary outcome variable.

So, this is a retrospective look at the BAGS data that shows that if you were a group of patients who received regular albuterol and you were Arg/Arg, in yellow, your AM peak flow deteriorated during the course of the trial, in contrast to whether you received as needed beta agonists and were Arg/Arg, in red, or whether you received regular albuterol and were Gly/Gly. This retrospective analysis was believed by the ACRN to be hypothesis generating, not definitive and, therefore, led to another study which I will share with you.

At the same time, Robin Taylor reported on the influence of beta adrenergic receptor polymorphisms in some studies he had done looking at, again, asthma exacerbations in this context. If you look at the far right of all-comers in this trial, you see that albuterol and salmeterol are comparable and superior to placebo in preventing exacerbations. If you look at the Gly/Gly and the Gly/Arg groups, there were really no significant

differences. However, in those individuals that were Arg/Arg at the B16 locus, you can see that there were more exacerbations with those treated with albuterol but this was not seen with the salmeterol therapy.

So, we began to see in the asthma community some signals, some subtle signals in retrospective data about the issue of the potential relevance of polymorphisms at the beta receptor. Therefore, I told you that the Drazen trial, retrospective, was hypothesis generating to allow us to go forward to actually create a prospective, randomized, placebo-controlled, double-blind trial of regular versus minimal albuterol in each genotype. This has affectionately been called the BARGE trial.

In this trial, in order to minimize beta agonist use, patients were provided with ipratropium for rescue as a primary inhaler and then had a backup to use albuterol of symptoms were not relieved by ipratropium.

This is a fairly complex study design but

which we believed was important to answer the question. First, individuals between the ages of 18 and 55 years of age who had an FEV 1 of at least 70 percent predicted, and naive to inhaled steroids, were screened and genotyped. If they were either found to be Arg/Arg or Gly/Gly at the B16 they were matched on the basis of FEV 1, enrolled in the trial, went in a 6-week run-in period in which individuals were all on placebo with just rescue therapy. They were then randomized to receive 16 weeks of active treatment or placebo; then had an 8-week run-out; were crossed over to the opposite trial; and then a following run-out arm.

So, a complex study design that allowed each patient to serve as their own control of being on scheduled albuterol versus placebo and using the backup rescue. These are individuals who were about 31 years of age, had fairly normal FEV1's of about 90 percent predicted and were matched in pairs on the basis of the genotype of interest.

This is the data as published in Lancet.

This shows the curves of either the albuterol modeled or raw means data versus the placebo modeled and raw means data. In particular, if you can look at the left-hand side of the slide, this is the Arg/Arg group. The right-hand side is the Gly/Gly group.

Let's look at the Gly/Gly group first. If you look at the Gly/Gly patients in the orange line on the top, you can see that, as you would expect, those patients on albuterol scheduled therapy improved by their morning peak flow during the course of the study. In contrast, during the time they received placebo, in green, they really showed no improvement in their peak expiratory flow. In contrast, the Arg/Arg patients behaved differently. In green is the placebo and you can see the Arg/Arg patients on placebo actually improved and those Arg/Arg patients on albuterol, in orange, failed to improve their peak flow during the course of the trial.

The primary analysis with this study was to look at the treatment differences and the mean

change in AM peak flow by genotype at week 16. You can see that the albuterol versus placebo Arg/Arg patients had a difference in their mean peak flow of 10 L/min; the albuterol versus placebo Gly/Gly comparison, a difference of about 14. Therefore, the treatment difference of the mean Arg/Arg minus the Gly/Gly was a difference of about 25 L/min, which is what this study was powered to find and what we had used in other studies to power it. So, this was determined to be statistically significant.

There were other outcomes that paralleled the change in peak flow. This is looking at the difference between regular versus placebo changes in FEV 1 over the 16 weeks. You can see that the Gly/Gly subjects had an improvement in their FEV 1, whereas the Arg/Arg patients had a deterioration in FEV 1. The same thing could be seen with morning symptoms of an increase in the Arg/Arg patients versus a decrease in the Gly/Gly patients, and a complementary pattern of seeing a difference in inhaler use in the different groups, whether it be

ipratropium as first-line rescue versus albuterol.

In summary, the BARGE data concluded that morning and evening peak flow, FEV1's, symptoms and rescue inhaler use improved significantly in Arg/Arg patients with asthma when beta agonists were withdrawn, and when ipratropium was substituted, as compared with regular albuterol used. The pattern was reversed in the Gly/Gly patients who actually improved with regular beta agonist use. The authors suggested that Arg/Arg patients, who are known to be one-sixth of asthmatics, may actually benefit from minimizing short-acting beta agonist use.

I included this study also because of the important caveats from the investigators and their conclusions. They emphasized that this study was conducted in only individuals with mild disease, not patients with concomitant inhaled steroid doses and, therefore, whether this data can be extrapolated to more severe disease or to those patients who are on concomitant inhaled steroid doses just could not be answered by this particular

trial, suggesting that both issues need to be studied more in the asthma community.

Obviously, the million dollar question is, indeed, do similar effects occur with long-acting beta2 agonists, and what is the impact of concurrent use of inhaled steroids? Obviously, Dr. Chowdhury addressed the committee to really deliberate today to answer those questions. I don't have the answers for you and, fortunately, I am not charged to do that. That is your tough job today.

I would have some comments on what I believe to be future studies that may help you to answer those questions. Much as the BAGS trial was hypothesis generating for BARGE, the SOCS and SLIC trial from the ACRN did retrospectively look at their two studies of long-acting beta agonists alone. That was the SOCS trial that I shared with you, and the SLIC trial which looked at combination of inhaled steroid and long-acting beta agonists and the tapering of such.

The data from these two retrospective

studies has been presented at meetings, suggesting that there was a signal of a same pattern of a difference in morning peak flow based on whether you were Arg/Arg or Gly/Gly at the 16 locus, and that the pattern with salmeterol, with or without the inhaled steroid, seems to be the same.

I carefully indicated that, indeed, these are retrospective studies, very small in design and, clearly, will be hypothesis generating for more robust, longer-term studies that the ACRN, and I believe the industry, will conduct. Therefore, the ACRN now has a study called LARGE that is in the middle of operation that is very similar to the BARGE study but will look at an inhaled steroid, with or without the addition of a long-acting beta agonist, to answer the question of whether the same patterns in a prospective, carefully designed study can be extrapolated.

Now, we do have some data to answer the question on a safety issue about does regular use of long-acting beta agonists delay awareness of asthma progression or effect from recovery? We

have been concerned that if patients are so well controlled with symptoms with their long-acting beta agonists will they be aware that they are having an asthma exacerbation, or will they fail to recover from an exacerbation in the way that they expected to?

This is one representative study that I think illustrates the point. This is the Matz article I showed you earlier of an accumulation of data from earlier published studies. At the arrow, the day of diagnosis is the point in time at which the patient had an asthma exacerbation as defined by these authors. You can see that if you look at the change in asthma symptom score about four days or so before the actual diagnosis of an exacerbation these individuals began to have an increase in symptoms, were treated in completion of an exacerbation satisfactorily, and you see that their symptoms decreased after the exacerbation. In this particular trial you actually see that there is a change in the asthma symptom score that was different in the two different study groups.

Now, one of the things that this provides I think is some reassuring issues that on the basis of symptoms patients are well able to detect a difference in their symptoms, and to know whether they are having an asthma exacerbation, and they recover as we expect. There seems to be no adverse effect of the addition of salmeterol. In fact, these patients seem, by symptoms, to recover even quicker.

We did the same analysis with the PACT pediatric trial that I shared with you just for interest, to do the same pattern looking at symptoms, the issue of albuterol use and the issue of peak flow. We plotted the three arms of the study to look at whether the patterns were any different. In relevance to you today, the patients who were on combination therapy as compared to inhaled steroid alone had no difference in their pattern. So, all three groups were equally able to perceive symptoms of an exacerbation and to adequately recover in the same kind of a pattern. So, we are beginning to, I think, have more data

that resolves this concern that has been raised.

Now, why we are here today in particular is to discuss the evidence for increased severe asthma exacerbations with long-acting beta agonists. Indeed, for these studies, as Dr. Chowdhury outlined for you, the major issue at hand is, indeed, severe asthma exacerbations as has been defined by these trials. I am not going to review them for you as you clearly have received preliminary information and I suspect you will have other members of the audience that will provide far better detail of these than I can do. Suffice it to say that these are studies that have raised questions in the asthma community about the role of long-acting beta agonists, and my own particular comment on these is the fact that, whereas they are compelling for a signal and certainly warrant a very careful review of the trials of what they can tell us and what they cannot tell us, it is very difficult from these trials to discern whether these individuals were, indeed, using concurrent inhaled steroids during the course of the trial.

Therefore, it makes it certainly somewhat difficult to do a full analysis and, therefore, no questions are easily answered.

In summary, I think the committee today has a very important job of reconciling what I believe to be a very crucial question. How do we all reconcile the finding of these very rare severe, life-threatening episodes that are reported in the SMART an formoterol trials with what I hope to have shown you is obviously the far more global evidence that the use of long-acting beta agonists, particularly in combination with inhaled steroids, results in a decrease of overall asthma exacerbations? You all are faced with the data that I believe show that there is very strong evidence of the ability of inhaled steroids and long-acting beta agonists to both achieve asthma control and to reduce overall asthma exacerbations, as defined by the trials that I have shown you and others. So, that piece of data needs to be kept in context.

I would comment that there clearly is more

evidence in adults than children so most of the decisions made are based on adult data. I believe that the remaining concerns about safety have to ask the question about whether, indeed, there is an influence of genotypic predictors, as has been picked up as the signal with the intermediate beta agonists. I believe that we have to look at phenotypic predictors.

I think the era of treating all patients equally for asthma is gone and we need to gain insight about phenotypic predictors of responses to all our therapy. I think this needs to include age, severity of disease, bronchodilator reversibility status, ethnicity and a variety of others. Clearly, we have had some signals that there may be ethnic differences in responses to albuterol based on whether you happen to be Puerto Rican or Mexican-American. So, we need to get more information.

We need to have larger and longer trials which incorporate multiple outcomes, including the concurrent use of inhaled steroids, and we need to

be able to ultimately answer questions of whether this is a class effect of a dose effect.

I don't envy the committee. I know that you will deliberate carefully. And, I appreciate you allowing me to provide you an overview in anchoring your thoughts for your deliberation. Thank you very much.

DR. SWENSON: Dr. Sorkness, I want to thank you for a very fine talk. Since you are going to be leaving before the day is out, I wanted to particularly leave some time for members of the panel to ask you questions at this moment. So, we will take questions from the panel on the talk or issues around it.

Questions for the Speaker

DR. MARTINEZ: Thank you so much for that very, very nice presentation. During your presentation you said that in the PACT trial you were the principal investigator within the CARE network. The decision was made, you said, to use methacholine responsiveness as a criterion for inclusion into the trial and not reversibility. I

am trying to quote you as best as I can, because this could have introduced bias into the results, unquote.

DR. SORKNESS: Yes.

DR. MARTINEZ: Are you suggesting that some of the results of the studies that you have shown to us, including the GOAL study in which exacerbation was shown to be less in combination than in use of inhaled corticosteroids alone, may be explained by bias introduced by the fact that, for example, in the GOAL study 15 percent reversibility was a criterion for inclusion?

Or, a second question, has anybody tried to separate the studies in this meta-analysis that you presented to us between those that demanded 15 percent reversibility and those which did not?

DR. SORKNESS: It is a great question, Fernando, and I think it allows me to clarify my intent of saying that. Clearly, because of a variety of reasons, whether it be historical of our belief that bronchodilator reversibility convinces us that this is, indeed, reversibly asthma and,

therefore, the documentation of such allows enrollment into a clinical trial, or it convinces us that reversibility allows other drugs to show comparability. The majority of trials, whether they be industry sponsored or not, clearly have used bronchodilator reversibility as entry criteria, and clearly most of that which I shared with you is that. That has historically been the context.

My point in this the fact that I believe that there are a much broader group of asthmatics in the world today that don't have that much bronchodilator reversibility or may have very little and truly have asthma. So, our assumptions of our outcomes in the therapies are predicated on the fact that we tend to enroll a fairly defined population.

I think, second to that, there is certainly some data from ACRN and other groups that bronchodilator reversibility as a phenotype clearly may be more predictive of response to long-acting beta agonists or for inhaled steroids, for that

matter. So, we have isolated a particular phenotype and enrolled them in our trials.

The ACRN, because of that and I think because of our mission of trying to more globally answer questions in a broader asthma population, in general have suggested that people can be in these studies whether you have a bronchodilator response or PC 20 as evidence of having asthma. Both issues are collected by entry is not predicated on having simply a bronchodilator effect.

In the PACT trial I wanted to emphasize that I think, because of at least some concerns about the generalizability of the PACT results, we felt that PC 20 predominantly was the right entry criteria. Bronchodilator reversibility was collected. And, clearly, the PACT data will have the capability of looking at both genotypic and phenotypic predictors of responses. I can say that about the PACT data. I haven't, Fernando, really been privy to know whether many of these other studies teased out bronchodilator responsiveness. So, that is my answer to the question.

DR. SWENSON: Just for the record, that was Dr. Martinez that posed that question. Dr. Sorkness, to what extent are the exacerbations, as they are detected in these multiple studies, based on the criteria of increased use of a short-acting beta agonist or the rescue use? Because that seems pertinent to the question of whether long-acting beta agonists simply just, for a while, reduce the need for short-acting and so allow whatever underlying process toward exacerbation to go further without recognition.

DR. SORKNESS: As a very general comment to this, it is a difficult question to answer simply because whether it be asthma exacerbations or treatment failure there is clearly, in my mind, not a uniform definition of either in the trials that have been described. I think, in fairness, the vast majority of at least the mild and leading on to the use of prednisone exacerbations in general have been anchored by asthma action plans that have been a combination of symptoms, albuterol use and, on some occasions, peak flows below some

safety criteria. So, many of these studies have at least incorporated an asthma action plan of albuterol symptoms and peak flow leading to the use of prednisone. So, I think it becomes kind of a composite decision that the patient makes in concert with the physician for those studies.

Having said that, the vast majority of the studies, at least in my mind, that have used the term asthma exacerbation in general have been defined by the need for prednisone, with or without in some cases either an ER visit or a hospitalization, but certainly the asthma exacerbation in many of the studies could have been achieved simply by the issue of prednisone by that action plan. But the definitions are very variable and I think that does make it harder to bring all of these together to get the best insight.

DR. SWENSON: Miss Sander?

MS. SANDER: Thank you. I need a little bit more information on what you just said. Whenever there is the term "rescue" medications used, that is any and all reasons not just rescue

examples?

DR. SORKNESS: I am not sure I understand, Miss Sander.

MS. SANDER: So, rescue would imply that they had an emergency need for that medication. Would it include all uses such as early intervention, prevention of exercise?

DR. SORKNESS: In my mind, most of the studies have in their action plans specified that the use of albuterol to relieve symptoms and/or to treat a peak flow at a certain safety level were used in the definition of an action plan of going on to treat the exacerbation. Most of the action plans in these trials, or at least the ones certainly from the ACRN and CARE, did not incorporate pre-exercise intended scheduled albuterol use in that paradigm. It was strictly albuterol use for relief of those symptoms or relief of a drop in a peak flow to make it return to some baseline safety level.

MS. SANDER: Thank you. Also one other question, were there any expectant mothers in any

of these?

DR. SORKNESS: I can't say this with absolute confidence but I would be highly suspect that any of the trials were conducted that did not have a safety pregnancy test at entry and did not have some appropriate monitoring of pregnancy status during the trial. The vast majority of studies that have been privy to even mandate that if a methacholine challenge procedure is being done at a study visit a pregnancy test be done. There is a series of questions that coordinators and investigators ask about the chance of a pregnancy to make decisions as far as people continuing in trials. So, I would be very surprised if individuals were enrolled being pregnant. Unfortunately, life is not perfect and I think that there are certainly trials where a woman became pregnant during the trial. Most of the studies I know of, that actually required a mandated withdrawal because of the potential influence of pregnancy on stability of asthma. So, I don't think there is much we can gain in insight, quite

honestly, if that is some of what you are driving at. I just don't think it exists in these trials.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Yes, thank you for what was a very clear presentation. I wonder if you might comment about, from the benefit side, any differences in these trials based on race.

DR. SORKNESS: That is a tremendous question. I think the fairness of answering the question is that most of the trials that I am aware of--and I say this carefully because I don't know the literature in its extreme--probably did not have the ability to have a satisfactory subset of a particular racial or ethnic group to be able to cull out to do a reasonable racial analysis. In the beta agonist trial by Drazen, et al., I know for a fact that because of NIH NHLBI guidelines of enrollment of at least a third of minority participants, that we did do a statistical analysis in that trial and it showed that the minority ethnic group did not do differently on any of the outcomes versus Caucasians, negative or benefit.

They had equal responses, as did actually a gender analysis.

I really do not know of any other trial that could answer your question explicitly but I think it is very important, especially given some of what we are learning about the potential role of ethnicity, and that mandates that we all make a far more serious effort for doing trials big enough with groups to answer the question.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Dr. Sorkness, as I recall there were a number of bronchial biopsy studies using ICSs. I don't recall any regarding using either long-acting beta agonists or short-acting beta agonists. Do they exist?

DR. SORKNESS: I am not sure I can answer that with comfort. I actually do believe that there are bronchial biopsy studies in individuals on long-acting beta agonists alone and certainly on combination. That is not clearly my area of expertise and I really think I would be remiss in trying to answer the question of what I know about

those studies. I am a clinical researcher. Certainly, some of my partners do those kinds of studies but that is clearly not an expertise that I would feel comfortable answering. And, there may be somebody else on the committee that clearly knows that data far more than I.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: Chris, on your last slide you have a note that says, "need for larger and longer trials which incorporate multiple outcomes." My question is, you know, clearly long-acting beta agonists decrease exacerbations and, yet, we have very good data that severe pulmonary events and death are increased. So, you can't use a trial that is looking at exacerbations to answer the outcome that we are interested in here. Since I work more in a smaller frame in terms of allergic disease, not large clinical trials, can you give me more of an idea of what you think a large clinical trial and multiple outcomes that we should be looking at for these endpoints of death, intubation, severe pulmonary outcomes?

DR. SORKNESS: Cal, I think it is difficult and I will try to answer as best I can. I do believe we are in an era where the most important studies are not monotherapy in asthma with long-acting beta agonists but with combination. So, that is the first issue.

I believe that whereas the SMART trial and some of the formoterol pivotal trials and others that have raised the signal of concern are helpful and we need to take that under consideration. I find that the way that those studies were constructed leave me wanting more. The methods by which patients were accrued; the issue of whether you really knew whether people were on inhaled steroids concurrently and were adherent with such; that you took into account and balanced severity of disease at the beginning; that you truly looked at what we believe clinically as the best that we can ask of this array of overall asthma exacerbations and control of disease; a year long study to deal with seasonality, especially in kids; looking at some markers of inflammation.

I think that we are at a stage that we would feel better and have more confidence in the risk/benefit relationship if we had those kinds of trials done both in adults and children, and particularly were able to answer in our own minds whether the combination together--adherence, people taking them, being on them, controlling for the issues--that we really knew what we were doing with those particular trials. And, I think that is the best that we can do.

DR. PRUSSIN: Let me just follow that up. The SMART trial was stopped because of difficulties with accrual and slow accrual. Again, we are talking about a huge clinical trial. In your estimation, since this is what you do, is it possible to do that large a trial and get the information in a much more rigorous way, as you are proposing? I mean in terms of accrual. Is this a feasible endeavor to go into? Because we have been told that SMART simply became impossible to carry forward.

DR. SORKNESS: Yes, I think the reality is

such that it is I believe, and I am investigator so I am asked to do these things--I think it is impossible in this day and age to recruit large enough subjects even in a multicenter study that are naive to either inhaled steroids or long-acting beta agonists at entry so that you are bringing in this naive population to answer the question. I don't think those patients are out there anymore because we have done such a good job with guidelines and because all these trials showing that when you give people good medicines, by golly, they get better.

So, I think that if you, indeed, enroll a far broader population of phenotypes, of patients that have certain entry criteria, and then you randomized them to an inhaled steroid with and without a long-acting beta agonist, and followed them for long enough, I think those studies can be constructed. And, I think that is one of the challenges to do and I suspect that they will be done.

DR. SWENSON: Well, thank you, Dr.

Sorkness. We appreciate very much that fine talk and discussion. At this point we will turn the program now over to GlaxoSmithKline and, to do so and to introduce her colleagues, Elaine Jones will take over.

GlaxoSmithKline Presentation

Opening Remarks

DR. JONES: Good morning. My name is Elaine Jones and I am Vice President of Regulatory Affairs at GlaxoSmithKline. On behalf of GlaxoSmithKline, I would like to thank the agency and the advisory committee for this opportunity to review data pertinent to the discussion of the safety of long-acting beta 2 agonists in the treatment of asthma.

Our presentation today will focus on our data with the inhaled long-acting beta 2 agonist salmeterol. As we begin the presentation today, I would like to set the stage by speaking first about the burden of asthma. As the committee members are well aware, asthma is a chronic disease associated with significant morbidity and mortality. In the

United States alone asthma affects approximately 20 million patients. Asthma exerts a tremendous societal burden as evidenced by the half million hospitalizations and over 4,000 deaths in the U.S. in 2002.

There are many risk factors that have been identified that put patients at risk for an asthma-related death. Some of these include excessive reliance on rescue medications and use of inhaled corticosteroids, disease severity and a delay in seeking care. Ethnic origin is also an important risk factor, demonstrated by the fact that the rate of asthma deaths in African Americans is approximately 2.5-fold higher than that of Caucasians.

The tremendous burden of asthma has fueled a continual development of new medications to treat this disease and GSK has a long history in the development of respiratory medicines. Salmeterol was the first inhaled long-acting bronchodilator, and its approval in the United Kingdom over a decade and a half ago represented an important

advance in the management of asthma.

To date, regulatory authorities have granted approval to market salmeterol in over 100 countries. In the United States there are three salmeterol-containing products that have been approved for marketing. These are Serevent inhalation aerosol, Serevent diskus and Advair diskus which contain salmeterol as one of its components. Each one of these products has been approved for use in patients with asthma or COPD, and each of these approvals required a full clinical development program.

It should be noted that the inhalation aerosol formulation, which contained chlorofluorocarbons, has been discontinued by GSK as part of the phase-out of CFC-containing products consistent with the Montreal protocol.

Worldwide approvals by regulatory authorities have led to a great deal of clinical experience with salmeterol. Over the last 15 years the exposure to salmeterol is the result of the use of salmeterol formulated as a single agent and the

use of salmeterol formulated with fluticasone propionate in a single device. In total the worldwide exposure is now estimated at 45.2 million patient-years.

Based on extensive clinical experience and a systematic review of numerous clinical trials, evidence-based guidelines from the National Heart, Lung and Blood Institute's expert panel report recognize the pivotal role of long-acting beta agonists in the treatment of asthma. While the safety of long-acting beta 2 agonists is the topic of today's meeting, it is important to consider the safety of these medications in the context of their overall benefit/risk profile. Part of the context is provided by current asthma treatment guidelines which position the use of inhaled long-acting beta agonists with inhaled corticosteroids as the preferred treatment option for patients with moderate to severe persistent asthma.

Asthma is a serious disease with significant morbidity and mortality and salmeterol has become a well-established pharmacological

therapy in the management of this disease. As you know, no medication is without risk and today's meeting provides an important opportunity to review safety data for inhaled long-acting beta agonists. We look forward to discussing the safety of salmeterol with the committee.

Salmeterol has been shown to be highly effective in the treatment of asthma and, since its approval 15 years ago, clinicians have accrued considerable experience with its use. Based on the extensive body of evidence in patients with asthma, including 64 studies in approximately 45,000 patients in the U.S. alone, GSK believes that salmeterol continues to exhibit a favorable benefit to risk profile.

Dr. Kate Knobil will now provide a brief overview of the efficacy of salmeterol, followed by a discussion of safety data. Following Dr. Knobil's presentation, I will return to the podium to introduce the experts here with us today and then we will take questions from the committee.

Salmeterol Review

DR. KNOBIL: Good morning, everyone. For my presentation today I will first present a brief overview of the benefits of salmeterol for the treatment of asthma, followed by a review of the salmeterol safety data. My review of the safety data will focus on the postmarketing safety surveillance studies, SNS and SMART, and the results from epidemiology studies of salmeterol. In addition, I will describe the ongoing studies currently being conducted by GSK to further evaluate the efficacy and safety of salmeterol. Finally, I will close with an overall assessment of salmeterol for the treatment of patients with asthma. Given time limitations, I will not be able to cover all of the information that is in your briefing document. However, any questions you may have may be addressed during the Q&A.

For several decades beta agonists have been widely used to treat bronchoconstriction. This slide shows the structures of albuterol and salmeterol, and you have seen these already today, and highlights the long lipophilic tail that helps

anchor salmeterol in the beta adrenergic receptor. Albuterol is highly selective for beta 2 receptor, thus having fewer cardiovascular effects than earlier less selective beta agonists. Short-acting beta agonists are very effective but are limited by their relatively short duration of action of 4-6 hours.

This limitation was largely overcome by the development of selective long-acting beta 2 agonists, such as salmeterol, which are effective for at least 12 hours. In addition to having a longer duration of action, in vitro studies have shown salmeterol to be at least 50 times more selective for the airway beta 2 receptor than albuterol.

The benefit of the longer duration of action of salmeterol can be seen in the data pooled from the two registration studies for salmeterol metered dose inhaler. At the time that these studies were conducted regular albuterol use was a common treatment for asthma and so was included as an active comparator. For salmeterol, shown in

green, a single dose results in a clinically significant improvement in FEV_1 within 30 minutes, with maintenance of effect for at least 12 hours. This is in contrast to albuterol, shown in grey, which has a more rapid onset of effect but the bronchodilator effect lasts only 4-6 hours. Additionally, as shown on the right, the bronchodilator effect of salmeterol was maintained after 12 weeks of treatment with no diminution of FEV_1 response over time.

Studies of up to one year in duration have confirmed that the bronchodilator properties of salmeterol are maintained with long-term use. In this study, 12-hour FEV_1 area under the curve, or AUC, was obtained after the first dose and following 8, 20 and 48 weeks of treatment. For salmeterol the mean FEV_1 AUC was similar at all time points, and in all cases was significantly greater than placebo, demonstrating maintenance of bronchodilator effect. In addition to important bronchodilator effects, salmeterol is very effectiveness at reducing the symptoms of asthma.

The data shown here are from the same two studies for salmeterol MDI that I showed previously. Over 12 weeks treatment with salmeterol resulted in a significant reduction in asthma symptoms scores for chest tightness, shortness of breath, wheezing and cough compared with placebo and albuterol given 4 times daily. Although not shown here, in these and other studies salmeterol also reduced nocturnal symptoms associated with asthma.

Salmeterol has also been shown to be an important treatment option for patients with asthma who are not adequately controlled on inhaled corticosteroids. This landmark study by Greening and colleagues examined the effect of adding salmeterol to inhaled corticosteroid therapy, in this case beclomethasone, as compared to increasing the dose of inhaled steroids. The addition of salmeterol to a low dose of inhaled corticosteroid was shown to result in a greater improvement in lung function, as shown by peak expiratory flow, then when compared to the higher dose of inhaled steroids. In addition to the improvements in lung

function, the use of salmeterol resulted in greater improvements in symptoms and rescue albuterol use.

The addition of salmeterol to a low to medium dose of inhaled steroid has also been shown to reduce the recurrence of asthma exacerbations. Shown here again is the study by Matz and colleagues, and was of similar design to the study that I showed previously. When compared to increasing the dose of fluticasone propionate, or FP, the addition of salmeterol to the low dose of FP significantly increased the time to the first asthma exacerbation requiring oral corticosteroids. Further, significantly fewer salmeterol-treated patients experienced one or more exacerbations, 8.8 percent compared to the increased dose of FP at 13.8 percent of patients.

Another means of evaluating the patient benefit of a medication is to assess the impact on quality of life. In this 12-week study that was designed to assess asthma-specific quality of life, patients with asthma were randomized to either salmeterol or placebo, with all patients receiving

albuterol as needed to use for symptoms. Salmeterol MDI was shown to significantly improve quality of life compared with placebo, and the minimally clinically important difference of 0.5 was achieved for each domain as well as the global score.

To summarize, the benefits of salmeterol have been well established and salmeterol has been accepted as having an integral role in the treatment of asthma.

I will now move on to the safety portion of the presentation, beginning first with the postmarketing surveillance studies for salmeterol. These studies are of interest because at the time of launch of salmeterol in both the U.K. and in the U.S. there was concern that the regular use of beta agonists may lead to deterioration of asthma control. This was based primarily on studies of short-acting beta agonists, particularly fenoterol, that suggested worsening of asthma with scheduled use. These studies could not determine a cause and effect relationship, however, they did bring

significant attention to the appropriate use of this class of medications.

The first study that I will discuss is the Serevent Nationwide Surveillance Study, or SNS, which was performed in the U.K. between 1990 and 1992. This 16-week randomized, double-blind study evaluated over 25,000 patients with moderate to severe asthma. The study compared salmeterol MDI to albuterol given 4 times daily in patients 12 years of age and older. Both treatments were added to the patient's current asthma therapy.

At visit 1 patients were randomized in a 2:1 fashion to either salmeterol or albuterol. The primary endpoint for SNS was combined serious adverse events and all medical and non-medical withdrawals. This very broad endpoint was not restricted to respiratory events. For this endpoint the percentage of events was similar for the salmeterol and albuterol groups. Additional endpoints of interest included asthma-related deaths, hospitalizations and withdrawals. Based on national health statistics in the U.K. and on the

2:1 randomization, 10 and 5 asthma-related deaths were predicted in the salmeterol group and albuterol group respectively.

In this study, 14 asthma-related deaths occurred, with 12 in the salmeterol group and 2 in the albuterol group, resulting in a relative risk of 3. This difference was not statistically significant but did raise concern. The results for asthma-related deaths were not consistent with the data for asthma-related hospitalizations. As you can see here, the data for this endpoint did not indicate an increase in risk with salmeterol. The only statistically significant difference between the groups was seen for the percentage of withdrawals due to worsening asthma, with a lower percent observed in the salmeterol group compared with albuterol.

In light of the results of SNS, including the asthma-related deaths and spontaneous reports, GSK, in conjunction with the FDA, designed the Salmeterol Multicenter Asthma Research Trial, or SMART. The study was initiated in 1996. SMART was

a randomized, double-blind surveillance study of 28 weeks duration that was conducted at over 6,000 sites in the United States. Patients with asthma who were 12 years of age or older, with no previous use of inhaled long-acting beta agonists, were included. All other asthma medications were allowed during the study.

SMART consisted of a single clinic visit at which patients were assessed for eligibility and then randomized to receive either salmeterol or placebo which was added to their usual asthma care. Subjects were given a 28-week supply of study medication and were not required to return for clinic visits. Instead, patients were contacted every 4 weeks by phone primarily to collect information on serious adverse events, including respiratory-related events.

The combined endpoint of respiratory-related deaths or life-threatening experiences was chosen as the primary endpoint. Asthma-related death was also of interest but because this is a rare event the sample size

required for this to be the primary endpoint was too large to be feasible. Even with the broader combined endpoint, it was determined that a sample size of 30,000 patients would be required. However, after 15,000 patients were enrolled in the study the actual rate of primary events was found to be approximately half of what was expected and the target sample size was increased to 60,000 patients.

Key secondary endpoints were respiratory-related deaths, combined asthma-related deaths or life-threatening experiences, and asthma-related deaths, all of which were subsets of the primary endpoint.

Two independent review committees were involved with SMART. They were the mortality and morbidity review committee, or MMRC, and the data safety monitoring board, or DSMB. Each serious adverse event was adjudicated in a blinded fashion by the MMRC to determine if it was respiratory related and, if so, whether it was asthma related. The categories for this adjudication were

unrelated, unlikely related, possibly related or almost certainly related. Only respiratory- and asthma-related events considered possibly related or almost certainly related comprised the primary and secondary endpoints. The DSMB met regularly to evaluate blinded aggregate data which included the cases adjudicated by the MMRC.

An interim analysis was planned when approximately one-half of the patients had been enrolled. At the interim analysis the study did not reach predetermined stopping criteria, however, there was a suggestion of worse outcomes in salmeterol-treated patients, especially African Americans. For this reason, the DSMB recommended that ideally the study should be completed within 2 years or, if that was not possible, the study should be terminated and the results disseminated. Following discussions with the DSMB, GSK made the decision to stop the study due to difficulties in enrollment and the findings in African Americans.

I will now move on to the results of SMART. Overall, the baseline characteristics of

age, sex, ethnic origin and baseline peak expiratory flow were well matched between the treatment groups. Approximately 70 percent of the population was Caucasian and 18 percent was African American. For reference, approximately 15 percent of the patients with asthma in the United States are African American.

Asthma medications were reported at baseline and were similar between the treatment groups. The most commonly reported asthma medications were inhaled or oral beta agonists which were reported in over 90 percent of patients. Forty-seven of the patients reported use of inhaled corticosteroids at baseline.

While baseline characteristics were similar between the treatments for the total population, this was not the case when comparing baseline characteristics between Caucasians and African Americans. The baseline characteristics indicate that African Americans had more severe asthma as measured by peak expiratory flow, nocturnal symptoms, and history of hospitalizations

and intubations. For example, the proportion of African Americans reporting a hospitalization for asthma during the previous 12 months was more than twice the percentage reported for intubation for asthma in their lifetime. In addition to these markers of increased severity in African Americans, the reported use of an ICS at baseline was lower than that in Caucasians.

The results for the primary and key secondary endpoints will be shown on this slide. Due to the amount of information, I will take a few moments to summarize the data. These figures are also available in your briefing document for reference.

First let me orient you to the slide. The relative risk point estimate and corresponding 95 percent confidence intervals for the primary and secondary endpoints will be displayed graphically. The values that correspond with these data will be shown on the right side of the slide. The total population will be represented in yellow, the Caucasian subgroup in green, and the African

American subgroup in orange.

I will start by showing the results for the total population as this was the primary analysis. Then I will show the results for Caucasians and African Americans as this post hoc analysis was requested by the DSMB at the time of the interim analysis.

The number of primary events, combined respiratory-related death or life-threatening experiences, was approximately two-thirds of what was expected. The primary endpoint for the total population, as shown here on the slide, was not statistically significantly different between treatment groups as the confidence interval includes 1. As I review the key secondary endpoints for the total population, which are respiratory-related deaths, combined asthma-related deaths or life-threatening experiences and asthma-related deaths, it is important to remember that each is a subset of the primary endpoint.

For the secondary endpoints, statistically significant differences were observed between

treatment groups for the total population, including asthma-related death which I will discuss in more detail in a moment. The numbers of primary events in the Caucasian subgroup, shown in green, were similar between the treatment groups. However, in the African American population, shown here in orange, a significantly greater number of primary events occurred in the salmeterol treatment group.

For the key secondary endpoints the relative risk of events was higher in African Americans compared with Caucasians. In particular, a significantly greater number of combined asthma-related deaths or life-threatening experiences occurred in the salmeterol group in the African American population, while there was no difference between treatment groups in the Caucasian population.

The number of asthma deaths in SMART was approximately half of what was expected. There was a significantly higher number of asthma-related deaths seen in the overall population for patients

receiving salmeterol compared with placebo and the same pattern was seen in the ethnic subgroups. While the relative risk of asthma deaths appears similar between ethnic groups, note that there were approximately 4 times as many Caucasians in this study than African Americans. Therefore, the rates for all asthma-related endpoints were much higher in the African American population.

The effect of inhaled corticosteroids was also of particular interest to the DSMB at the time of the interim analysis. A post hoc analysis was conducted to explore the association of baseline use of ICS with the primary and key secondary outcomes. As I mentioned previously, 47 percent of the patients reported using inhaled steroids at baseline. The results for the total population are shown here, again in yellow, for reference. Results for subjects reporting inhaled corticosteroid use at baseline will be shown in blue, and those not reporting ICS use at baseline will be shown in white.

For subjects reporting ICSs at baseline

there were not statistically significant differences between the treatment groups for the primary and secondary outcomes. Patients receiving salmeterol who did not report the use of inhaled corticosteroids at baseline, here in white, experienced significantly more combined asthma-related events than those receiving placebo. The number of deaths in those patients not reporting inhaled corticosteroid use at baseline was 9 in the salmeterol group versus zero in the placebo group so direct calculation of relative risk cannot be performed. In the patients reporting corticosteroid use at baseline the numbers were 4 and 3 respectively.

Although SMART was not designed to assess the effects on inhaled corticosteroid use, these data suggests that ICS may have had a beneficial effect on asthma outcomes in SMART.

Finally, the data were analyzed by both ethnicity and inhaled corticosteroid use reported at baseline. Caucasians are shown, again, in green and African Americans in orange. Patients

receiving inhaled corticosteroids are represented by solid lines while dotted lines represent patients not reporting inhaled corticosteroid use at baseline. The relative risk for the primary endpoint was higher in African Americans than Caucasians, and those not reporting inhaled corticosteroids at baseline had higher relative risks within those populations.

Similar to the primary endpoint, the relative risk for combined asthma-related events was higher in the groups that did not report inhaled corticosteroids at baseline independent of ethnicity.

If we focus specifically on the number of asthma-related deaths, shown here at the bottom of the slide, it is evident that these events were rare. There were more asthma-related deaths in patients receiving salmeterol who did not report ICS use at baseline in both Caucasians and African Americans. Again, direct calculation of relative risk cannot be performed for asthma-related deaths for patients not reporting inhaled corticosteroids

at baseline since there were no deaths in the placebo group for this endpoint.

SMART was not designed to determine the effect of inhaled corticosteroids and ethnicity on these endpoints, and the number of events in each subgroup is quite small. Therefore, these data should be interpreted carefully.

In summary, there were more events, including asthma-related deaths, reported in the patients receiving salmeterol. There was also a suggestion that both African Americans and patients who did not report using inhaled corticosteroids at baseline had a higher risk of asthma-related events. However, the number of events in SMART was lower than expected, preventing definitive conclusions from the data.

A careful review of the data did not reveal any clear explanation of the results. Possible explanations include a direct pharmacologic effect of salmeterol; the presence of polymorphisms in the beta receptor gene; or patient-related factors, including a delay in

seeking medical care. It is well accepted that the prevalence of patient-related risk factors is not equally distributed across ethnic groups so the differences in outcomes seen between the ethnic groups in SMART may be associated with disparities in access to medical care and asthma management and may not reflect biological differences between the groups. Unfortunately, none of these hypotheses can be confirmed or refuted by the data from SMART. While there are no clear explanations for the data, the findings were communicated to physicians to allow for informed treatment decisions.

In collaboration with the FDA, a number of activities were undertaken to communicate the results in order to inform physicians about SMART. On the day the study was stopped a "dear healthcare professional letter" was delivered by overnight mail to the 229,000 healthcare professionals in the United States who had prescribed salmeterol or salmeterol-containing products within the previous year. Simultaneously, notices on both the FDA and GSK web sites were posted.

A second letter was sent out to health professionals when the prescribing information for Serevent and Advair was changed to include the preliminary results of the interim analysis of SMART. The information was elevated to the highest level of prominence in the form of a boxed warning. When the final results were obtained the labeling for both products was updated.

This is the boxed warning that was added to the prescribing information for Serevent and Advair. It describes the final results of the interim analysis of SMART. For your reference, the full label, including the boxed warning, is available in your briefing package.

The results of the interim analysis were presented at the American College of Chest Physicians meeting as a late-breaking abstract. This was the first available national meeting with high attendance of respiratory physicians. The manuscript is now in press at Chest, the journal of the American College of Chest Physicians.

Epidemiology studies offer an additional

method to investigate associations between drug exposure and serious outcomes. The major advantage of these studies is the utilization of comprehensive medical and pharmacy databases. These databases allow identification of a greater number of events than can be achieved in traditional randomized clinical trials. The primary limitation of observational studies is the fact that assignment of treatment is not random and treatment effects may be confounded by differences in baseline characteristics, including co-morbid disease, differences in asthma severity and selective prescribing. Since many more events can be evaluated in an observational design, this may be a more informative way to assess treatment effects on the rare endpoint of asthma-related death.

This figure displays the relative risks from all large published cohort and case-control studies that evaluated whether salmeterol use was associated with the occurrence of severe respiratory and asthma-related outcomes. The

dotted line represents a relative risk of 1.

The first study determine the relative risk of respiratory-related death among patients with asthma receiving salmeterol compared with those receiving theophylline on the left side of the highlighted area, or those receiving ipratropium, which is on the right side of the highlighted area.

The second study, which was conducted in the United States, evaluated three endpoints, asthma-related emergency room visits, hospitalizations and ICU admissions, comparing salmeterol with theophylline recipients.

The last two were separate case-control studies that evaluated the relative risk of asthma-related ICU admission or asthma-related death associated with salmeterol use relative to no use.

This last and most recent study, shown here on the far right, included 532 pairs of asthma deaths and matched controls and is the largest case-controlled study evaluating asthma-related

death ever conducted. Notably, none of these studies showed a significant increase in the relative risk of these serious outcomes for salmeterol.

GSK is committed to a comprehensive research plan to further evaluate the safety and efficacy of salmeterol. We believe that these currently ongoing studies will provide valuable information regarding the safety and efficacy of salmeterol in patients with either asthma or COPD. In order to address some of the issues raised by SMART, two studies are under way.

The first is a year long clinical study evaluating the incidence of asthma exacerbations in 460 African American subjects. Results are expected in 2007. The second is an epidemiology study utilizing data from 7 Medicaid plans to examine racial variation and association of asthma-related prescription medication use with asthma morbidity and mortality. The results are expected in 2006.

Studies have suggested that response to

short-acting beta agonists may be affected by genetic polymorphisms in the beta 2 receptor. However, there is one study that has suggested there is no similar association with salmeterol and clinical outcomes including exacerbations. This was the Taylor study that Dr. Sorkness showed earlier. Since there were no genetic samples collected in SMART we are conducting two studies to address whether clinical outcomes in patients receiving salmeterol are affected by genotype.

The first study is a 38-week clinical trial evaluating response by beta 2 receptor genotype in 540 subjects with asthma. The results are expected in 2007. The second study will evaluate polymorphisms in beta 2 adrenergic glucocorticoid pathways with respect to clinical response in approximately 1,000 subjects from completed GSK clinical trials.

Finally, while asthma has been the focus of today's discussion, there are ongoing studies in patients with COPD that will help address whether the results of SMART are relevant for patients with

COPD. The first is a 3-year study of all-cause mortality in approximately 6,200 subjects with COPD. Results from this study are expected in 2006. In addition, we are conducting 2 year-long replicate studies examining the rate of moderate to severe COPD exacerbations, with results expected in 2007.

Asthma is a serious chronic disease with significant morbidity and mortality. Salmeterol is one of the most thoroughly studied medications for asthma and has been shown to provide substantial therapeutic benefit, including improvements in lung function, and asthma-related quality of life, and reduction in symptoms, rescue medication and asthma exacerbations.

The extensive clinical trials have led evidence-based asthma treatment guidelines to recommend long-acting beta agonists with ICS as the preferred option for patients with moderate, persistent asthma. There are conflicting data for salmeterol. SMART and SNS suggest that salmeterol may be associated with an increased risk of rare

serious asthma-related events including asthma-related death. But when large cohorts of patients are evaluated in epidemiology studies this association is not observed. The low number of serious asthma events in SNS and SMART does not allow for definitive conclusions, and the fact that the events of concern are also those that are experienced by patients with asthma, regardless of treatment, makes assessment of cause and effect relationships difficult.

Ultimately, what are the implications of the data for patients with asthma? Well, specific treatment decisions for an individual patient can only be made by their physician. It is our responsibility to provide the complete information so that the physician can make well-informed treatment decisions. We have done this in the prescribing information for products containing salmeterol.

From the time that salmeterol was introduced in the United States in 1994 the prescribing information has provided specific and

appropriate guidance on its use. This includes that salmeterol should not be used to treat acute symptoms. It is not a substitute for inhaled or oral corticosteroids, and consideration should be given to adding anti-inflammatory agents, for example corticosteroids.

In 1995 further information was added, including a warning that salmeterol should not be initiated in patients with significantly worsening or acutely deteriorating asthma. As I have already mentioned, detailed information on the rare asthma-related events seen in SNS and SMART had been incorporated in the prescribing information so that informed treatment decisions can be made. This includes the boxed warning, as well as other language to address the inconclusive nature of the results and the potential for a class effect of inhaled long-acting beta agonists.

In conclusion and based on the weight of evidence, we firmly believe that salmeterol remains a valuable medication that has improved the level of care for patients with asthma and COPD.

Additionally, GSK is committed to further research that will not only help better characterize the efficacy and safety of salmeterol but will also help better understand asthma in general. There is a large volume of data from clinical trials of salmeterol, as well as extensive clinical experience with this medication. Taken together, these continue to support a favorable benefit to risk profile and, therefore, salmeterol should remain available to physicians and patients.

I thank you for your time and I will now turn the podium back over to Dr. Jones.

Closing Remarks

DR. JONES: I would like to introduce three additional experts here with us today. Prof. Richard Beasley is the director of the Medical Research Institute of New Zealand. He is also an international expert on beta agonist safety and asthma epidemiology. Dr. Eugene Bleecker is professor and section head, Pulmonary, Critical Care, Allergy and Immunologic Diseases at Wake forest University Health Sciences. Dr. Bleecker is

also the co-director of the Center for Human Genomics, and was a member of the MMRC for SMART. Finally, Dr. George O'Connor is professor of medicine in the Division of Pulmonary and Critical Care Medicine at Boston University School of Medicine, and is director of the Adult Asthma program at Boston Medical Center. In addition, he was the chairman of the DSMB for SMART.

We would be happy to address any points of clarification and questions. Thank you.

Questions by the Committee

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I think one possible hypothesis based on the SNS study, where there was increased withdrawal due to asthma in the placebo patients, is the possibility that there ended up being an imbalance in severity by the end of the study due to disproportionate withdrawal of more severe patients from the placebo group. That is obviously not so easy to tease out but I would question whether, in fact, one looked at baseline severity in those who withdrew versus those who

didn't in both groups but particularly in the placebo group.

DR. KNOBIL: For SNS we don't have that cut of the data to provide for you, but it would probably make a lot of sense that the patients who withdrew were more severe.

DR. SCHATZ: But for SMART data--

DR. KNOBIL: Oh, for SMART we saw the same thing in that there was greater withdrawal in the placebo group than in the salmeterol group but, again, we don't have that cut of the data for you today.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I have two questions, one related to measures of adherence within or between the groups and whether anything has been done with that. The second is would you give us the status of the ongoing studies at this time? You have listed four with expected results. Can you tell us the enrollment at this time; how far along you are? I understand the word "commitment" but can we see something about progress at this time and status?

DR. KNOBIL: All of the studies that I mentioned to you are right now currently enrolling. As you might imagine, enrolling limited populations of only African Americans takes a little bit longer than general populations. As well, in the genetic studies we are making sure that we have balanced groups with the different genotypes. So, that does take some time. So, what I can tell you is that they are enrolling but I can't tell you when they will be done enrolling.

DR. GARDNER: And adherence?

DR. KNOBIL: Oh, I am sorry. During the monthly telephone contacts we did ask the question--if you could show the slide, please? On a scale of 0-10, with zero meaning you missed all of your doses and 10 means you took all of your doses, what number represents how well you followed the study physician's instructions? In the study the mean response, patient reported response was 8 for each group. Again, this is patient reported and patients did not return to the clinic so we cannot verify this. We did not ask them to bring

their cans in. We did not weigh canisters and we didn't have a chronolog. But I think from studies of chronolog, we know that patients sometimes report taking more medication than they actually do. So, I can't really verify the actual compliance of the patients.

DR. GARDNER: As far as you can tell, was there similar adherence between the African American subjects and the Caucasian subjects?

DR. KNOBIL: Yes, as far as can tell there was no difference between any specific group.

DR. GARDNER: Finally, on the Medicaid study, that doesn't require enrollment. Can you tell me where that is being done and how far along that one is?

DR. KNOBIL: Yes, that one is being done in seven states. What we are doing right now is the first phase of the study, which is to see if we can identify enough patients with high enough proportion of African Americans to make an analysis feasible. So, that is where that study is right now.

DR. SWENSON: Dr. Moss?

DR. MOSS: I have two separate questions. The first one has to do with the dissemination of the information in your letters and the labeling revisions. I think the goal of this meeting is to disseminate information properly to the physicians and the community. The question I have is when you sent out those letters and put on the box labels, do you know if that changed the prescription practices for the physicians that received those letters or for the general community in terms of the prescription of your medication?

DR. KNOBIL: I don't know if that information changed the way physicians prescribe the medications. We don't have any specific data to that effect.

DR. MOSS: Did overall use of your compound decline after those letters were sent out?

DR. KNOBIL: The rate of use did not change after those letters were sent out. But, you know, we can't guess what would have happened; all we saw was no change.

DR. MOSS: You saw no change. I think that raises a concern about, you know, we are trying to disseminate information and are we doing that in the proper way?

The next question I have may be answered by you but might also be answered by either Dr. Bleecker or O'Connor. I think it is really hard to figure out why someone died. Taking care of people I see this. It is really hard to define specifically what a cause of death is. I was just wondering if you can give us some insight into how you define respiratory versus asthma deaths in the SMART study.

DR. KNOBIL: Dr. Bleecker, would you like to address that?

DR. WEAN: While Dr. Bleecker is coming up, I want to get back to the earlier question you raised. I am David WEAN, Senior Vice President of Regulatory Affairs at GlaxoSmithKline. I don't think it appropriate to say that because we can't posit a change in prescribing habits because of the letters and the label that they were not effective.

The important thing is that the information was disseminated in a very large way to prescribers and, thereby, to patients. To expect that you would see a drop-off in use of these drugs that have therapeutic benefit because of that communication I think would be an inappropriate assessment about the effectiveness of that communication.

DR. MOSS: But I think one thing we have learned is that publishing articles and papers does not get information out to the people that need the information to be received. In the same way, I am not sure that sending letters out to physicians who get a lot of mail is an effective way of communicating information.

DR. SWENSON: Dr. Bleecker?

DR. BLEECKER: I was asked to talk a little bit, and George O'Connor could complement on how the mortality review committee in SMART adjudicated cases. I agree, it is often very difficult, and as we did this we probably all learned. I joined the mortality review committee

after about a third of the cases had been done. The members of the committee before that had been Roland Ingrham who was professor of medicine at Emory. He had retired. The chairman of the committee was Hal Nelson who is a professor of medicine at Colorado, and the third member was Scott Weiss who is professor at Brigham and Williams and also head of their pulmonary and respiratory epidemiology program.

We had data on most patients available both from death certificates and from the medical monitors who worked with Covance. We used that to answer questions which were related to the cause of death; was this respiratory related; and you heard before the likelihood or unlikelihood of that during Kate Knobil's presentation; and then was it asthma related. All three of us adjudicated this independently. If we agreed on all of these characteristics the case was not discussed further. All of the cases in which there was any disagreement, ranging even between "unrelated" and "unlikely" were discussed in detail in timely

conference calls. I think at times we did the best we could on relating to that.

The least amount of information was available on deaths toward the end of the study that were picked up from the national death registry. On those deaths we had to rely on death certificates or more limited information.

DR. MOSS: Can I just follow-up on that? Can you explain a little bit how you differentiate asthma from respiratory deaths? A respiratory death that is not asthma, is that pneumonia? What were criteria to differentiate those specific things?

DR. BLEECKER: Well, often asthma entered into those deaths. Let me give you an example of respiratory death. Because someone during an auto accident had trauma to the chest--and this did occur in some of the younger individuals--and died, and that clearly was related to an automobile accident and because of the nature of the event and other things was not related to asthma. It was more difficult if someone entered the hospital with

pneumonia, was intubated and in an intensive care unit. I think under those circumstances, some of those deaths were adjudicated depending on the course on the ventilator or those serious events as possibly related to asthma. So, at times it is very hard to distinguish that from the records. Again, I think the fact that they were performed independently and you needed to look for concurrence and discussion, I think a reasonable approach was performed.

DR. SWENSON: Dr. Gay?

DR. GAY: Based on the appropriate emphasis that you have begun to make on genetic testing, as we have seen based on the information that Dr. Sorkness elegantly presented before, do you have any preliminary estimates of what you feel would be the prevalence of Arg/Arg gene presentation in patients with greater severity of asthma or based on ethnic differences?

DR. KNOBIL: Yes, I would not be able to predict the different prevalences of those genetic subtypes and I would ask Dr. Bleecker to comment on

that. The one thing I would add is that in the one genetic study we are making sure that there are equal numbers of each genetic subtype so that we don't have a predominance of one and very few of another. Dr. Bleecker?

DR. BLEECKER: I would like to add a few comments to that because I think there are some important aspects of this. First of all, we have centered on basically one variation within the beta2 adrenergic gene. Looking at that gene more carefully--and there have been published studies on this, especially from the Liggett group as well as some work from our laboratory which has been presented at last year's ATS and Academy of Allergy meetings--there is a good deal more variation in that gene, and there are relationships between the arginine genotype and some of that other variation. Some of that may be very important in trying to sort out the hypothesis of whether variation in this gene affects therapeutic response and potentially affects outcome.

The second important issue is there is

more variation, and African Americans have a higher prevalence of the Arg/Arg genotype, about 22 percent, and that is what was seen during the screening for the ACRN BARGE trial versus about 12-14 percent in Caucasians. The implications of that on outcome are difficult, and I think it is very important that the studies that were outlined by Dr. Knobil on studying specifically an African American cohort in which they are going to look at outcome such as exacerbations and genotype are critical because those kinds of studies are not being done because of the limitations in recruitment by the NIH NHLBI asthma clinical network.

DR. SWENSON: Dr Prussin?

DR. PRUSSIN: I have a similar question that I raised before with Dr. Sorkness. You have some very nice studies that are undergoing, but do you think they are going to address the question at hand in terms of asthma deaths or severe pulmonary endpoints? They are fairly small studies relative to the SMART study and, when all is said and done

in three or four years, it is not clear to me at least that you are going to have any kind of handle on asthma death. Could you comment on that?

DR. KNOBIL: Yes, as I mentioned, it is very difficult to prospectively study asthma-related death because the rate is relatively low and you need a very large N to get conclusive results. The one study that will help us get there though, I believe, is the Medicaid study in that we can get information from the 7 Medicaid plans and look at the different racial subgroups, look and see what medications they were on and see what contributed to those patient's deaths, whether it is a long-acting bronchodilator, short-acting bronchodilator or some other related medication. So, I do believe that in that observational design we will be able to get some more information about asthma-related death. The other studies are mainly going to address asthma exacerbations and other responses such as lung function, rescue albuterol use, and we will be able to look at those in relationship to genetic makeup as well.

DR. PRUSSIN: The difficulty I have with that though is that there is a lot of data showing that salmeterol improved asthma exacerbations. You have shown that. Clearly, the more severe endpoints of death are tracking differently. So, you are thinking of it as the tip of the iceberg, that however exacerbations are going to track asthma deaths are going to track and clearly they are behaving differently. So, just because you have certain data on asthma exacerbations in certain subgroups, that may not be proportional or relate to asthma. We don't have any prospective studies ongoing or planned to really address the endpoint that I think this committee has been asked to address, which is asthma death. So, it could very well be a different phenomenon than what is causing asthma exacerbations.

DR. KNOBIL: That is true, and there are other factors beyond asthma treatment that may be contributing to asthma-related death as well, including access to care or how a patient's asthma is managed. We don't know the answers to that

either. So, that is why in order to actually even look at asthma-related death an observational design is probably going to provide more information more quickly.

I take your point that it seems that a prospective study would be the gold standard. The issue there is that if the rate of asthma-related death was similar to what we saw in SMART, in order to see an effect you might have to have a study as large as 800,000 patients. As you can see, that would be very difficult to do. So, yes, it would be nice to be able to do it prospectively but it is going to be more difficult than doing it in an observational design.

DR. JONES: Actually, I think Dr. Beasley wanted to make a comment.

DR. BEASLEY: Yes, in response to that I would like to caution in terms of considering a prospective clinical trial as being the gold standard when you are looking at a rare outcome such as mortality. I think we saw that in the SMART study, where it was required to study

approaching 30,000 subjects to obtain around 35 respiratory-related deaths, and there was a real compromise in terms of design of the study to actually achieve that and individuals were given 7 canisters at the beginning of the study without any formal clinical follow-up, which is something which would not be done on label in terms of salmeterol therapy. In terms of the other issues of the label, many of the subjects had asthma severity where salmeterol would be inappropriate as sole therapy.

So, I think that when you try a prospective controlled trial to look at a rare outcome such as death you often have to incorporate a methodology that clearly is outside the spectrum of what is recommended clinical practice. That clearly happened with the SMART study so that we have to consider the SMART study results not applicable to what would be considered good clinical practice, and the alternative is actually to increase the number of deaths through case-control methodology and that was the method we used in New Zealand to identify the risks

associated with fenoterol.

In that regard, I think that the Anderson study in the BMJ is considerably more powerful in terms of looking at the role of bronchodilator therapy and the rare outcome of asthma mortality. They were able to look at over 500 deaths, match them with subjects who came from the same proportion of the population of patients in terms of severity, who were subjects with a previous hospital admission, and then they were able to stratify their analysis by looking at an even more severe subgroup. When they did that there was actually no increased risk associated with the use of salmeterol therapy.

So, I think that in terms of the epidemiological approach to a rare outcome of asthma mortality looking at the role of medication use, the epidemiological view is very clearly that the case-control methodology is more powerful and more accurate than a prospective clinical trial. I think in some respects almost the learning point from the experience with the SMART study was the

compromise that had to be obtained in terms of clinical practice to achieve a study which, even with 30,000 people, did not have sufficient power.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: Do you have a tabulation for the whole group and for each of these subgroups and for each of the endpoints of the absolute risk or the attributable risk? Because from a risk/benefit point of view the relative risk isn't very informative because, of course, you can have a 3-fold relative risk of a very, very rare event and that may be important if you are judging something like an environmental pollutant that you can remove but is not really important when you are judging a very effective drug which improves people's quality of life. So, I wonder if you have that tabulated. I have done some back-of-the-envelope calculations but it would be helpful to have the actual numbers where we looked at the percent of deaths per patient-year or number of deaths per 1,000 patient-years, or something of that sort that would be attributable, assuming that there is some

attributable risk to the use of the drug, or even just the total risk among asthma patients per 1,000 patient-years or 10,000 patient-years, or whatever.

DR. KNOBIL: Unfortunately, we don't have those data. We have not done those calculations.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Would you please clarify what the entry criteria were for both studies, the British one and the one done in the United States? How was asthma defined? Were any of the usual parameters--response to beta 2 agonists or methacholine used to define asthma in these two studies?

DR. KNOBIL: These studies were a little different than normal clinical trials, say, to register a medication for asthma. It was the opinion of the investigator if the patient have asthma. They did not have to show reversibility. There was no smoking criterion. In this case they had to be 12 years of age or older. In SNS they had to have moderate to severe asthma and in SMART they were not allowed to have concomitant

administration of beta blockers. That is about all.

DR. MARTINEZ: Was response to bronchodilators measured?

DR. KNOBIL: It was not measured.

DR. SWENSON: Miss Sander?

MS. SANDER: Yes, when we are looking at possible causes of death, are you able to know if patients who died were using salmeterol as if it was an acute bronchodilator?

DR. KNOBIL: In SMART the only question we asked was if the patient was using the medication as the physician told them to. That is the data that I showed you earlier. We do not have any data on whether they were using it as a rescue medication.

DR. SWENSON: I realize that there are more questions to be posed to GSK but we need to take a break at this point. We have a general question session in the afternoon and the rest of these questions should be addressed at that time. We will be back again in 15 minutes.

[Brief recess]

DR. SWENSON: We will resume the meeting with Dr. Eric Floyd, from Novartis, to discuss formoterol and its place in this controversy.

Novartis Presentation

Introduction

DR. FLOYD: Good morning. Dr. Swenson, members of the FDA advisory committee, Dr. Chowdhury, members of the Food and Drug Administration and guests, my name is Eric Floyd. I am Vice President and Global Head of Drug Regulatory Affairs for the therapeutic areas of dermatology, respiratory and infectious diseases. On behalf of Novartis Pharmaceuticals Corporation, I thank you for the opportunity to review the current safety experience today for a long-acting beta agonist, Foradil.

There have been numerous safety concerns expressed publicly regarding use of long-acting beta agonists. The purpose of our presentation today is to discuss implications of recently available data related to the safety profile of

long-acting beta agonists. This morning Novartis would like to present to you the results and conclusions of our review of available safety data for Foradil. Based upon our review of clinical trial data and postmarketing experience, we would like to demonstrate that formoterol exhibits a favorable risk/benefit profile.

To provide a brief regulatory overview, Foradil was first approved for marketing in France in 1990, and subsequently approved in other European countries. Foradil received FDA approval to market in the United States in 2001. Foradil is currently approved in over 80 countries worldwide and to date, we currently have over 13 million person-years of exposure.

Foradil Aerolizer was marketed as a dry powder capsule for oral inhalation and was approved in 2001 for a dosage regime of 12 mcg twice daily for maintenance therapy for individuals with asthma 5 years of age and above for the following indications, acute prevention of exercise-induced bronchospasm in individuals 5 years of age and

older when administered on an occasional as needed basis, and for chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

Outside of the United States, Foradil is approved at 12-24 mcg twice daily and is a highly prescribed bronchodilator, and is also indicated for the maintenance therapy of asthma specifically in adults and children 5 years of age and older; for the prophylaxis and treatment of bronchoconstriction in patients with asthma; prophylaxis of bronchospasm induced by inhaled allergens, cold air or exercise; prophylaxis and treatment of bronchoconstriction in patients with reversible or irreversible COPD, including chronic bronchitis and emphysema. In some countries it is also approved as metered dose inhaler and multi-dose dry powder inhaler, 10 mcg, Certihaler.

In order to provide a more detailed review of our current data to date, I would like to introduce our speakers today. Dr. Gregory Geba, who is the Vice President and U.S. Head,

Respiratory, Dermatology and Infectious Diseases, Clinical Development and Medical Affairs for Novartis Pharmaceuticals, will present the safety profile of Foradil.

He will be followed by Dr. James Donohue, who is Professor of Medicine, Chief of Pulmonary Division, University of North Carolina, Chapel Hill, who will present the clinical implications.

In addition to the key speakers, we also have additional advisors available to address any specific questions you may have. Specifically from a statistical perspective we have Dr. Gary Koch, Professor of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill. I would now like to turn the podium over to Dr. Geba.

Efficacy and Safety of Foradil

DR. GEBA: Thank you, Dr. Floyd. Dr. Swenson, committee members, members of the FDA and interested attendees from the community, it is my role to review with you all of the clinical data and postmarketing data we have available for

Foradil, the other long-acting beta agonist being discussed today. We firmly believe that Foradil is a drug that provides clinical benefit with a favorable benefit/risk profile.

As indicated in the previous presentation by Dr. Floyd, and later on in this presentation by Dr. Donohue, the clinical features of Foradil have led to its inclusion in both U.S. and international guidelines in the treatment of moderate to severe persistent asthma.

These are the key points of the presentation. We will describe pharmacologic differences that exist between formoterol and salmeterol, which may or may not have clinical impact; a Phase 4 trial, 2307, which examined asthma-related serious adverse events in adolescents and adults; our integrated Foradil clinical database; and postmarketing adverse event data. The totality of the evidence does not elevate concern for a safety signal for Foradil which continues to support its favorable benefit/risk profile.

These are the chemical structures of formoterol on top and salmeterol on the bottom. Please note that at the end of the molecule that interacts with the beta receptor, the catechol end of the molecule, the molecules are actually similar in having a hydroxyl group at position 5. However, they are different at positions 6 where you see different side chains. Most importantly, at position formoterol has a much longer allophanic chain, as previously shown. Thus, although both molecules bind to the beta 2 receptor, differences in structure allow salmeterol to bind to an additional site within the beta 2 receptor termed an exosite. Prolonged salmeterol activity depends on binding with the exosite when formoterol's activity is independent of an exosite. In addition, mutation of the exosite region could affect the duration of action of salmeterol. One of the consequences of structural differences is that formoterol is a full agonist at the beta 2 adrenergic receptor, whereas salmeterol is a partial agonist.

Typical experiments illustrating this point are performed with human bronchial explants which show that the bronchodilatory effects of isoprenaline are decreased by prior incubation of tissues with salmeterol but not formoterol. The potential clinical implication of this difference is that in the setting of beta 2 receptor down-regulation the effect of rescue bronchodilators may be greater for full agonists than for partial agonists.

I would like to now move on to a discussion of the Phase 4 trial 2307. This trial was recently completed and is detailed in your briefing book. Why was this study done? Protocols 040, 041 and 049 were 3 pivotal studies conducted to support registration of Foradil in the United Sates and 040 and 041 were 12 weeks in duration and were conducted in adolescents and adults; 049 was conducted for one year in children ages 5-12.

Trial participants were randomized to receive Foradil 12 mcg BID, 24 mcg BID or placebo. In 040 and 041 there was also a comparison to

regular doses of albuterol 180 mcg QID. Please note that all groups were allowed to take additional doses of albuterol as needed for residual symptoms and all groups were allowed anti-inflammatory agents.

Shown here are the proportion of patients with asthma-related serious adverse events. These studies showed more serious asthma-related serious adverse events in the higher don formoterol arms compared to the lower doses or the approved formoterol arm as well as the placebo arm.

In light of these findings, the agency did not approve the higher dose of Foradil. After discussing this observation with the agency and with their guideline, we pursued a safety study whose primary endpoint was asthma-related SAEs. The inclusion and exclusion criteria for protocol 2307 were identical to protocols 040 and 041 which were our pivotal trials. Indeed, the resulting population studied in protocol 2307 was similar to that of the pivotal trials in adolescents and adults, which was the population studied and

requested, as shown in this slide.

Apart from the trial duration which is different, age differences were pretty similar.

FEV 1 at baseline was fairly similar. Please note that the proportion of black patients in this trial mimicked the proportion of patients in the U.S. population. There are some subtle differences in terms of ICS use and reversibility. Actual reversibility for 2307 was slightly less than 040 and 041 but otherwise the study populations were very, very similar.

The design of this safety study is shown here. Using identical entry criteria--again, these are identical entry criteria to those employed in our pivotal studies--after a 2-week run period, shown here, patients were randomized to receive, in a double-blind fashion, one of the following treatments, either formoterol 12 mcg BID formoterol 24 mcg BID--again, 12 mcg BID was the approved dose; 24 mcg was the higher dose. They received either of those two doses or placebo in another group or, in an open-label group, received

formoterol 12 mcg BID plus an additional up to 2 rescue doses of formoterol 12 mcg BID, which constituted the intermediate dose arm.

Please note that to increase the rigor of this study, after 16 weeks of treatment we planned to contact all patients, including those who discontinued, to record all adverse events. This assured that all patients would be evaluated for AEs irrespective of treatment efficacy and trial persistence.

Results of the study are shown here. Please note that there was a correction made to the briefing book provided by the agency. The lower dose arm had a somewhat higher number of patients who reported serious asthma-related AEs. However, after review of the specifics of these cases, the agency excluded 2 of these events in the Foradil 12 mcg arm, reducing that number from 5 to 3. Thus, the final event rates were 0.2 percent in the placebo group; 0.6 percent in the low dose group; 0.2 percent in the intermediate dose group; and 0.4 percent in the high dose group. Overall, there

were far fewer events than expected based on the pivotal trials.

Displayed on this slide are the point estimates and 95 percent confidence intervals--which I hope you can see as red on a blue background--for the proportion of patients experiencing asthma-related SAEs in each treatment group. As previously mentioned, the rates are low for all treatment groups. The 95 percent confidence interval for all Foradil doses combined overlaps the 95 percent confidence interval for placebo and excludes 1 percent. These data reflect the revised rates after an FDA adjudication.

In conclusion, the observed rate of adverse events was far lower than we expected from our pivotal trials despite demographics that were similar to protocols 040 and 041. Absolute differences between groups were very small. Higher SAE rates in the higher dose of Foradil arm, previously observed in adolescents and adults in protocols 040 and 041, were not observed in this larger, specifically designed safety study.

Now I would like to review with you a comprehensive safety analysis of our clinical trial database. We performed an extensive review of safety based on our clinical trial database which focused on deaths and asthma-related adverse events. In terms of deaths, we examined all controlled and uncontrolled trials in the Aerolizer and Certihaler databases. All studies irrespective of trial duration were examined to assure that the very rare case of sudden paradoxical asthma, culminating in the demise of a patient, was captured.

For the analysis of asthma-related adverse events we focused on controlled trials of greater than or equal to 4 weeks duration so as not to dilute the denominator for adverse events in trials of longer duration with very short trials, sometimes as short as 24 hours, which were performed to assess short-term changes in lung function.

For controlled trials the database included nearly 6,000 patients on Foradil, shown

here; for uncontrolled trials over 2,700. For trials of 4 weeks or greater in duration the number was over 5,000 on Foradil, whereas the placebo-controlled trial database was comprised of over 3,700 patients who had been randomized to Foradil.

Looking at our controlled trials, there were 3 deaths overall, one death in the Foradil group, representing over 1,600 patient-years of experience; one death in the albuterol group, representing 241 patient-years of experience; and one death in the placebo group, representing nearly 600 patient-years of experience. The rates of death, therefore, was 0.41, 0.17 and 0.06 in the albuterol, placebo and Foradil arms respectively. The Foradil death was asthma related, shown here, representing a rate of 0.06 asthma deaths per 100 patient-years of exposure. So, here we are expressing it as a rate per years of exposure to the drug, which represents less than one asthma death per 1,000 years of treatment.

In reviewing the uncontrolled clinical

database, it is important to note that these studies were those that did not incorporate comparator arms. They were all open-label and included trials conducted as part of compassionate use programs. In addition, patients tended to be older, with a high proportion of elderly subjects; had more severe asthma; used more beta agonists at baseline; and exhibited noon-asthma-related mortality at a higher rate, indicating a higher degree of general medical morbidity compared to the control database. There were 5 deaths overall, 3 of which came from one study in France which allowed entry of severely ill patients.

Now I would like to move on to address significant asthma exacerbations. This term includes asthma-related adverse events which were meaningful enough to prompt patient discontinuation whether severe or not and, to get to Dr. Schatz' point, included asthma-related adverse events reported as serious whether or not they caused a discontinuation. So, we are looking at patients that dropped out of the trial due to an

asthma-related event that was meaningful enough to stop therapy.

Displayed are the discontinuation rates due to an asthma-related adverse event in multiple dose, placebo-controlled trials of greater than or equal to 4 weeks in discontinuation. These are the discontinuation rates. Please note that there were fewer asthma-related discontinuations in the Foradil arms compared to the placebo arm or to albuterol. So, the rate overall for an formoterol doses was 7.1; for placebo it was 10.7; for albuterol 8.1. Please note that this was especially notable for the approved dose of Foradil, 5.6 versus 10.7.

A reverse pattern was observed for asthma-related serious adverse events. Foradil patients experienced more events than placebo. Here the imbalance was greater for the higher Foradil dose. The numbers are shown here, 3.5 for the approved dose versus 3.1 for albuterol, 0.9 for placebo and a higher rate for the albuterol 48 mcg dose. Again, this dose is the approved dose in the

U.S.

When both types of events are taken into consideration, the rate of significant asthma exacerbations, that is, asthma-related AEs meaningful enough to cause the patient to discontinue and asthma-related events that were labeled as serious whether or not they caused discontinuation, was actually lower for Foradil at its approved dose than the rate for placebo or for albuterol. Note that at the highest dose of Foradil that rate was similar to the placebo rate. But for Foradil at its approved dose the rate was 7.1 versus a placebo rate of 10.9.

In summary, based on this analysis of our clinical trial database for asthma-related adverse events, we observed a rate of significant asthma exacerbations for the approved Foradil dose that was lower than placebo rates.

I would like to now move on to a review of postmarketing data. In order to explore the adverse event profile of Foradil on the market and to provide some estimates as to how it might

compare to other drugs in its class, we performed an analysis of postmarketing data based on FDA AERS database, that is the FDA's adverse events reporting system.

We must recognize that this type of postmarketing analysis has its limitations. Although spontaneous reporting of ADRs remains the most common method used for monitoring the safety of marketed drugs and is useful for detecting safety signals, it is limited by the fact that a substantial percentage of ADRs are not reported. The reporting rate also tends to be lower the longer a drug is on the market. This is a well-known phenomenon and is known as the Weber effect. In addition, targeting drugs to lower or higher risk patients may alter apparent ADR occurrence, and notoriety associated with a drug or class may alter reporting rates. A final concern is that the ADR that is being reported in this instance is the disease itself, It is a manifestation of the disease itself.

We examined FDA adverse reports for death

or outcome of death and found that rates were highest in the first years after launch and declined each year thereafter. This analysis is shown in your briefing book.

We will now review the reporting rates for these and other events of interest. Please note that reporting rates are reports with case definition on the drug of interest divided by the exposure worldwide since the drug was marketed in the U.S. per 100,000 patient-years.

Relative rates of reporting can also be assessed by simply calculating the percentage of reports at case definition by the total number of adverse events reported. This does not take into consideration the exposure to the drug of interest and may inflate the Weber effect if there is a difference of time on the market. Shown here are the reporting proportions, on the left, and the reporting rates per 100,000 patient-years, on the right, for Foradil and salmeterol.

As you can see, the reporting proportion for formoterol, a drug that was established on the

U.S. market in 2001, compared to salmeterol, which was on the market since 1994, is somewhat higher. However, one must adjust for the exposure to the drug which was far greater for salmeterol. When adjusting for this higher number of exposures for salmeterol the result ratio flips. That is, when we adjust for actual exposure to the drug we note that the rate for Foradil was somewhat lower than that of salmeterol.

In conclusion, well-described pharmacologic differences exist between formoterol and salmeterol although the clinical relevance is not known. In pivotal trials conducted for U.S. registration, a potential safety signal emerged in the Foradil high dose group, leading only to the approval of the 12 mcg dose, that is 12 mcg BID, and the request for postmarketing asthma safety study 2307. Study 2307 examined asthma-related serious adverse events in adolescents and adults and did not provide evidence of a safety signal for Foradil at any dose.

An analysis of the pooled Foradil clinical

trial database and a review of postmarketing adverse event data, with its limitations, do not provide evidence of a safety signal for Foradil. The totality of the evidence, therefore, does not elevate concern for a safety signal and continues to support the favorable benefit/risk profile of Foradil in the treatment of asthma.

Thank you for your attention. Dr. James Donohue will now present the clinical implications.

Clinical Implications

DR. DONOHUE: Thank you, Dr. Geba. Dr. Swenson, members of the advisory committee, Dr. Chowdhury and Dr. Meyer and members of the FDA, ladies and gentlemen, I am here today as a clinician investigator to talk about the clinical implications of the long-acting beta agonist class. As an older physician, I can talk a little bit about life before the introduction of the long-acting beta agonist class into our clinical practices. While the alternatives were short-acting beta agonists, theophylline, various epinephrine agents, oral beta agonists, each of

these treatments had different benefit/risk ratios or profiles from the long-acting beta agonist class. I would like to discuss a little bit the implication of the roller-coaster effect on our patients with asthma's lives, the lack of nocturnal coverage with most of these shorter-acting agents and issues with compliance. There have always been issues with the short-acting beta agonists for the need to frequently dose; special issues with our children and whether or not they could be dosed in the schools; the difficulty in our blue-collar workers, of course, who need frequent dosing of their medications.

The short-acting beta agonists have, as I say, benefits and risks. Overdosing of the short-acting beta agonists was associated with tremor, particularly with the peak. There were changes in metabolism, hypokalemia and changes in glucose metabolism which may or may not be clinically significant but could be under certain circumstances. There was also tachycardia associated with people using some higher doses or

people who had more co-morbidity issues. Then also, to inform us, we had very useful data from Saskatchewan looking at thee use of short-acting beta agonists in Canada. These are combined data for formoterol and albuterol.

These are the deaths per 100,000 per year and the number of canisters. We can see that as we start getting up in the number of canisters, especially win formoterol, one sees an increase in deaths due tot he short-acting beta agonists or associated--not necessarily due to but associated with the short-acting beta agonist class. So this was, of course, a concern to all of us and is part of the recommendations presently in the guidelines.

We also had different side effect profiles of other medications available to us before the long-acting beta agonists and drugs we would have to consider today as substitutes. First and foremost, theophylline, particularly the longer-acting forms. Their safety profile is important to look at. There was a narrow therapeutic window, as everyone knows, with these

drugs. There were very, very important drug interactions. In fact, if we look at our elderly asthmatic population, commonly these patients would enter the hospital with use of an antibiotic or a medication for reflux causing a drug-drug interaction and making the patient theophylline toxic. Furthermore, if we look at drug interactions in the hospital, there is a huge safety concern about medication errors, and what-have-you, and theophylline were always at the top of the list.

Other medications we had were oral beta agonists, both short-acting and long-acting and, again, much less of an efficacy profile as compared to the long-acting inhaled agents and a much greater safety risk with tachycardia, tremor and reflux. Oral corticosteroids have to be used more and more when patients have more and more exacerbations and I don't have to review the laundry list of side effects that are well-known to everyone in the room.

Now, throughout the world we have--I have

outlined in yellow here the G8 nations because of last week's meeting, but we can see the variation in prevalence of asthma symptoms as we get more industrialized societies. We see a very large increase in the number of patients who suffer with airways disease.

On the other hand, there are facts that I find very, very consoling and comforting. This is the death rate due to asthma in the United States going back to 1960 up to 2002. These are the deaths per 100,000 so we can sort of get the rate that you are asking for. Then we have the African Americans here and the Caucasian population here.

Short-acting beta agonists were introduced in the 1970s. We had the inhaled corticosteroids introduced in the 1980s. There have been enormous efforts in patient education, efforts by the expert panels of the National Institute of Health for guidelines and just generalized education programs, along with the introduction of effective controller medicines along with the long-acting beta agonists that seems to have led to a decline, although still

very high, relatively higher in the African American population, but to the general United States population, from 5,400 to a little bit above 4,000. So, we are clearly doing something right. What the attribution would be here to the various things introduced is, of course, beyond my ability to say but, clearly, all these things together have helped us to improve the lives of our patients.

Now, what about the long-acting beta agonists? Just briefly, you have seen an awful lot of this data this morning and, at the risk of being a little bit redundant, the first benefit, of course, is in patient symptoms. These are better bronchodilators. I think we would all agree that the data are overwhelming on this. There is a reduction in the roller-coaster effect, and I will come back to that in a minute; better control because of the longer duration of effect and nocturnal symptoms. Because of the control, we have less use of rescue medications. We have improved morning lung function and also less diurnal lung function variability. It doesn't

completely eradicate it but it does minimize to some extent some of the early morning dipping that leads to waking up or even worse outcomes. Also, equal important perhaps, it gives us protection against exercise-induced bronchospasm and that is the exercise of normal daily activities in normal life, and it is nice to have that kind of protection on board so you don't have to continuously dose yourself.

Looking at the formoterol data, Dr. Geba has shown us the safety data. We saw that there are 3 pivotal trials that you have in your briefing documents. There is superior improvement in the FEV 1 over placebo over the course of 12 hours. This duration of action is sustained for 12 weeks so there doesn't appear to be a signal that there is any tolerance or reduced efficacy. There is a reduced need for nighttime rescue medicine, and the onset of action is similar to albuterol, as has been outlined.

Just again showing the similar 12-hour studies, this is the 040 and the 041 that you have

seen a moment ago. This is at week 12. Here we see the 12-hour curve and this is the mean change in baseline FEV 1. Here is the short-acting albuterol and placebo, and here is the sustained effect of the long-acting beta agonist, in this case formoterol. First of all, let me draw your attention to the pre-dose or trough. Often we power clinical trials on long-acting beta agonists and this changes well over 10 percent here, around 12 percent, and that usually can be transferred to as meaningful clinical improvements such as symptoms in the morning and what-have-you. Over the course of the day you see the roller-coaster. That in itself means nothing but what this means here is that as these drugs flow off here our patients become symptomatic and have to disrupt their daily activity to take rescue albuterol.

Also one other thing I would like to show here is the peak effect. Patients perceive change and when you have a nice plateau effect a lot of side effects such as tremor are much less perceptible to a patient.

Other outcomes besides bronchodilator is rescue medication. These again are from 040 and 041, the run-in for the 3 arms, formoterol, albuterol and placebo. We see over the course of 4, 8 and 12 weeks a nice decline in the rescue albuterol. These parameters are less rigorously defined but we think the minimal clinical improvement in that parameter is 0.8 puffs per day ranging to 1. So, it appears to be in the ballpark of something that means something to a patient and we could quantitate that.

Simply, formoterol reduces nocturnal symptom scores. I am showing 040 and 041 which I believe are the adult studies run-in and over 12 weeks and the companion study here. We see a nice decline from about 0.5 to 0.1 in the nocturnal asthma symptom score parameter.

To end up, one of the studies that I take consolation from as a physician is the FACET study. Again, points are well taken here today, we are talking about deaths. It is very difficult in asthma studies though to power our studies, as

everyone in the room has heard over and over again, on death as the outcome. Exacerbations are extremely important and the reason that I take a lot of comfort from this study is that it is a one-year study. Also, the exacerbations are precisely defined, as Dr. Sorkness mentioned this morning.

In this study we see--again in the mechanical function, 835 patients, 12 months--a marked improvement after the run-in. The patients were in the run-in symptomatic on inhaled corticosteroids. But this study gives us some look at what is the added value of adding a long-acting beta agonist--added clinical value--to inhaled corticosteroids.

Here are the two budesonide arms. I think there is no surprise that on the mechanical function we do see a change of 7 or 8 percent. But I think one takes a better message away from looking at exacerbations. First of all, if inflammation is ongoing and not being checked the patient is going to know that they are going to

breakthrough with an exacerbation. This is our best clinical surrogate for the so-called masking of inflammation, that is, the breakthrough of exacerbations. In a study of one-year duration we have adequate duration to bring this signal out.

So, in this study, as Chris Sorkness pointed out this morning, we have an arm with 100 BID of budesonide and with formoterol. Then, the second arm is 400 BID with the addition of formoterol. And, the exacerbations were described as mild with an increase in terbutaline, the rescue medicine, and severe, defined by a 30 percent change in peak flow and oral prednisone. The decline in mild exacerbations was about 29 percent and 40 percent with the combination. But with the higher dose, high dose budesonide reduced the exacerbation rate by 49 percent. When one adds formoterol to it it went to 62 percent. So, there is a net gain there and the actual clinical implication of that is that it appears to be significant. We really haven't put a number on that yet but that, in my mind, is a very reassuring

piece of evidence that supports the use of this class of drug.

Using the best evidence that one has, the expert panels--many of the members of which are in the room here--have come together, and you have seen this before over and over again, and have concluded that inhaled steroids and long-acting beta agonists have a complementary effect. One can lower the dose of inhaled corticosteroids by using the combination, and not everyone responds to inhaled corticosteroids although a great majority do.

For more severe patients we would be using higher doses of inhaled corticosteroids and long-acting inhaled beta agonists and, hopefully, we will be able to avoid the use of prednisone and its very difficult side effect profile.

So to summarize, long-acting beta agonists have really become an established part of the current standard of asthma treatment in the United States and also internationally. It is an integral part of internationally established guidelines

using the best evidence that we have at our disposal at the present time. It is well established that long-acting beta agonists have a place in the treatment regimen for asthma but must be conjunction with inhaled corticosteroids for those with moderate and severe persistent asthma.

Again, I don't think at the present time there is an alternative inhaled controller bronchodilator or one on the immediate horizon that is suitable for asthma. So the LABAs, the long-acting beta agonists, have provided documented improvement in symptoms, airway function and quality of life and you have heard a great deal about that today. For whatever reason, since the introduction of long-acting beta agonists, controllers and a national effort in education and guidelines, asthma hospitalizations and mortality have decreased, which is very reassuring at least to me and I think to many others. Long-acting beta agonists in conjunction with inhaled steroids represent a medication category critical for optimal care of patients with moderate to severe

asthma. Thank you very much.

Questions by the Committee

DR. SWENSON: The time now is open for questions to Novartis. Dr. Schatz?

DR. SCHATZ: Some of the things we are hearing suggest a possible disconnect between exacerbations, as has been studied and defined usually to include oral steroids and emergency departments or hospitalizations, and then death or near death. So, I guess my question has to do with 2307. How were SAEs defined? However, were asthma-related SAEs defined?

DR. FLOYD: Dr. Geba?

DR. GEBA: To answer this question I would like to bring up a slide that gives the definition of asthma-related and the definition of serious.

We used predefined asthma terms, MedDRA terms, MedDRA preferred terms. Asthma-related AEs were defined as asthma, dyspnea, bronchospasm and chest discomfort, cough, wheezing, etc., acute respiratory failure and hypoxia. For the definition of SAEs it was one of the above plus one

of the following, death, life-threatening hospitalization, disability, congenital abnormalities--this is regulatory definition, and required intervention to prevent further impairment--standard definition.

DR. SCHATZ: Just to follow-up, intervention could mean oral corticosteroids?

DR. GEBA: Yes, it could be. It could be medical intervention.

DR. SWENSON: Miss Sander?

MS. SANDER: Yes, on slide CO-10 it says "sustained improvement in FEV 1 at 12 weeks." Was the albuterol depicted here scheduled or was it based on symptoms?

DR. GEBA: The albuterol dose in these trials was scheduled.

MS. SANDER: I have another question on the next slide. It says "Foradil reduces rescue medication use." Is that albuterol use? And that is for exacerbation? Is that right?

DR. GEBA: The presumption is it is exacerbation. It was albuterol usage rescue

defined by the patient who was symptomatic and, therefore, referred to rescue medication with albuterol. Correct.

MS. SANDER: So, that phrase there, "rescue medication" is defined as rescue needed by the patient.

DR. GEBA: Yes.

MS. SANDER: So, not scheduled.

DR. GEBA: No.

MS. SANDER: Thank you.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: I have a question about the 049 pediatric study. The slide that shows the serious AEs looked distinctly different than the AE profiles in the adult trials. Can you give us any further insight into that, any other data that you might have regarding those differences in children in the 5-12 age range compared to the adults?

DR. GEBA: I would like to point out that the age range of patients in our so-called adult trials was actually 12 and on so it would include adolescents and adults. This population of

patients was 5-12 so it was definitely a younger population of patients and truly children in 049. There was a difference in rates of exacerbations in these trials and the point I guess that I would like to focus on, if you could bring that slide up, the 3 trials together, the 3 pivotal trials, slide CS-7, please. Thank you.

What we noticed in the 3 pivotal trials was that for the Foradil high dose arm there was a higher event rate compared to the lower don formoterol arm. You did notice, and we did as well, that the rate for those events was still higher in the lower dose of the Foradil arm for pediatric patients.

We were most concerned, as the agency was, and this was guided by conversations that we had with the agency to determine whether or not there was a dose effect going from 12 to 24 mcg. Upon discussions with the agency, we designed a trial to prospectively test whether or not there was a dose effect between 12 mcg and 24 mcg, and we were requested to study the identical patient population

as in 040 and 041. So, we recognize that this area has not yet been fully analyzed and evaluated, and we are not certain as to why the issue occurred in this age group.

DR. SWENSON: Dr. Gay?

DR. GAY: Thank you. The data of the SMART study suggests that a predominance of the number of adverse outcomes began to occur after about 90 days. That is where the split in the Kaplan-Meier curves begins to become much more significant. A number of the studies that you performed are at 90 days or a little bit longer. I wonder if you have available any post-study data of a 3-month or 6-month follow-up that may show any change or any increase in the number of adverse events, such as asthma-related deaths or significant numbers of exacerbations, that go with your most recent study or even the earlier studies, 040 or 041?

DR. GEBA: Right, in the longer and most recent studies there were none of those events that would contribute to this. We only had one death in

all of our clinical trials of over 6,000 patients with 16,000 patient-years of experience.

We would like to point out that there is a continuity, one would argue. We analyzed this data in terms of the event rates for serious adverse events to determine whether or not they occurred randomly during those first periods of time during the trial allowing us to, therefore, pool and express these rates as rates per 100 patient-years of exposure. And, that is what we have done.

On the slide shown here is depicted the Foradil versus placebo asthma-related serious adverse event proportion and, as you can see, there is a distribution in that 3-month window. Also, I would point out that even in the briefing book if you look at the rates of events that occurred in SMART, you can detect already a separation by an earlier time point than the 3-month time point. So, we were fairly confident that we could pool the data sets that we have, limited by the fact that we don't have trials as long as for salmeterol, and come up with a reasonable estimate as to the event

rates based on this type of analysis.

DR. GAY: Just in follow-up, I want to make sure I understand this correctly. My question clearly is going to lead to less rigorous data but I am concerned about follow-up time longer than your study duration, longer than the 12 or 16 months, not within that specific time frame.

DR. GEBA: Right.

DR. GAY: Is this data concerning that time up to 3 months post the end of the study?

DR. GEBA: No, we did not routinely follow patients beyond the time of their study treatment, except for a routine visit usually performed 2 weeks post study.

DR. GAY: Thank you.

DR. GEBA: Thank you.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Thank you. I am going to talk in reference to the pooled Foradil clinical trial database in which you have shown, and correct me if I am quoting wrongly, that for less severe events--let's call them that way for a

moment--there was no difference between formoterol and placebo or albuterol. But for more severe events there was a difference.

So, let me propose to you, and I would like to elicit your comments, that there could be two different ways in which the deterioration of asthma may occur, which may occur in different patients with different risk factors and with different asthma phenotypes. I am proposing this to you as an interpretation of your data. Let's call one of them loss of asthma control, in other words, slow deterioration; increase in symptoms with more wheezing, more cough. I saw that all those elements were present in your definition. For those, let me propose to you that there is no difference between formoterol and placebo or albuterol.

But it could be that there is a different set of patients in whom these symptoms don't occur every day and they have a more brisk, brittle form of the disease. It is in these patients that you see that placebo is associated with 0.3 percent.

These patients justify the fact that in placebo you only see 0.3 percent and you see much more win formoterol. This goes to issues that have been raised by other members of the committee as to how we can explain that in terms of the everyday symptoms, in terms of control of asthma we see improvement with the use of all medicines in this class, but we are seeing in many studies a signal that there could be more severe disease. Could it be that we are in the face of two different forms of expression of asthma deterioration that have different responses to this class of medicines?

DR. GEBA: Yes, we have not done a sufficient enough analysis of these events. I would point to Dr. Cioppa from Novartis to respond to that question. Thank you.

DR. DELLA-CIOPPA: Thank you. My name is Giovanni Della-Cioppa and I am Vice President for Clinical Research. Dr. Martinez, your explanation is certainly one possibility. There is also another possible explanation that we would to bring to your attention, keeping in mind that we are

talking here about clinical trials, and we are talking about clinical trials of bronchodilators. Despite the fact that these trials are blinded, many patients have a clear perception of an improvement of their lung function quite rapidly. So, one could assume that these two kinds of events represent very similar events in terms of magnitude, in terms of gravity, in terms of impact on the patient's well being.

But if I am a patient on placebo, or I think I am a patient on placebo and I start going down the drain--as shown this morning, there are a few days of unfolding of the event--then I will abandon the trial and experience, therefore, a discontinuation due to asthma. If I am a patient on active and I know I am on active I will be more reluctant to get out of the trial, and stay on the trial, and the same event will be labeled by the investigators as a serious adverse event.

It is baffling, this kind of mirroring situation by which people on placebo get out from the trial due to asthma and the people on active

who stay on the trial and get serious adverse events. So, the two explanations are not mutually exclusive but I just wanted to offer an alternative explanation because we are seeing it again, and again, and again, and we are seeing it in the pooled database, as shown by Dr. Geba.

DR. MARTINEZ: However, as much as I can accept your arguments, I would suggest that either of the two explanations, or both, are potentially reasonable for the data as it has been presented.

DR. SWENSON: Dr. Meyer?

DR. MEYER: Thank you. I just wanted to make something explicit prior to lunch as sort of a summary from the agency standpoint from these morning's presentations. We have heard presentations from two sponsors that centered around new data from studies and, of course, we will have our own perspective on those after lunch. But these are very different studies. These are almost apples and oranges. They were purposefully so because they were meant to address very different questions.

The SMART study was meant to address a signal that was coming out from postmarketing data where we didn't feel like that could be adequately addressed by the postmarketing data or perhaps even by epidemiology studies but raised even, even pre-approval by the SNS study, a signal of very rare, very dire events that were not well predicted by the more common adverse events, even serious adverse events, in shorter-term trials. Hence, a very large, very prolonged study.

The formoterol 2307 study was not designed to answer that kind of question. It was designed to answer the question of events seen in shorter-term trials, representing more sort of common serious adverse events that were detected in the database, and really was meant to explore a dose effect, as was previously stated.

So, I just wanted to be very explicit about the fact that what we are talking about here in the end are two very interesting studies but they are addressing, and perhaps answering to the degree they did answer them, very different

questions.

DR. SWENSON: And Miss Watkins has one announcement, after which we will adjourn for lunch.

MS. WATKINS: I would like to remind the committee that, in the spirit of the Federal Advisory Committee Act and the Sunshine Amendment, discussion about today's topic should take place in the form of this meeting only and not occur during lunch, breaks or in private discussions. We ask that the press honor the obligations of the committee members as well.

Additionally, the committee members, once you get lunch in Salon E, there is reserved seating for the committee members in Salon D, and we ask that you take advantage of that.

DR. SWENSON: There is one other question here. Dr. Newman, I apologize for leaving you out.

DR. NEWMAN: Thank you. I just want one clarification, if I could. You emphasized the pharmacological differences between this drug and salmeterol. Are you suggesting that because of the

pharmacological differences the studies, such as SMART, are somehow not relevant to your drug?

DR. GEBA: No, we can't go that far and I don't want to overstate those differences. I just wanted to point out that the molecules are different; that the receptor binding mechanism is somewhat different; the onset of action, those types of things are different between the two molecules. Whether or not that has an implication in terms of outcomes of the sort that we have been discussing this morning is conjecture. It cannot be ascertained. But for completeness we included a full discussion of the molecule and differences from the other one that is relevant in its class.

DR. NEWMAN: Just in follow-up on that, so in terms of the pharmacologic action and factors such as desensitization of the beta receptor, there still is a desensitization effect, is there not?

DR. GEBA: Well, we have some data that distinguishes the two, and to approach that I would ask Dr. Trifilieff to respond to that question. Dr. Trifilieff is from basic research in Novartis.

DR. TRIFILIEFF: So, the question was about agonist desensitization? In theory, full agonists will induce much more desensitization than partial agonists. But what you have to take into account also is the density of the receptors because basically a partial agonist, by definition, would need more receptor in order to achieve the same efficacy as a full agonist. So, in a situation where you have low density of the receptor a full agonist will need a 4 receptor; a partial agonist will need 40 receptor. So, you have a greater desensitization for partial agonists compared with full agonists.

DR. SWENSON: I wish to thank everyone for their participation. We will reconvene at one o'clock rather than 12:45 as is presently on the schedule.

[Whereupon, at 11:50 a.m., the proceedings were recessed, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. SWENSON: Good afternoon, everyone. We will resume the meeting with the FDA presentation. To begin, Dr. Sally Seymour will first speak, to be followed then by Dr. Harry Gunkel, after which the panel will have the opportunity to raise questions to the two presenters.

FDA Presentation

Salmeterol

DR. SEYMOUR: Good afternoon. My name is Sally Seymour and I am a medical officer in the Division of Pulmonary and Allergy Drug Products. I am going to be speaking to you today about the long-acting beta agonist salmeterol. Much of what I will present today has been presented this morning but I am going to present you the agency's perspective.

The objectives of my presentation today are to discuss the regulatory history of salmeterol, which was the first long-acting beta agonist approved in the United States. In the

regulatory history I will emphasize the agency's actions in response to the safety concerns with salmeterol. I will then review the postmarketing clinical studies with salmeterol which were conducted by the sponsor, including the SNS study and SMART. Following the discussion of the postmarketing studies, I will briefly discuss the postmarketing spontaneous event reports for salmeterol. Then I will highlight the sections of the product label which include information about the postmarketing studies.

Let's begin with the regulatory history. Serevent Inhalation Aerosol was approved in February, 1994 for asthma. The indication is long-term twice daily administration in the maintenance treatment of asthma and the prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airways disease. Indications for exercise-induced bronchospasm and for COPD were added later. However, the focus of the discussion today, as you know, is on asthma.

As mentioned earlier, the sponsor chose to

discontinue Serevent Inhalation Aerosol as part of the CFC phaseout and, thus MDI is no longer marketed. Serevent Diskus is a dry powder formulation of salmeterol which was approved in February, 1997 for similar indications as the Inhalation Aerosol. The Discus is approved in children down to 4 years of age.

Finally, Advair Diskus, which is a combination product of the corticosteroid fluticasone propionate and salmeterol, was approved in August, 2000 for asthma, and later the indication for COPD with chronic bronchitis was added.

Let's start at the time of the salmeterol inhalation aerosol NDA. The NDA for salmeterol inhalation aerosol was supported by 2 Phase 3 12-week active and placebo-controlled clinical trials in 556 patients with mild to moderate asthma. At 12 weeks the clinical studies demonstrated an improvement in the salmeterol group versus placebo in the following endpoints, FEV 1 and peak expiratory flow rate, mean percent days and

mean percent nights with no asthma symptoms, and less rescue medication use.

I would like to point out that at the time of the NDA review the results of the SNS study were known and considered. The SNS study, as you know, was a postmarketing study in the United Kingdom and I will discuss that shortly. An advisory committee meeting was held in February, 1993 to provide advice and make recommendations regarding the salmeterol inhalation aerosol NDA. The advisory committee was supportive of approval of the salmeterol NDA in adults and subsequently salmeterol inhalation aerosol was approved in February of 1994 for asthma.

Shortly after approval reports of life-threatening respiratory events and fatalities with salmeterol use were reported. Multiple meetings were held with the sponsor to discuss the reports. Some of the postmarketing event reports suggest that there was possible inappropriate use of salmeterol. This concern led to revisions in the label in January, 1995. The warning section

now included the following statements: Serious acute respiratory events, including fatalities, have been reported with salmeterol. Salmeterol is not for acute symptoms. Salmeterol is not a substitute for oral or inhaled corticosteroids. Salmeterol should not be initiated in worsening or acutely deteriorating asthma, and patients should have a short-acting beta agonist for acute symptoms.

The sponsor also conducted a physician and patient education program which included a "dear healthcare professional" letter. In addition, as you know, the sponsor committed to a large safety study, the Salmeterol Multicenter Asthma Research Trial, or SMART. SMART was initiated in July, 1996, and I think it is important to point out in the regulatory history what the sponsor mentioned earlier, that the SMART study had to be amended in June of 1999 to double the population from 30,000 to 60,000 patients because of fewer than expected outcome events.

A planned interim analysis was performed

in 2002 after approximately 26,000 patients had been enrolled. The DSMB reviewed the interim analysis data. The data indicated that the point estimates suggested an excess risk with salmeterol and that African Americans may be at particular risk. DSMB recommended to continue the study if timely recruitment was feasible. If timely recruitment was not feasible, the DSMB recommended to terminate the study and disseminate the findings to the clinical research communities within 3-6 months.

Based upon the interim analysis and difficulty with enrollment, the sponsor terminated SMART in January, 2003. A "dear healthcare professional" letter was also issued in January, 2003. The sponsor submitted preliminary data from the interim analysis of SMART to the agency and, based upon the preliminary data the product label was revised in August, 2003. It is somewhat unusual for the agency to make labeling changes based upon preliminary data, however, the agency felt the SMART information was important to include

in the product label. Labeling changes included a boxed warning and information in the clinical trial section of the label regarding the findings of SMART. These labeling changes were applied to all salmeterol-containing products, including Advair. When a safety signal is noted with a drug substance the agency's practice is to apply labeling changes to all products containing the drug substance unless there are data to establish the absence of the safety concern for a particular product.

In August, 2003 the sponsor submitted the full SMART data set. The sponsor indicated at the time that the National Death Index or NDI search had been performed and noted that some of the additional deaths were still being adjudicated. In February, 2004 the sponsor submitted the full SMART study report which included the adjudicated NDI data. After review of the study report the label was once again revised to include more details regarding the results of SMART. That brings us up to date on the regulatory history.

Now let's discuss the postmarketing

studies which I touched upon in the regulatory history, the first of which is the SNS study. The SNS study was a randomized, double-blind, active-controlled, parallel group 16-week trial in the United Kingdom. The population was 25,000 patients with asthma who were randomized in a 2:1 fashion to salmeterol 50 mcg BID or salbutamol 200 mcg QID Salbutamol is a short-acting beta agonist known as albuterol in the United States. Note that this was not a placebo-controlled study. It was an active-controlled study in which both arms were treated with regularly scheduled beta agonists. Clinic visits were conducted at 4, 8 and 16 weeks. Outcome measures were serious adverse events and reasons for withdrawals.

This table displays the key findings in the SNS study, and recall that the randomization was 2:1. I would like you to note the following, first, there is a numerical increase in respiratory and asthma-related deaths in the salmeterol group with a relative risk of 3. However, this was not statistically significant. Second, there was no

difference in the respiratory and asthma-related hospitalizations or other respiratory and asthma-related serious events between the salmeterol and salbutamol group. Finally, there were significantly fewer asthma- and respiratory-related withdrawals in the salmeterol group and this was statistically significant.

As mentioned earlier, the results of the SNS study, which showed a numerical increase in respiratory- and asthma-related deaths, although not statistically significant--these were considered at the time of approval of salmeterol and were discussed in the February, 1993 advisory committee meeting. The benefit of salmeterol was felt to outweigh the risk. Thus, salmeterol inhalation aerosol was approved in 1994.

Following approval of salmeterol, there were reports of serious asthma events, including fatalities. In working with the agency, the sponsor committed to a large safety study, the Salmeterol Multicenter Asthma Research Trial, or SMART, which I will discuss next.

SMART was a multicenter, randomized, double-blind, placebo-controlled, parallel group study of 28-week treatment duration. The sample size was initially planned to be 30,000 but then was increased to 60,000 in 1999 because of a fewer number of events than expected. Subjects were greater than or equal to 12 years of age with a clinical diagnosis of asthma. They were currently taking prescription asthma medications but no long-acting beta agonists. Subjects were randomized to salmeterol 50 mcg BID or placebo BID for 28 weeks treatment in addition to usual asthma care. Subjects underwent one clinic visit in which they were given a 28-week supply of salmeterol or placebo, and telephone contact was made every 4 weeks.

The primary endpoint for SMART was the combination respiratory-related deaths and respiratory-related life-threatening experiences. Respiratory-related life-threatening experiences were defined as intubation and mechanical ventilation.

Ideally, the endpoints for SMART would have been asthma-related deaths and serious asthma exacerbations but, based upon historical data, the number of events was expected to be low. Thus, the primary endpoint of the study was broadened to respiratory-related deaths and respiratory-related life-threatening experiences. It was thought that a respiratory-related life-threatening experience was a marker of fatal asthma and asthma-related deaths.

As you can see in the list of key secondary endpoints, asthma-related deaths was one of the important secondary endpoints, in addition to all-cause death, asthma-related deaths and life-threatening experiences and all-cause serious adverse events or SAEs.

SMART was designed as a non-inferiority trial and was designed to show that there was no difference in the outcomes between salmeterol and placebo. SMART was powered to rule out a 40 percent increase in the combined respiratory-related deaths and life-threatening

experiences and a 3 times increase in asthma-related deaths. These numbers may seem high but, again, they were based upon the numbers of expected events and the ability to power and conduct the study. As you may recall, the SNS study with 25,000 subjects suggested a relative risk of 2 for respiratory- and asthma-related deaths for salmeterol versus salbutamol.

An interim analysis was planned after approximately half the subjects were enrolled. Prespecified stopping criteria were the following, a relative risk of 1.4 for the primary endpoint and a relative risk of 3 for asthma-related deaths, with an alpha of 0.01.

An interim analysis was performed in 2002 after 26,000 subjects were enrolled. The DSMB reviewed the interim analysis data in a blinded fashion. The data suggested a potential treatment group difference, thus, the DSMB was unblinded. After unblinding the DSMB, the data suggested an increased risk for salmeterol use. An exploratory subgroup analysis suggested that African Americans

could be at particular risk. However, the study did not meet the prespecified stopping criteria. The DSMB recommended to continue the study if timely recruitment was feasible. If timely recruitment was not feasible, the DSMB recommended to terminate the study and disseminate the findings within 3-6 months to the clinical and research community. Due to difficulties with enrollment and the interim analysis finding, the sponsor terminated SMART in January, 2003.

Before discussing the results of SMART I would like to note the following: The results are from a terminated study which did not meet prespecified stopping criteria. I think it is important to note as I present the results that the non-inferiority objective was not met. In fact, the data I will show you suggested a difference in some endpoints between salmeterol and placebo.

The results are based upon the 28-week treatment period. The protocol specified that investigators could report SAEs and deaths for up to 6 months after the 28-week treatment period.

The initial SMART data submitted to the agency included events collected not only from the 28-week treatment period but also events spontaneously reported in a 6-month post-study period. The agency believes the data from the 28-week treatment period is clinically the period of interest. Thus, the results I will discuss will be based upon the 28-week treatment period.

The results also include data from the National Death Index search. Although this was not specified in the protocol, the agency determined the NDI search data was acceptable to capture outcomes during the 28-week treatment period. Finally, the results are based upon life table analyses to help account for censoring the subjects during the study.

This table shows the subject disposition for SMART. As you can see, subject disposition was similar between treatment groups and other categories of disposition not listed, such as loss to follow-up, were well matched between the treatment groups.

Similarly, subject demographics were similar between the treatment groups, with the mean age in both groups of 39 years of age; 64 percent females and 36 percent males in both treatment groups. Note that the ethnic origin was similar and that the majority of the subjects were Caucasian, with 18 percent African Americans.

The results for the primary endpoint, which was the combined respiratory-related deaths or respiratory-related life-threatening experiences are shown on this table. Respiratory-related and life-threatening experiences, again, were defined as intubation and mechanical ventilation. The relative risk for the total population is 1.4. Note that the confidence interval does not exclude 1 but the lower bound approaches 1. Remember that the study was terminated early. If the study had continued, it is possible the confidence interval would have tightened and excluded 1.

On post hoc subgroup analysis Caucasians do not appear to be at increased risk, however, African Americans had a relative risk of 4.1, with

confidence intervals that excluded 1. Thus, African Americans appear to be at particular risk for the primary endpoint.

This table shows the results for some of the key secondary endpoints for SMART. The following should be noted: Note that the number of events was low. For asthma-related deaths there were 16 deaths in 26,000 subjects. For the total population asthma-related deaths were increased in the salmeterol group with the relative risk of 4.37 and confidence interval that excluded 1. These results are similar to the results of the SNS study which showed a numerical increase in respiratory and asthma deaths with a relative risk of 3 for salmeterol versus salbutamol. Respiratory-related deaths could include other causes of death, such as pneumonia, in addition to asthma-related deaths. For the total population respiratory-related deaths were also increased in the salmeterol group with a relative risk of 2.16 and confidence intervals that excluded 1.

Subgroup analyses for asthma-related

deaths and respiratory-related do not suggest a difference in risk between Caucasians and African Americans. For combined asthma-related or life-threatening experiences the salmeterol group was noted to have more events, with a relative risk of 1.7 and confidence intervals that excluded 1. Subgroup analyses suggest that the African American subgroup is driving the results for the total population. In the African American subgroup the relative risk is 4.92 with confidence intervals that excluded 1. Although not on this slide, it is important to note that there is no difference in all-cause death or all-cause hospitalizations between treatment groups.

What about the effect of inhaled corticosteroid use on the outcomes? As you heard earlier, SMART was not designed to look at the effect of inhaled corticosteroid use on outcomes. However, because of their role in the management of asthma, information regarding inhaled corticosteroid use is of interest. The following should be noted though, a subgroup analysis looking

at the effect of inhaled corticosteroid use was not prespecified in the protocol. All analyses looking at inhaled corticosteroid use are post hoc exploratory analyses. Inhaled corticosteroid use was recorded at baseline only. Inhaled corticosteroid use was not randomly assigned. Baseline inhaled corticosteroid use may reflect an imbalance in other factors that could influence clinical outcomes. Therefore, any difference in outcomes between groups, defined by baseline inhaled corticosteroid use, may not be attributable to inhaled corticosteroids. Approximately half of the total population used inhaled corticosteroids at baseline and 38 percent of African Americans used inhaled corticosteroids at baseline.

This table shows the post hoc analyses for the primary endpoint by baseline inhaled corticosteroid use. On the left side of the table are the results for subjects using inhaled corticosteroids at baseline, and on the right side of the table are the results for subjects who didn't use inhaled corticosteroids at baseline.

In the total population the relative risks are similar for subjects who used inhaled corticosteroids at baseline and subjects who did not use inhaled corticosteroids at baseline. Recall that in the African American subgroup there was a strong signal for the primary endpoint. When analyzed by inhaled corticosteroid use there was an increased number of events in the salmeterol group versus placebo for the primary endpoint whether on inhaled corticosteroids or not at baseline. Thus, African Americans appear to be at increased risk for the primary endpoint regardless of baseline inhaled corticosteroid used.

This table displays the key secondary endpoints for the post hoc exploratory inhaled corticosteroid use analyses. Again, the numbers are small, making it difficult to draw any definitive conclusions. However, note again that in the African American subpopulation there was an increased risk for salmeterol for these secondary endpoints regardless of baseline inhaled corticosteroid use.

Although definitive conclusions regarding inhaled corticosteroid use cannot be made from the SMART data, the data suggests that the risk for salmeterol exists regardless of baseline inhaled corticosteroid use. Thus, the agency recommended a boxed warning on Advair, the sponsor's combination product.

To summarize SMART, SMART was a large, simple safety study in 26,000 subjects, and was stopped early due to interim analysis findings and difficulty with recruitment. For the total population the relative risk for the primary outcome events, respiratory-related deaths or respiratory-related life-threatening experiences, was 1.4. The confidence intervals approached 1 but did not exclude 1. The relative risk for asthma-related deaths was 4.37, with confidence intervals that excluded 1. The relative risk was 2.16 for respiratory-related deaths, with confidence intervals that excluded 1. The data suggests that there was a treatment group difference favoring placebo for the endpoints shown

on this slide.

In a Caucasian subpopulation there were no treatment group differences for the primary endpoint events, but there was an increase in asthma-related deaths and respiratory-related in the salmeterol group. In the African American subpopulation there was a numeric increase in the salmeterol group for the primary endpoint events, asthma-related deaths and respiratory-related deaths, and also combined asthma-related or life-threatening experiences and on that endpoint the confidence interval actually excluded 1. As we discussed, no definitive conclusions regarding inhaled corticosteroid use can be made in the SMART study.

Now that I have addressed the controlled postmarketing studies, let's look quickly at the postmarketing spontaneous adverse event reports for salmeterol. The Adverse Events Reporting System, or AERS, was reviewed for deaths reported for salmeterol use between May, 1994 and February, 2005 and 201 deaths were reported with salmeterol use in

the United States. These cases were reviewed by the Office of Drug Safety. Ninety-one of the deaths were determined to be asthma-related and 10 were possible asthma-related deaths. After a review of the reports the determination was that it is difficult to draw any conclusions regarding salmeterol use in asthma-related deaths and postmarketing reports. In general, it is challenging to analyze post reports for events that are associated with the underlying disease such as asthma-related deaths.

Next I would like to briefly mention some of the sections of the label that have information related to the SMART findings. The most significant labeling change in response to the SMART results is the boxed warning shown above, and I think you were shown this earlier. In addition, a summary of SMART and results of the primary and key secondary endpoints were added to the clinical trial section, and there are copies of the product labels in the briefing package for details. Note that these labeling changes were made to all

salmeterol-containing products.

To summarize what I have discussed, I reviewed the regulatory history for salmeterol and specifically focused on the agency's handling of the safety concerns with salmeterol including several labeling changes. I discussed the SNS study which showed a numerical increase in respiratory and asthma deaths in the salmeterol group. However, these were not statistically significant and showed fewer withdrawals due to respiratory or asthma events, and this was statistically significant.

I discussed SMART, which was a large, simple safety study, stopped early due to interim analysis findings and difficulties with enrollment. The results of SMART suggest that there is a difference in outcomes between salmeterol and placebo. In the total population there was a relative risk of 1.4 for the primary endpoint although the confidence interval did not exclude 1. In addition, an increase in asthma- and respiratory-related deaths, with confidence

intervals that excluded 1, was also noted for the total population.

In the African American population there was an increase in primary events and an increase in combined asthma-related deaths or life-threatening experiences, and both of these endpoints had confidence intervals that excluded 1. SMART was not designed to assess the effects of inhaled corticosteroid use on outcomes.

Because of the postmarketing studies, the product labels have been updated twice, including a boxed warning for all salmeterol-containing products, and I have shown you the boxed warning and the labels are in your packet.

So, based upon the safety concerns raised in the postmarketing studies, we pose the following questions to the committee: The product labels of salmeterol-containing products have been modified to include warnings related to the SMART study. Based on currently available information, what further actions, if any, do you recommend that the agency take to communicate or otherwise manage the

risks of severe asthma exacerbations seen in the SMART study?

Based on the currently available information, do you agree that salmeterol should continue to be marketed in the United States?

Note that question one is slightly different than the question in the briefing book and that we used the term "severe asthma exacerbations" in this question.

Question three, also related to salmeterol, which is what further investigation, if any, do you recommend to be performed by GSK, the sponsor, that can improve the understanding of the nature and magnitude of the risk of salmeterol?

That concludes my presentation and I would like to turn the podium over to Dr. Gunkel.

Formoterol

DR. GUNKEL: Good afternoon. My name is Harry Gunkel. I am also a medical officer in the Division of Pulmonary and Allergy Drug Products. I will be reviewing with you some data pertaining to the second of the drugs that we are considering

today, formoterol.

In this portion of the program, after briefly introducing the product, I will summarize those elements of the regulatory history that have brought us to this point today. As Dr. Chowdhury stated this morning, and somewhat differently from the situation with salmeterol, the story of asthma exacerbations win formoterol was really told in the NDA review of the Phase 3 studies. So, we will spend some time reviewing the results of those studies that are relevant to today's topic.

Next, we will briefly review the Phase 4 postmarketing study with Foradil; then report the findings from a recent review of spontaneous postmarketing reports, and then summarize and offer some concluding observations.

The only formoterol product approved in the United States at this time is Foradil, manufactured by Novartis who we heard from this morning. Some of the data that I will show you today will look familiar to you. Foradil is a dry powder formulation for inhalation with the

aerolizer device. It is a racemate of two enantiomers of formoterol fumarate.

So, let's briefly review some of the relevant milestones of the regulatory history of Foradil. In a few minutes I will review in more detail the important Phase 3 studies and the results. For now, I want to just point out the findings that affected Foradil's regulatory status. Foradil is approved for asthma, COPD and exercise-induced bronchospasm but, as Dr. Chowdhury noted earlier, our interest today is confined to asthma.

The new drug application for Foradil for use in asthma was first submitted in June of 1997. The clinical program that comprised the NDA investigated 2 different doses of Foradil, 12 mcg administered twice daily and 24 mcg twice daily. You will see as we go on that these doses, which were used in adolescents and adults, were also used in children.

The result from the Phase 3 studies that concerns us today was the finding that patients who

had received the higher dose of formoterol experienced more serious asthma exacerbations than those who received the lower dose, and we will see those specific results in just a moment. At the same time, the reviewers found no evidence that the higher dose consistently resulted in greater efficacy. Therefore, only the lower dose of Foradil, the 12 mcg BID dose was ultimately approved in February, 2001. We saw in Dr. Seymour's presentation that the events of concern that occurred with salmeterol did not occur commonly and so it was also with serious asthma exacerbations that were observed win formoterol.

The Division was interested in further investigation of the event but believed that routine postmarketing surveillance would not be eliminating when the event of concern was also the underlying disease being treated. So, given these circumstances, the Division asked Novartis to commit to conduct a Phase 4 study. Novartis did so and conducted a Phase 4 study to obtain additional information about doses of formoterol other than

the one approved.

It is important to note two things. First, the Division's judgment about the relative safety of the higher dose of formoterol was informed by the results of the Phase 3 studies in the NDA and not from the results of the Phase 4 study that followed. Second, the Phase 4 formoterol study was planned and designed before results of the SMART study were known.

With that regulatory background, let's move on to review some of the Phase 3 data. For all practical purposes, 3 clinical studies comprised the pivotal evidence for the efficacy and safety for formoterol in asthma. Dr. Geba introduced you to studies 040 and 041 that were performed in adolescents and adults 12 years of age and older. The third study was 049, a study of children 5-11 years of age. The FDA reviewer's conclusions about the safety of the 2 doses of formoterol were primarily formed from the results of these 3 studies.

Studies 040 and 041 were essentially

identical, except that 041 included some pharmacokinetic measurements. Both studies were randomized, double-blind, placebo- and active-controlled 12-week studies in asthmatics 12 years of age and older who had FEV1 40 percent or more of predicted and 15 percent reversibility of their bronchoconstriction.

Patients were randomized in approximately equal proportions to 1/4 treatments, Foradil 12 mcg BID, Foradil 24 mcg BID, albuterol 180 mcg QID or placebo. The pediatric study, 049, enrolled children from 5-12 years of age whose FEV 1 was 50-85 percent of predicted and who also had 15 percent reversibility.

This study was similar to the other studies in using the same doses of Foradil, 12 mcg and 24 mcg BID, but was different in not including an active control group. Also note that this was a one-year study with an objective of evaluating for long-term safety of Foradil for children.

Before we review the adverse event results of these studies, let's look at results of the

bronchodilator effects of the treatments. This graph summarizes the results. The graph displays FEV 1 results over the 12-hour post-dose period at the last study visit. Time in hours is shown across the horizontal axis. Average FEV 1 in liters is on the vertical axis. These results are from study 040 and the results were essentially the same in study 041.

Results for the placebo group are shown in open circles and for the albuterol group in open triangles. The other 2 curves represent the formoterol doses. The 24 mcg dose of formoterol is shown in closed circles and the 12 mcg dose is shown in open squares. As you see, bon formoterol doses were significantly better than placebo. Although the 24 mcg dose was significantly better than the 12 mcg dose at some individual time points, there were no significant differences at other time points and the results were inconsistent between the 2 studies. There were no differences in the areas under the curve. As mentioned earlier, the lack of difference in efficacy between

then formoterol doses was weighed in evaluating the adverse event findings.

This slide summarizes the heart of the matter. The rates of serious asthma exacerbations are shown in each of the 3 NDA pivotal studies. As you see, the absolute rates of the events are low but the differences between then formoterol doses in each study are evident nevertheless. In each of the 2 adult studies there were more serious asthma exacerbations in the 24 mcg dose group than in the 12 mcg dose group, and more than in the albuterol and placebo groups as well.

Three adult patients had events of particular severity. One patient in study 040 who received the 24 mcg dose, a 24 year-old male, required intubation and mechanical ventilation for his exacerbation. In study 041 a 66 year-old female experienced cardiorespiratory arrest and died, and a 49 year-old man had a respiratory arrest but survived.

Note that the overall rates are higher in the children in study 049, as was pointed out this

morning, but also that the proportionally greater rate of events in the higher don formoterol group is maintained in this study. Recall two factors that might contribute to the higher incidences of events in children. First, there was no adjustment of doses given to children. So, these higher rates may reflect relatively higher doses given to children on a body weight basis. But also, the pediatric study duration was 1 year versus 12 weeks for the other 2 studies, allowing more time for events to be reported.

So, to summarize the relevant issues that arose from the Division's review of the Foradil NDA, as a result of more serious asthma exacerbations occurring in the higher dose formoterol group and no efficacy advantage, that dose was not approved. Serious asthma exacerbations were seen consistently across the 3 pivotal studies and were more pronounced in the pediatric study. Finally, a commitment was made to conduct a Phase 4 study to obtain additional information.

It is important to reiterate here that the Division's concern about asthma exacerbations associated win formoterol had been substantiated within the NDA itself, and it was not the purpose of the Phase 4 study to do that. That said, let's examine the Phase 4 study and its results.

This was a randomized, parallel group, placebo-controlled study with a 16-week treatment period. There were 5 clinic visits during the treatment phase of the study. For the study to provide useful comparison to the Phase 3 results, it was desired that the patients enrolled in this study should be as similar as possible in characteristics likely to affect the outcome of primary interest, asthma exacerbations. Therefore, patient entry criteria were in most identical to those used in the Phase 3 studies. Note that children were not included in this study. Indeed, as we will see in a moment, the original study protocol was confined to adults and it was only upon amendment that adolescents down to 12 years were allowed in the study. Events that might have

indicated recent exacerbations or altered state of the underlying disease as indicated by changing medications were appropriately a basis for exclusion from the study.

Patients were randomized in approximately equal proportions to receive 1/4 treatments during the study, as shown. The 2 Foradil adult dosage groups were treated in double-blind fashion, while the fourth group, who received extra on demand doses of Foradil, were treated in an open-label fashion. Albuterol rescue was allowed during the study, with more doses allowed for the 3 double-blind treatment groups.

The study was conducted over a 2-year period between February, 2002 and March, 2004. All told, 2,085 patients received treatment. Of those, about 86 percent completed the study. Of the 294 patients who did not complete the study, the most common primary reason was occurrence of an adverse event. This was the case for 103 patients overall or 4.9 percent of the total treated population. Other reasons for discontinuing the study early are

noted on the slide.

After this study started the Global Initiative fir Asthma promulgated guidelines for the management of asthma. The sponsor of the study and the investigators determined that the study criteria were not consistent with these guidelines, particularly in the use of inhaled corticosteroids, and so the protocol was amended during the course of the study to, in effect, liberalize the concomitant use of inhaled corticosteroids.

A third amendment about half way through the study was enacted in order to accelerate enrollment because patient accrual was lagging behind projections. This amendment made several changes, including lowering the age of eligibility to 12 years; changing the criterion for FEV

1

reversibility from 15 percent observed to 12 percent historical; and shortening the washout periods required for other medications for example.

The next 2 slides display the baseline characteristics of the 4 treatment groups. In the far right column of these tables the same

characteristics from all patients in the Phase 3 studies are shown to allow us to examine whether the populations were reasonably comparable. For some characteristics, for example, age and gender, the populations were similar. Note, however, that the proportion of African American patients in the Phase 4 study was about twice that in the Phase 3 studies. Also note the higher FEV1 reversibility of patients in the Phase 4 study, which probably reflects the amended entry criteria that were just described.

For characteristics indicating acute asthma exacerbations in recent past, the preceding year, the study treatment groups were about the same. These data suggest a population in relatively good control, with fewer than 10 percent needing an ER visit or hospitalization in the preceding year.

On this slide is a summary of the outcomes of primary interest from this study, adverse events. The treatment groups and the number of patients in each are shown across the top row. No

deaths at all occurred in this study. More than 50 percent of patients experienced an adverse event of some kind. Between about 10-16 percent of patients experienced asthma-related adverse events.

Determining whether an adverse event was asthma-related or not was prospectively defined by the study protocol. It was an event with one of the following MedDRA preferred terms, cough, wheezing, dyspnea, dyspnea exacerbated, status asthmaticus, respiratory distress, bronchospasm, acute respiratory failure or hypoxia. the fourth row down shows the number of those asthma-related AEs that met the regulatory definition of serious. There were only 9 such events in total in this study of more than 2,000 patients. In all 9 cases, hospitalization was the event that categorized the event as serious. One patient required intubation and mechanical ventilation for his exacerbation. He was a 51 year-old man who received the 24 mcg dose of formoterol on the study.

Serious asthma exacerbations per se was not a specific endpoint prospectively named or

defined by the sponsor in this study. I call your attention to the next row in the table. I would like to state that no patients with serious AEs were excluded in this review. However, we were interested in which patients with serious asthma-related AEs actually had specifically serious asthma exacerbations. There were 2 such patients who had a serious asthma-related AE which was not an exacerbation. The 2 that were not were both in the low formoterol dose treatment group. In both these patients the verbatim event that met the asthma-related criterion was respiratory distress. In one patient, however, the respiratory distress was judged due to a myocardial infarction and, in the other, due to pneumonia. Finally, the last row in the table shows the number and proportion of patients in each group who had an asthma exacerbation of any kind or seriousness.

This table provides more detailed information about the 9 patients with serious asthma-related AEs. There were 12 events in the 9 patients, with some patients having more than 1

event. Of these 9 patients, 2 were African American.

This slide more succinctly summarizes the key results from the formoterol data we have been considering. It shows the number and proportions of patients by treatment who had serious asthma exacerbations. The 4 studies of interest, the 3 pivotal Phase 3 studies and the Phase 4 study, are shown in the 4 rows of the table.

To recapitulate, serious asthma exacerbations occurred more frequently in the higher don formoterol group in the Phase 3 studies and the effect was more pronounced in the children. No difference was seen in the Phase 4 study, and this slide illustrates that the rate of events in the 24 mcg dose group was, in fact, quite a bit lower overall in the Phase 4 study than in the Phase 3 studies.

Before concluding, let's briefly go over the results of a recent review of postmarketing spontaneous reports on formoterol. The Adverse Event Reporting System database contains 180

domestic reports for formoterol as this past June 14th. Eleven of those reports were for bronchospasm and obstruction events. Since the year of marketing, 2001, there have been 4 domestic reports of deaths in patients receiving formoterol. Two of those deaths were caused by myocardial infarction and the causes for the other 2 were not reported.

The following points are offered in conclusion: First, the observation made upon review of the Foradil NDA that serious asthma exacerbations occurred more frequently with 24 mcg BID of formoterol than with 12 mcg BID was the basis for not approving the higher dose.

Second, the serious asthma exacerbations were more frequent overall in children who received the same nominal doses of formoterol as adults in children and were studied in a 1-year study.

Finally, a Phase 4 study of limited size and restricted to adults and adolescents did not provide any additional information about these events.

With that brief review, let's restate the questions to the committee: The label of the formoterol-containing product does not include warnings comparable to the warnings that are present in the salmeterol-containing products. Based on the currently available information, should the label of formoterol-containing products include warnings similar to those in the salmeterol label?

And, based on the currently available information, do you agree that formoterol should continue to be marketed in the United States?

Next, what further investigation, if any, do you recommend to be performed by Novartis that can improve the understanding of the nature and magnitude of the risk of formoterol? Thank you.

Questions for the Speakers

DR. SWENSON: We now have about 10 minutes to take questions to both these speakers for the FDA presentation. Dr. Schoenfeld?

DR. SCHOENFELD: I guess I said this before but I will repeat it, I think that if we are

going to do a risk/benefit analysis at some point, then to counterbalance the benefit the risk should be couched in terms of the attributable risk, which would be the difference, I guess, in the event rate on the two treatments. I have calculated that, roughly speaking but I just had to do it on-the-back-of-an-envelope, that for salmeterol the risk for asthma deaths--and it is similar for everything else, there are about 10 events per 26,000 patient-years of follow-up. So, the risk is 1/2,600. I just wondered, you know, do you have any tabulation in your database of all those risks for the various subgroups, or at least could you confirm whether I am right here?

For the other compound, the actual total patient follow-up that is reported is something in the order of 260 patient-years of follow-up. So, it is so small an amount of follow-up that risk at the rate of 1 per 2,600 would be completely undeterminable.

But if someone in the agency is sort of done these calculations, I would much prefer to see

those rather than what I do on the back of an envelope.

DR. SEYMOUR: We have not performed those calculations based on patient years.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I was wondering, in the SMART study, whether the NDI surveillance included those who had discontinued the trial.

DR. SEYMOUR: I have to defer that to the sponsor; I am not quite sure.

DR. KNOBIL: The NDI database included everyone who had been enrolled in the study whether or not they had discontinued study drug.

DR. SWENSON: Dr. Gay?

DR. GAY: I will restate a question that I asked previously to the sponsor. We do see an increase in adverse events in children but, clearly, that is a much longer study. Is there any breakdown of the timing of these events within 90 days, within 180 days, within the final 6 months of the study?

DR. GUNKEL: I have a little bit of

information, not everything that you would like. I was able to find that information for the children who received the 24 mcg dose, the dose really of concern. There were 11 children who had serious asthma exacerbations in that study overall. Five of those 11 occurred after day 84, which would be 12 weeks. So, if we try to compare the children to the adults, for example, that were in a 12-week study, then the rates up to that 12-week time point are roughly comparable in children versus adults--with all the usual caveats about the studies weren't designed to do that, and so forth. I don't have similar information for the 12 mcg dose group.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: This is a question for Dr. Seymour. Dr. Seymour, we know that socioeconomic status plays a big role in adverse events and asthma medications. I was wondering if there had been any attempt to stratify the cohort for the SMART trial as far as socioeconomic status, particularly those individuals that were associated

with severe adverse events.

DR. SEYMOUR: I am not aware of any stratification but I can ask the company if they have done any type of socioeconomic stratification.

DR. KNOBIL: We did not collect much SES data. What we did have, we had educational level and we had zip code. So, we only have very crude measures. So, we did what we could with what we had and we didn't see any impact of income based on zip code or educational level.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I have two questions for Dr. Seymour. First, if I understand correctly from your slide 19, discontinuations were very similar in the salmeterol and the placebo group and, therefore, in this case attributing the results perhaps to different rates of discontinuation in both groups wouldn't be fair. Am I interpreting the data correctly?

DR. SEYMOUR: Yes, I think so. The discontinuation rates were similar between treatment groups.

DR. MARTINEZ: The second question is that in the materials provided to the advisors there is a stratification by the baseline percent predicted peak flow, which is the only type of information that I could gather with respect to severity. If we are going to consider that 60 percent peak flow or below is more severe than more than 60 percent peak flow, you haven't commented at all about that. The interpretation that at least I make is that there appear to be different ways in which this behaves in this post hoc type of analysis. For combined respiratory-related death or life-threatening experiences, it appears that it is those subjects who have more severe disease, if peak flow can be considered disease or even perhaps more related to what could be considered COPD in adults, who show more risk than those with a higher peak flow. For asthma-related deaths, it is difficult to say anything but there doesn't seem to be a very clear difference between the two groups. Has the agency interpreted that table in any way similar or different to the one I just proposed?

DR. SEYMOUR: I need to know what page you are referring to.

DR. MARTINEZ: It is page 45 of the materials provided to us, page 45 of the section called "salmeterol postmarketing study review, SMART study."

DR. SEYMOUR: Just a second. I can tell you I don't think we have formed any formal conclusions based on this data.

DR. MARTINEZ: Just to propose an interpretation, what I can see here is that the rates that are observed for asthma-related deaths, although they cannot be calculated for the less than 60 percent, see by the absolute numbers don't look very different. In other words, there appears to be an increase in asthma-related deaths both for those that have more than 60 percent and for those that have less than 60 percent.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I just want to understand whether the analysis of severe adverse events was intent-to-treat. That is, if a patient stopped

medication but then still, during the 28 weeks of follow-up in the SMART study they had an event, they would count it, I assume? And, what about in the other studies?

DR. SEYMOUR: My understanding of SMART is that that is correct, it was on an ITT.

DR. SCHOENFELD: And the other studies?

DR. GUNKEL: The same.

DR. SWENSON: Dr. Moss?

DR. MOSS: I have a question that kind of builds on what Dr. Schoenfeld talked about and a little bit about what Dr. Meyer talked about this morning. It seems to me that we are being asked to compare two studies that are different in terms of the size of the studies. So, it is very hard for us in the Foradil study to draw conclusions be the study is a lot smaller. I was just wondering, Dr. Meyer, if you could talk in a little bit more depth about why the SMART study had 26,000 people in it, and what was the thinking of the FDA to have the Foradil study only have 2,000 or so in it. I realize you are looking for different outcomes but

what was your thought process in asking them to do those Phase 4 studies very differently?

DR. MEYER: Sure. I think, first off, it would be wonderful to have such a large outcome study of formoterol but we don't, and that was not the purpose of the Phase 4 commitment. In the Phase 4 commitment we saw a dose response or an apparent dose response phenomenon for the outcome of serious adverse events in 12-week studies and we wanted to reassure ourselves, since we were not approving the 24 mcg dose, that in fact this was a real finding. We also wanted further data to relate even the 12 mcg dose to placebo in that same kind of setting.

So, while we, again, would have liked to have had a SMART-like study of formoterol as well, that really wasn't the question that was being posed in asking for the Phase 4 commitment. The Phase 4 commitment was really to try to better clarify what we had seen in the Phase 3 studies in terms of an apparent dose relationship to adverse events and whether that 24 mcg dose really would

prove to have a clear safety signal in relationship to the 12 mcg dose.

Open Public Hearing

DR. SWENSON: Any further questions?

[No response]

At this point, we are moving into the open public hearing session. To begin this I need to read a short statement and we will have at least one discussion or statement from a public member.

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

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the 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 the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

At this point, I would like to ask Mr. Chris Ward to come to the podium. Mr. Ward, your podium.

MR. WARD: Thank you. Good afternoon. My name is Chris Ward. I am an asthma and allergy patient and current president of the Asthma and Allergy Foundation of America. We have not received payment from any entity for this testimony or for the cost of our travel and participation in this meeting today.

On behalf of the almost 20 million Americans with asthma, AAFA appreciates the opportunity to testify to this advisory committee

concerning the safety of long-acting beta agonist bronchodilators. Since 1953, AAFA has been dedicated to improving the quality of life for people with asthma and allergies. Patients, their families and their caregivers turn to our organization for education, research and advocacy.

AAFA appreciates the heightened vigilance at the FDA regarding drug safety and thanks the advisors for reviewing the available data and meeting today to discuss potential safety concerns with this class of drugs. Asthma, of course, is a treatment-intense condition for many patients and your advice to the agency today will impact millions of individuals who depend on these products as part of their regimen for asthma control.

There are three key messages I would like to convey on behalf of patients with asthma. First, as we understand it, there are no concerns with the efficacy of this class of drugs and their important role in asthma control, which is reflected in both the national and international

guidelines for asthma clinical care that use the word "preferred" when recommending these products in conjunction with inhaled corticosteroids for moderate to severe persistent asthma. There is strong, consistent evidence from clinical trials that this approach leads to improvements in lung function and symptoms, and reduces the need for short-acting beta agonists. When we weigh this evidence of effectiveness against the evidence of potential risk which is, at best, still undefined, we believe it would be difficult for asthma patients to understand why these products would not continue to be available to them.

Second, we believe there is an element of scientific and clinical progress in asthma that may be missing from this discussion. Mainly, there seems to be progress in the pharmacogenomic understanding of how beta agonists have different effects in different individuals. We believe the results of the government trial, published last October, demonstrating different responses to the short-acting beta agonists based on genotype is an

important step forward. We understand that a similar clinical trial is just now getting underway for the long-acting beta agonists. In other words, from the perspective of asthma patients, there is current and ongoing investigation into this important clinical question. We understand very well that a subset of patients may be at higher risk than others. But we are only beginning to understand why this is the case. At this point in time then, it would seem advisable to defer any conclusive decision about the availability of these drugs to all patients until there are more definitive answers.

Third, with regard to the consideration of whether the labeling changes to salmeterol should be approached with formoterol, it is our position that FDA's responsibility lies in working closely with the product sponsor to answer this question and to determine a product label that is consistent with the available medical evidence. In fact, we are encouraged that both product sponsors are working closely with the agency to further

understand and clarify the nature and magnitude of potential risk of this class of drugs. We believe the safety of asthma patients should be front and center in this ongoing work.

In conclusion, we certainly urge all parties to continue this important discussion. however, AAFA believes that at this time there are too many questions to be able to draw conclusive decisions on medications that have been effective for millions of patients to be able to control their asthma.

Again, on behalf of these patients, I thank you for the opportunity to testify on this important issue and I am pleased to answer any questions you might have. Thank you.

Committee Discussion

DR. SWENSON: Thank you, Mr. Ward. At this point the meeting schedule calls for a break but we are somewhat ahead of schedule so what I would like to do is to move into our committee discussion section, and we will have a break at some mid point there. The first part then of this

committee discussion would be open now I think to general questions to all parties involved and further exposition of points that may not have been raised earlier this morning. We will then break, at which time we will come back to our vote on the specific questions that are being asked of us by the FDA. So, to begin with, we had two people earlier this morning that I had to close out and I will ask Dr. Kercsmar if she wishes to pose her question from this morning.

DR. KERCSMAR: I had a question regarding other medication use in the SMART trial that maybe the sponsor can answer. During the 4-week follow-up telephone calls, were there any data obtained on other medication use, particularly the use of short-acting beta agonists?

DR. KNOBIL: Well during each 4-week follow-up telephone call the patients were asked if they were continuing on the medications that they had said that they had started at baseline or at the previous call, and if they had started or stopped any new medications or any of their old

medications. So, if anything was stopped, obviously, they were asked which ones were stopped and which ones were started.

During the course of the study there were some patients who did stop and start medications but, for the most part, throughout the study patients remained on their beta 2 agonists. We didn't ask them how much of their short-acting beta agonists they were taking however so we don't have any information on that.

DR. SWENSON: Dr. Gay, you had one question from this morning.

DR. GAY: It was answered earlier, thank you.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: This question is for Dr. Knobil as well. It is very impressive that you have done such a large study and it must be as frustrating to you as it is to us to hear people periodically say, as they have today, well, we really can't learn anything from this because there were only 26,000 people there, or something like

that; we can't draw any conclusions. And, I know how difficult these are to do. However, you have given us data also from the SNS study which was conducted in England, and published, and it is commented that in one year of enrollment they enrolled 25,000 people. And, in the SMART trial over seven years you had about the same number of people. I am wondering what changed during the intervening approximately five to six years that made enrollment so much more difficult here. Because, Dr. Castle comments in her paper that companies are often accused of delaying things so that they can stop enrollment when they aren't getting enough, and it is kind of an indictment by Dr. Castle who, by the way, was a Glaxo employee. So, can you help us understand why it seemed to have been easier to enroll that many people in a year in England?

DR. KNOBIL: Well, I can't really comment on how easy it was to enroll in England since I wasn't involved with the initial study. However, I do know that for SMART one of the major stumbling

blocks was the fact that patients could not have had any exposure to long-acting bronchodilators to begin with. As enrollment waned over the course of the time, we actually held focus groups with physicians and patients to figure out why we weren't able to get more patients in the study more quickly. Again, what came out was that many patients were already taking long-acting inhaled beta agonists. They were not interested in the placebo-controlled trial. There were a lot of new medications coming out during the time that the study was running. So, the interest level for the study went way down. That is the feedback we got from our investigators and the patients who may have been enrolled. So, those were the major factors.

DR. KERCSMAR: That is helpful. Thank you.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: Well, I hate to keep going back to the same thing but I think it is important to understand. Now I am confused. Intent-to-treat

based on people who discontinue medication but are still in the study is one thing but then there are the people who drop out. Although the percentages are similar statistically, numerically they are still greater in the salmeterol group. Do you think the surveillance for adverse events is comparable in those who dropped out versus those who didn't drop out?

DR. KNOBIL: There is one point of clarification. It was statistically significantly different in the number of patients who dropped out of the study in the placebo group versus the salmeterol group. More patients on placebo did drop out.

Now, over the course of the study we did follow up with the patients. Even if they dropped out of the study and said they didn't want to take study medication, we still attempted to contact those people and get follow-up information up to the 28 weeks and actually even beyond that as the FDA has already mentioned. We would collect that information up to 6 months after if we could get

that information. But for the deaths we did look for all patients enrolled in the study by the NDI database. So, at least for the deaths we were able to follow-up on those more than, say, patients who refused to be contacted any further.

DR. SWENSON: Dr. Knobil, I have a question from this morning that I wasn't able to ask and since you are standing I will go ahead and pose it to you. That is, in the SMART study--and you just alluded to the fact that a zip code analysis as a proxy for socioeconomic status and questions unrelated to the biologic activity of the drug turned out negative, and you are going to reiterate that that was definitely a negative finding--

DR. KNOBIL: Yes.

DR. SWENSON: --that you found no information by that analysis?

DR. KNOBIL: No, and to be fair, the analysis by zip code is quite a crude way to look at socioeconomic status and we really didn't find any differences between the groups and nothing to

suggest that that was involved. However, if we had had more detailed information that might have been a little bit more helpful.

DR. SWENSON: Okay, and the second part of my question then was, given that there was a difference in the use of inhaled corticosteroids between Caucasians and the African American subgroup, did you make any effort to attempt any type of matching with the two groups? For instance, could you have pulled out a cohort of Caucasians that had the same rate of inhaled corticosteroid use as the African American group, and then did that yield any further information? You may not have done it but I am just asking.

DR. KNOBIL: Well, we discussed matching to try to get to a better understanding of the events, and the numbers of events are so low that even if you found somebody to match the amount of information that you would get out of that is not really very helpful, and I would turn to our statistician to see if there is anything else that I could add to that.

[Not at microphone; inaudible]

DR. KNOBIL: For those of you who didn't hear that, he said the event rate was still too low to be able to do that.

DR. SWENSON: Thank you. Miss Sander?

MS. SANDER: Am I to take it from your presentation that kids need less formoterol? I think it said in one of your slides that--no?

DR. GUNKEL: That is one possible explanation for the difference in the rates that we saw. The other is simply the duration of the study, but one other possibility is that they do need, on a body weight basis, less formoterol but we can't say that definitively and conclusively from our data.

DR. SWENSON: Just a quick point here, when we have this queue of questions it is difficult for anyone else to activate their microphone. So, if you have a question go ahead and signify that you are ready. We will note it and then have you in line. Thanks. Our next question is by Dr. Newman.

DR. NEWMAN: Thank you. One question that I have to the sponsors, and maybe the FDA has a comment on this as well, that is, when I look back at how, at the SMART study, was powered and then, in turn, one thing we are struggling with is having such a low frequency of serious adverse events--first of all, I am glad there are so few serious adverse events; fundamentally that is good--but I wonder if I could have you help explain to me why that frequency of serious adverse events was so much lower than was expected. Is there something different about the kinds of people who were recruited into these studies that would lead us to have this much lower rate?

DR. KNOBIL: Well, as you can imagine, powering the study was very difficult to do because when enrolling an asthma population there are no statistics out there that would tell you what the rate of events would be per asthma patient. For example, CDC statistics give you the rate of events for the total population, not just for the patients who have the disease in question. So, we

extrapolated from that. For example, the total number of asthma deaths that occurred--I believe it was in 1994 at the time--divided by the estimated number of patients in the United States, and started from there.

Then, in order to get some information about life-threatening events, we sent out a questionnaire to over 100 hospitals to tell us how many per asthma death or per respiratory death how many intubations would you have? So, since there was no information in the public domain for this, this was the best way that we could get that type of information. It turned out it was about 5 intubations per respiratory-related death. Then, taking into account more severe asthma and the higher rate in the African American population, we came up with the powering that we did. If you want anything more specific than that I will have to turn it over to someone who was more involved with the power calculations.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: I also have a question for

the Glaxo team. You know, inhaled corticosteroid and long-acting beta agonist therapy is really the standard of care for all mild asthmatics, and for the foreseeable future this is going to be the standard of care as far as we can tell, for the next ten years--five years, ten years. So, it is a huge issue that involves huge numbers of patients. You mentioned a Medicaid study. Can you elaborate on that a little? Because I think one of the charges we have is what types of future studies are needed to address this and at least I am still not clear as to the details of that study.

DR. KNOBIL: Yes, what I will do is I will turn it over to Courtney Davis who is an epidemiologist with us.

DR. DAVIS: Hi. I am Courtney Davis, senior director of epidemiology for GlaxoSmithKline. Our Medicaid study involves data from 7 states in roughly the same time period as the SMART trial was conducted. It is 1994 through 1999 Medicaid data. For each state the Medicaid claims data will be matched to the death

certificate files for all of those 7 states. So, that is how we will obtain asthma mortality and respiratory-related mortality data. In addition, of course, the claims will have the hospitalization data equivalent to the SMART outcomes as well.

Because Medicaid is one of the only available databases for epidemiology research that includes race, we will be able to stratify the analyses and look at African Americans and Caucasians separately so we can address the differences that were observed by race. And, because this is longitudinal data on these patients, including their pharmacy records, we will be able to look at potential effect modification by inhaled steroid use as well.

DR. PRUSSIN: Are you going to be able to stratify asthma severity?

DR. DAVIS: The best we can will be using proxies that will be available in the claims database. The longitudinality of the records, of course, vary. We have data at this point that has come in for 5 of the 7 states. On average the

follow-up is about 12 months, 11.7 months of data. So, we will be able to look back as far as we can in terms of prior utilization that includes serious events like hospitalizations and, of course, prednisone use.

DR. SWENSON: Miss Schell?

MS. SCHELL: I guess I have some question or clarification on the SMART survey itself. Since the variability of the different types of patients and their ability to assess themselves, and you just did phone follow-up calls, I wonder what kind of preparation you had for the patients prior to enrollment on how to assess themselves, what they considered was severe. I just don't know that they were able to answer back consistently over their course. Just clarification.

DR. KNOBIL: Yes, we had a whole telephone script that was written in such a way as to be as understandable as possible to ask patients about whether they had been hospitalized or whether they had been intubated. Obviously, you are not going to use the word "intubated" but whether they have

had a breathing machine, something like that. I will have to look over to someone who has been involved in the study from the beginning but there weren't any questions that asked them to assess just worsening. So, there wasn't any training on, you know, how should they assess worsening. There was no diary card. There was no peak flow. There wasn't anything like that. It was just mainly has this happened to you? Have you changed your medicines? Have you started any; have you stopped any? Have you had any averse outcomes?

DR. SWENSON: Dr. Moss?

DR. MOSS: I want to build a little bit on what Dr. Prussin was talking about earlier, and this is a question for either the Glaxo representatives or the Novartis representatives. It seems to me that part of the results of this SMART study and some of the Foradil studies potentially are related to the decreased use of an inhaled corticosteroid especially in the African American population. Would you guys agree with that? Do you think that some of these adverse

events would go away in the Serevent group if 100 percent of the patients were on inhaled corticosteroids? Do you think that is part of the issue?

DR. KNOBIL: Obviously it is difficult to say based on the data from SMART since it wasn't designed from the start to look at inhaled steroids. However, there is a suggestion that inhaled steroids did have a positive effect or beneficial effect on these outcomes. So, I do believe that if more people were treated appropriately for their asthma in accordance with the guidelines that we probably would have seen fewer events. I mean, that is just speculation.

DR. MOSS: I mean, we do these studies of 26,000 people and we still are left with not a definitive answer so at some point everyone is going to have to base things, in their own mind, on what they think is the right answer. I think based on the NHLBI guidelines in terms of moderate and severe persistent asthma, you could make a very good case that if somebody is on a long-acting beta

agonist they should be on inhaled a corticosteroid. So, if part of the goals of this meeting are to disseminate information properly, then maybe that is something that should be disseminated, and maybe this would be a good network to do that in.

DR. KNOBIL: Yes, I think it is important to note that even from the time that salmeterol has been approved in the United States there has been language in the label that mentions that early consideration of anti-inflammatory therapy should be considered. So, this is probably not a new thing. Dr. Beasley?

DR. BEASLEY: I think we do have some published data that can help answer your question, and that is taken from the United Kingdom case-control study where a proportion of asthmatics in the control group who were taking inhaled corticosteroids was almost the same as those taking short-acting beta agonist drugs, suggesting that almost all patients were taking the combination of both an inhaled steroid and a short-acting beta agonist drug. In that scenario, where management

is very close to the recommended guidelines, there was no increased risk associated with long-acting beta agonist therapy. So, I think that we can deduce from a study that was of high epidemiological quality, where management in the control group was very close to what is recommended in the guidelines in terms of inhaled steroid therapy, that there is no risk observed in relation to long-acting beta agonist therapy.

DR. MOSS: I just want to say one thing in response to that. I just want to say that I don't think this is the entire issue, that if everybody was on an inhaled corticosteroid that the effect would go away. But I think most people in this room I think would say that that is part of the issue, that people aren't being treated in what would now be considered the proper manner. So, if the goal here is to improve health of the people in this country, and people on NIH panels and people in this room feel that if someone is on a long-acting beta agonist they should be on an inhaled corticosteroid, then we should try to

disseminate that information.

DR. BEASLEY: There is one other bit of data that may be relevant to the African Americans, and that is that in New Zealand the Maori indigenous community had a far higher rate of mortality than the Caucasians, and it was about the magnitude of about three-fold or more. With the improvements in asthma management and in particular the use of inhaled corticosteroid therapy and a real emphasis on management within our community, that difference has largely resolved, suggesting that it is a reversible difference that is amenable to improvements in management.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I would like to ask both of the sponsors a question which I asked Dr. Sorkness this morning but she didn't have an answer. Based on what we know today, and I know there are other studies going on but based on what we know today, on the benefit side of these long-acting beta agonists do we have reason to think that there are any racial differences in terms of benefit? Do

African Americans benefit less from long-acting beta agonists? I am trying here to weigh the issue of benefit versus risk.

DR. GEBA: Greg Geba, Novartis. In terms of that analysis in our own data set, we have seen no difference in efficacy between Caucasians and African Americans in terms of the endpoints that were studies.

DR. NEWMAN: Were you powered to answer the question do you think?

DR. GEBA: No. The representation of African Americans in our trials was low. In the most recent trial that we shared with you before, the 2307 study, it was actually about 8 percent and there was no difference across treatment groups in terms of their response.

DR. NEWMAN: Just to make sure I understand your answer, you didn't see a difference but you didn't have adequate power to answer the question?

DR. GEBA: No, it wasn't specifically designed to look at that question.

DR. NEWMAN: So we don't know.

DR. GEBA: Right. In terms of our usage of inhaled corticosteroids, it was about 70 percent across all trials. There tended to be a slightly lower incidence of any event in patients that were taking inhaled corticosteroids, as is recommended also in our label.

DR. KNOBIL: Similarly, we didn't have a single trial that had enough African American patients to reach any conclusions, but when we pooled all of the data from African Americans there were no differences in response between African Americans and Caucasians.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: I have another question for GSK. If you could clarify some of your planned prospective trials, particularly those that aim to look at the influence of genotype or some of the polymorphisms in the beta receptor, if you could clarify what you hope to learn from those trials. I believe one of the ones that you talked about is using a combination product versus salmeterol

alone. The comment you made about difficulties in enrolling patients, not wanting to be in a placebo-controlled trial in view of the SMART data that is out there, do you anticipate being able to fill this trial with patients not wanting to go into an arm that is salmeterol alone?

DR. KNOBIL: Well, I will answer the last question first. It turns out that the genetic trial that you have mentioned is actually a little bit ahead of schedule so we are doing okay with enrollment there. In this trial we are looking at those two treatment groups, salmeterol versus the combination, with each phenotype that has been discussed today, the Arg/Arg, the Arg/Gly and the Gly/Gly. I would ask Dr. Bleecker to stand up and just tell us in a succinct way, I think better than I could, about what we can glean from the study.

DR. BLEECKER: The trial that is ongoing is a larger trial. There are six arms--and I could be corrected, each with 90 individuals, and they are not just looking at the two homozygote genotypes at 16, the Arg/Arg, Arg/Gly and Gly/Gly,

but also looking at the heterozygotes. That is a really important approach that has not been done for the most part until now. The kind of genetic effect, if this is the risk genotype, is that you would expect or hypothesize some intermediate effects from the heterozygotes.

Also, the sample size in each of the arms, 90 individuals in each of the arms, I think will allow some better exploration of the gene and what we would call haplotype analysis looking at a group of snips across the gene to see if the effect is either due to that whole haplotype or there is an effect to variation, snips, polymorphisms and other parts of the gene. So, I think from the point of view of advancing the understanding of whether--and this is still the question--there is a risk genotype that may be associated either with varying responses to drug or exacerbations, and being able to make those correlations this is a very good opportunity.

As I understand it as an outside consultant, the African American study that is

looking at exacerbations over a year period will also have the same kind of genetic analysis. So, again, that provides an opportunity for the first time in a large enough sample size to look at relationships, pharmacogenetic relationships between genotype and phenotype and response in African Americans.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: This is a question to both the sponsors. In thinking about mechanisms by which long-acting beta agonists might have increased morbidity and mortality, one sort of thinks about possibilities like, for instance, that these two drugs may be associated with increased inflammation rather than decreased inflammation. Sort of based on your experience with the preclinical animal studies in the Phase 1 and Phase 2 studies, was there any indication that either of these two drugs were pro-inflammatory, particularly for instance in bronchial biopsy studies in the Phase 1 and Phase 2 studies where there may be some increased inflammation?

DR. GEBA: Greg Geba, from Novartis. I would be happy to respond on Novartis side, if I could ask Alex Trifilieff to come up to respond to this question in terms of our preclinical studies.

DR. TRIFILIEFF If you look at all our animal models that is something we look at because beta2 agonists, especially upon acute exposure in animal models, are anti-inflammatory. So, we screen in different animal models and we always see an anti-inflammatory effect. We never saw a pro-inflammatory effect. These are the animal model data for Phase 1 and Phase 2.

DR. DELLA-CIOPPA: We have conducted a number of studies looking at anti-inflammatory markers with formoterol a few years ago because there was a rather big debate as to whether these agents actually had anti-inflammatory activities, and somehow they were used inappropriately based on this assumption. Rather large studies have been published, mainly by the group in South Hampton by Prof. Holgate and in Sweden by Prof. Sundstrom, and we could confirm in several severities that there

was no pro-inflammatory effect associated win formoterol taken alone.

There were, indeed, some signals of a reduction of some of the markers of inflammation but probably not to the extent of being of clinical relevance. But the few signals we did have went in the opposite direction. These studies are published.

DR. JOHNSON: I am Malcolm Johnson, from GlaxoSmithKline. We had a similar experience in the very early days of salmeterol development. If anything, we saw some mild anti-inflammatory effects in animal models. Clearly, they were not predictive of what you might expect in man. I think you asked the question this morning whether there were any biopsy studies that have been carried out to address this issue, and there are a couple that I am aware of.

One study was conducted by Prof. Peter Jeffrey at the National Heart Lung Institute, in London. It was a 6-week study in mild steroid-naive asthmatics in which patients wee

crossed over between either salmeterol monotherapy, fluticasone propionate monotherapy or placebo for 6 weeks. Bronchial biopsies were taken and markers of inflammation such as the numbers of eosinophils and T-lymphocytes and neutrophils in the airway tissue were assessed. I think the results were very reassuring because in the salmeterol monotherapy group there was no indication of a pro-inflammatory response and, as I said, these patients were steroid naive.

What was interesting in those studies is that there was a signal, which is to say that there was a reduction in neutrophils in the tissue with salmeterol that was not seen with steroids. In the steroid arm he saw a traditional anti-inflammatory effect of steroids whereby eosinophils and T-cells were reduced. So, the study was significant enough to pick up an anti-inflammatory effect of the steroid that we are very well accustomed to seeing. There was no pro-inflammatory effect of salmeterol and this effect on neutrophils in asthma, for whatever that means.

DR. BRANTLY: Were any of the biopsy studies done including blacks?

DR. JOHNSON: No, there were not. The other thing that I think is interesting just to quickly add is that there are some biopsy studies that are being carried out that have looked at the impact of adding salmeterol to inhaled steroids. One study, again from Prof. Holgate's group, showed that, in fact, in patients who were inadequately controlled on low doses of steroids where ongoing inflammation was not controlled, and that was shown during the 3 months of the study, adding the long-acting beta agonist salmeterol to that regimen then controlled inflammation, and the control of inflammation was equivalent to a much higher dose of the steroid.

The final study, carried out in Australia, actually looked at an index of airway remodeling. They looked at angiogenesis in the airways and, again, a long-acting beta agonist with a steroid appeared to control the ongoing vascularization of the tissue. Now, these are limited studies but, to

answer your question, in all of these together there is no evidence of a pro-inflammatory effect and there may be some emerging evidence of an increased anti-inflammatory effect when salmeterol is added to steroids.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I would like to go back to the Medicaid study. It is rare that we have a database that is able to address so many of our questions. In the case of Medicaid, besides the attributes you mentioned, we do have the opportunity to look a bit at asthma management. In fact, I have done that in some Medicaid data. So, I would like to ask about what you have planned, in terms of what you can see from the pharmacy data, including adherence as measured by refill patterns. Is that planned? If not, would you plan it?

DR. DAVIS: Yes, thanks for asking that. Persistency of use is part of our protocol currently. I neglected to tell you one more detail about the study which may be of interest. Our partner in conducting the study is Research

Triangle Institute so they are actually are linking the data and doing the hands-on analysis. So, GSK is sponsoring the study and is very actively involved in writing the protocol as a co-investigator but the lead investigators are located at RTI. In addition, we have a clinical advisory board which is also advising us on the protocol and the clinical interpretation, and that includes Dr. Beasley who is here today. It includes Ann Fullbrighy[?], up at the Channing Lab at Harvard, and it also includes Sheryl Winwalker[?] who is in Atlanta, Georgia. So, we have three outside clinicians who are also advising us.

But to get back to your original question, persistency of use is one of our variables of interest, including the regular use of inhaled steroids because we know from other observational studies that intermittent use of inhaled corticosteroids is often just a marker of severity, not necessarily associated with improved outcomes.

DR. GARDNER: That was a good choice of

partner. Can you tell us again, is it 2006 when you expect these analyses to be completed?

DR. DAVIS: That is right. The data from 5 of the 7 states have been obtained at this point so we are waiting on 2 more states, and that matching with the death certificates is slower in some states than others, as you could imagine, so once the additional data are received, and we are hopeful that it will be in the next few months, then the analytical portion will begin.

Also, just a final caveat, we must have sufficient power to conduct the study or we will not do a case-control study. The last thing we would want to do is conduct another study which would be underpowered and raise more questions rather than answering them. So, we do have criteria which must be met in order to continue the race-specific analyses as well as the inhaled steroid effect modification.

DR. GARDNER: One more thing, I can certainly understand your position on that about power, but I would encourage you, from the

standpoint of management, to nonetheless complete descriptive analyses from those data because they can be valuable in assisting many of the questions that appear here. So, even if you don't have the power to test a hypothesis, please do the descriptive analyses.

DR. DAVIS: Thanks. We will.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: I want to follow-up on Dr. Moss' comments about salmeterol monotherapy. I think the NIH guidelines support that. We have heard today lots of data supporting the fact that salmeterol monotherapy can associate with increased exacerbation rates. Yet, when you look at the package insert--and I know it is a little bit off the mark and perhaps the FDA staff can tell me how much off the mark I am--one of the issues we are addressing is the package insert. And, if you look at the labeling, it is "strongly advised" and I guess I would ask the two companies here could that labeling be made stronger, such as salmeterol monotherapy--or whatever the long-acting beta

agonist--monotherapy should not be used as chronic monotherapy in asthma, for example? Since everyone is in agreement on this from what I have heard today, yet the package labeling is a little softer in terms of terminology.

DR. WEAN: I noticed Bob wasn't moving--

[Laughter]

--I think one of the issues around labeling, and particularly around recommending concomitant use--if I say it wrong, Bob, please tell me--but there is a very fine line between your label that addresses your clinical data that you have shown in clinical studies and labeling that takes the guise of recommending treatment, of being treatment guidelines. I know that in discussions we have had with the agency, while we may want to put more information into the label, there is a desire not to have the label be a substitute for treatment guidelines being issued by NHLBI and other appropriate groups of experts. So, that is sort of the fine line that we have to walk between strong recommendations about such concomitant use

but also making appropriate reflections in the label.

DR. FLOYD: In follow-up, what we try to do is base the label based upon the outcome of the data that we have that is generated, but you must maintain flexibility for physicians to be able to use their discretion in appropriately prescribing these drugs. So, we work with the agency to make sure that the label is comparable to the information that is generated based upon the data from the Phase 3 studies.

DR. SWENSON: Miss Sander?

MS. SANDER: Yes, this is to both sponsors. Because managing asthma or achieving good asthma control is rarely just about taking one drug and includes, you know, environmental control. It includes receiving patient education that affect your beliefs and, therefore, your behaviors and your outcomes. I am wondering in these studies do all patients receive the same type of education and advice, or is it just related to the study drug?

DR. DELLA CIOPPA: You are touching upon a

very important point and the short answer is no. We make a huge effort to do so, but please keep in mind that all of these studies are in many states in the United States but most of these studies are in many countries, and some very diverse countries, and the bigger the studies are and the more rare the event we are looking for, the more countries we go to. It is not rare that we go to 17, 20, 25 countries, not to speak of all the possible states ion the United States. So, we do make a huge effort to try to harmonize as much as we can the instruction to patients, the ancillary activities that the patients should put into place to manage their asthma in an appropriate way. But the cultural differences, the background differences, the socioeconomic status differences will stay there so that is, indeed, a considerable source of variability in the results of the study.

On the other hand, should you go to only one place with perfect harmonization of the data, then another problem would occur, how could you extrapolate? How could you extend your results to

other states, other countries or other cultural situations? So, it is a balance.

MS. SANDER: So, even in one investigator's practice would all the patients receive the same information?

DR. DELLA-CIOPPA: Yes, they would.

MS. SANDER: They would?

DR. DELLA-CIOPPA: They receive the same information across the study, but the way this information is delivered may change. Within one center we are reasonably sure that they get the same information in the same way.

MS. SANDER: Right. Then, I guess this is for GSK regarding the phone calls. When you did the follow-up phone calls with the patients were there any clues in the answers that they gave you that some of them were struggling more than others and were at greater risk, and was there any kind of discussion with the patients about that? Was it interactive or was it just a survey each time?

DR. KNOBIL: You mean, was it a real person making the telephone calls?

MS. SANDER: No, no, no. The phone calls that occurred with the patients, and you said that you asked them, or that they were asked questions about the use of the study drug. Am I misunderstanding?

DR. KNOBIL: Well, what happened was a real person did have a script as to what questions should be asked. There were specific questions and every person got the same questions. Now, I guess what you are asking is if the patient said, well, I don't know or something like that the person on the phone would try to clarify as much as possible. But also remember that the person on the phone was not a physician; it is a telephone center. So, they could only clarify what they could and they might not pick up on every clue that someone who is familiar with asthma might pick up on. But they did have specific questions to ask and they got as many answers to those questions as they possibly could.

MS. SANDER: So, there was no trigger. You know, if a patient had these types of answers,

then this patient is at greater risk and the investigator needed to be contacted?

DR. KNOBIL: I see what you are saying, no, the information was collected but there were no recommendations made to the patient on what they should do. You know, if the patient was telling the operator that they were having problems, then the operator would tell them to go see their physician but there was nothing else within the study.

DR. SWENSON: Dr. Moss?

DR. MOSS: I am going to follow-up on a question I asked earlier to industry but I want to ask it to the FDA. So, you can sit down and take a little breather. Some of the questions to our committee deal with product labels and boxed warnings. I just wanted to make sure I understood the role of boxed warnings and product labels. Do you have any evidence that the product labels and boxed warnings meet the goals that you want them to? So, if we recommend that we are going to have some change in a product label, as Dr. Prussin was

talking about, or a boxed warning, does that really achieve what you want it to? Do you have evidence that people change practice based on that information? If not, then maybe that is not the right medium to disseminate information.

DR. TRONTELL: Anne Trontell, from FDA. There hasn't been a systematic study of the impact of black box warnings. Some have looked at changes in utilization measured by numbers of prescriptions but, again, that is an imperfect surrogate for the appropriateness of use. I believe there are some studies forthcoming but we are not yet privy to those results.

DR. MOSS: Getting back to what Dr. Prussin was talking about, can you just explain a little bit in more depth what is the goal of a product label or a boxed warning?

DR. MEYER: That is sort of two separate questions. The goal of the product label is to describe the substantial evidence that led to the FDA's decision on the approval of the drug. The standard for approval is that a drug is safe and

effective for use as described in the product labeling. So, it is to take that substantial evidence and to put it into a format that allows that drug to be used in a safe and effective manner based on what we have found.

I agree with the comments made earlier about the fact that that separates it out somewhat from what may be very informed opinion but opinion-based guidelines, for instance, and the labeling is not meant to strictly restrict the practice of medicine. The FDA is not in the business of restricting the practice of medicine, but it is to inform the practice of medicine.

As far as a boxed warning goes, it is really to describe situations of serious morbidity or mortality. The standard for putting in a boxed warning does not require certainty about the relationship of the drug to those outcomes. It is really driven much more by the outcome itself. If you are taking about death, and so on, and you have at least a reasonable suspicion--either from animal data or from human data be it from studies or be it

from postmarketing--that the drug may be associated, even if not certainly causally with a particularly bad outcome, that will often be enough to place a boxed warning into the label. That is intended to really raise to the forefront how serious the concern is. There are some subtleties in terms of changing how the drug can be marketed, and so on, but the intent is really to signal right up front to anybody using that drug that this is something you need to consider when you use that drug.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Just to follow on that point, we are being asked this afternoon what we would recommend to the agency in terms of actions for you to take to communicate. What are the other things in your repertoire, in addition to the things that have been described here, when you want to communicate?

DR. TRONTELL: Again, depending on how broadly you look at it, there is a number of so-called risk minimization interventions that the

agency has worked with sponsors to apply. In the communication arena the agency may speak to the public through a public health advisory, or some other press release or talk paper. So, there are ways we can make a more prominent announcement of concerns.

There can be additional requirements for patients to be specifically informed of risks, using patient labeling that is specifically oriented to the lay person in terms of understanding. So, that includes such written materials as medication guides which are required to be handed out with prescriptions, or a patient package insert. There is a variety of other educational materials that could go beyond the print media that could be considered.

Then, obviously if you wanted to get beyond the communication realm such as we have heard--"dear healthcare practitioner" letters and others--you start to talk about other ways of making the information prominent or actually trying to direct care in a specific way.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I would like to follow on Dr. Brantly's question before in relation to the potential for some of the observations that have been made to be associated with what he generically called changes in inflammation associated with the use of beta agonists.

Just a brief introduction, I think the issue we are talking about here is not a global effect, as was said before, of these medicines on individuals because the effects that we are seeing are seen in a very small number of individuals. I think relevant to this issue are the data that I would like some of the basic scientists from both companies to comment about, presented by Steve Liggett who has been one of the persons most assiduously working in this area, in which over-expression of beat adrenergic receptors in mice, as compared to under-expression of beta adrenergic receptors in mice, was associated with a very paradoxical effect, contrary to what they were really expecting. And, this is published in The

Journal of Clinical Investigation in August, 2003.

Contrary to their expectations, the mice in which a beta adrenergic receptor was over-expressed showed an increased expression of bronchoconstrictive receptors in airway smooth muscle, and those in which the beta adrenergic receptor was under-expressed showed a decrease in the expression of these bronchoconstrictive receptors for thromboxane, for histamine, and so forth and so on.

So, a possibility then cannot be ruled out, and should be seriously considered as a potential explanation for some of these effects, that there could be individuals out there whose genetics or phenotype of some sort that we haven't yet figured out could be associated with them becoming a little bit like the airways of these mice in which these beta adrenergic receptors are under- or over-expressed.

They didn't test in this study if corticosteroids affected this particular under- or over-expression so the issue of the potential

regulation by corticosteroids was not followed up. So, just because this issue had been raised by Dr. Brantly, I just wanted to know the opinion whether the possibility could be that phenotypic and genetic characteristics of a very small number of subjects could make them particularly susceptible to effects similar to those described by Dr. Liggett with respect to beta adrenergic receptors in the mice.

DR. BEASLEY: Yes, you raise an interesting point. I think what Steve Liggett's experiments were attempting to address really was he was looking at the balance between sympathetic and parasympathetic pathways. I think the prediction was if you over-express beta receptors you would see a corresponding decrease in muscarinic receptor function. In fact, what he saw was the opposite. In fact, there was a recompensatory rebound in muscarinic receptor function and, similarly, when he knocked out the beta receptor he got a decrease in muscarinic receptor. So, I think it underlines that, you

know, we know really little about how the neuronal pathways interact. Clearly, there is more work that needs to be done there.

I do have a slight concern in trying to make extrapolations from animal models that require over-expression or knockouts to what we can see in the clinical scenario, and I think it is probably shared by everybody. But you do raise a very interesting question that possibly in a subtype of patients, in a small minority, there may be an inappropriate balance between the two pathways, and were you to influence one pathway you might get a reaction from the other pathway. But, as I say, the problem is that you could model these systems in transfected cells. You can do them in over-expressing or knockout animal models but that is really all they are, they are animal models and making that extrapolation to man is obviously very difficult. And, we clearly do not yet have those sorts of studies, but it is a very interesting point.

DR. MARTINEZ: I was just raising it as a

possible explanation but certainly I am not saying that this is what may be going on. It is just a potential for explaining that in a very small minority of patients genetic and phenotypic characteristics may make this balance, not only with muscarinic receptors. He also studies thromboxane receptors and histamine receptors--

DR. BEASLEY: Yes.

DR. MARTINEZ: --maybe this balance is altered in ways that would not be expected for the great majority of the population.

DR. BEASLEY: I agree, and I think today's discussion about genotype implications has largely focused on polymorphisms of the beta receptor. Of course, we shouldn't forget there are also polymorphisms of the muscarinic receptor, of the glucocorticoid receptor, and when we are dealing with the body and we are dealing with patient response to drugs and maybe the patient's response to disease we are dealing with an integration of all these gentoypic polymorphisms. It is very difficult then to predict what you would see in

small proportions of patients.

DR. SWENSON: I would like to ask the Novartis personnel a question regarding the racemic nature on formoterol. I read that I believe it is the RR enantiomer that is the effective moiety is not at all blocked by the SS. But that is simply on bronchoconstrictor aspects. Have you any data as to whether the inactive enantiomer might have pro-inflammatory effects or some other effect that wasn't gauged in studies that I could see? This might bear on the problem with the danger signal evident in the larger doses that some studies from you have shown.

DR. TRIFILIEFF: I do not have any data to show you today but we did look at this possible pro-inflammatory or antagonism effect of the inactive enantiomer for formoterol. As you said, there was recently a clinical paper looking at the effect of bronchorelaxation in human comparing the different types of enantiomer for formoterol and there was basically no antagonism effect of the inactive enantiomer.

To come back to the preclinical situation, we had basically the same situation. If we look in our animal models or in vitro, we don't see any antagonism activity of the inactive enantiomer.

DR. SWENSON: At this point then we will take our break and the remainder of the meeting, when we return in 15 minutes, will be focused on the specific questions that the FDA wishes us to address.

[Brief recess]

DR. SWENSON: Well, we now move to the specific questions posed by the FDA to the panel around warning and the potential use and studies necessary for these two drugs that we have been discussing today. We will go through the questions in order that the panel already has. That is, we will jump from one drug to the other rather than keep all questions to one drug and then move to the next. We will be moving back and forth with these questions. Some of these will be, as you see, recommendations that each of you will be able to offer, as we go around the table, to the questions

that are asked. Then we will move to yes/no questions in regards to whether we feel that these drugs should be continued to be marketed with the present database that we have.

I would ask the panel members to make their yes/no votes on these questions on the basis of the information that we have presently, that we have heard today. Although there are significant studies in the pipeline that may well answer these, and both companies are making very strong efforts in this regard I believe, but your yes/no vote should not be based on the fact that any of those studies will be accomplished and will provide further answers. We need to vote yes/no on what we have today.

So, with that, let first just see if there are any questions or general comments by the panel. Dr. Schoenfeld?

DR. SCHOENFELD: I have a general comment. I made a calculation before that was wrong, which is one of the reasons I asked for somebody to come by and do a calculation with a computer because I

know how often mistakes are made, and I have made plenty of them myself and that is why we usually have people repeat important analyses. So, I miscalculated the risk based on the SMART study, and I just want to give you my current calculation, and I think that somebody else out there ought to check this calculation and stop me if it is wrong because I think it is a very relevant calculation.

That is, I calculate that the attributable risk for the treatment among the general population is roughly 1/700, and this is in regard to asthma deaths. That is, be an extra 1 patient in 700 would suffer an asthma death on the basis of treatment with this drug in the general population. And the figure among African Americans is roughly 1/200.

Now, I am enough of a Bayesian that when I see 1/700 in the general population and 1/200 in a subgroup that was sort of chosen out of the study to move the 1/200 towards the 1/700. Because it sort of caught our attention and maybe we should focus more on the average than on what happens in

subgroups.

That being said, that is the kind of risk that, if we take these data on their face, we are facing. What I can't really judge as a statistician is the benefit because I don't talk to asthma patients every day; I don't know how hard it is for them. I have no real way of knowing whether if I was an asthma patient with a risk of 1/700 I would take or not take. For instance, if someone my age has a risk of 1/300 of dying from natural causes or from all causes--something like that; maybe 1/200. I keep track of this but I haven't looked at it recently--

[Laughter]

--yes, I have gotten older! So, I don't really know whether this is a risk that is too large or not very important at all. Probably some of the panel members who actually treat asthma patients would know that and it may vary from patient to patient.

DR. SWENSON: Dr. Meyer, I might ask if you or any member of the agency want to just

comment, even with very little preparation, on this question.

DR. MEYER: No, I think I would prefer not to. I haven't seen the calculations and I think at this point I prefer not to.

DR. SCHOENFELD: I could go over the calculation if someone wants me to just say how I did it. Basically, I took 10. Okay, I took basically the data here which was 13,176 and that is a 28-week study. That was the mistake I made before. I multiplied by that 28 and divided by 52. So, that is roughly half that number I guess you would get roughly, which is roughly 7,000. Then, basically, I divide 10 into that and I get 700. That is how I got the 1/700. Now, how I made a mistake doing that the first time I don't know. It is 10 extra deaths. There were 10 extra deaths total, 10 extra asthma deaths. I think it was 3 versus 10 I think in the data.

DR. MARTINEZ: the question I was asking is it is 1/700 per year?

DR. SCHOENFELD: Per year of exposure. Of

course, every year that I am exposed I take this extra risk of 1/700 if I want to take the SMART study basically at face value. I guess one other comment is that it is very hard in a large, simple trial to know what causes a mortality difference or a difference in any endpoint. The whole idea of a large, simple trial is that you don't really control what happens to the patients carefully so you don't really know whether it is the effect of the drug or an effect of the effect of the drug. For instance, if a drug makes people feel better so they go their doctor less often they may have higher mortality. In a very carefully controlled trial, like the Phase 3 trials that I am sure were done you are controlling all these things. So, there is less chance that it is some supportive care that is being affected by the effect of the drug that is causing the difference. But in a large, simple trial you lose that and some people consider that the advantages and some people consider that the disadvantages of a large, simple trial.

DR. WEAN: If I might just very quickly--David Wean from GSK--respond to that, because I just find I can't allow a figure such as 1/700 to be put out onto the table and potentially be appearing in the press and public domain without appropriate caveats. We, quite honestly, can't fathom a cogent response to that calculation but what we do need to say is when you look at epidemiological data, which we presented to you, we don't see an attributable risk of that sort. We can also say that in trying to assess the issues that we are asking about today in a large database of over 25,000 patients, we had difficulty arriving at the intended rate for asthma- and respiratory-related death. So, I think that calculation, quite honestly, probably does more disservice to individuals that we are wrestling with appropriately advising around the use of these drugs for their asthma, and I just want to add that balance to that back-of-the-envelope calculation.

DR. SWENSON: Dr. Prussin, did you have a comment?

DR. PRUSSIN: This morning there was some discussion about ongoing clinical trials by GSK that we heard from their representatives, and I just wondered if Dr. Schoenfeld might speak a bit, since he is an epidemiologist, on what he sees as a relevant clinical trial to address the question of increased mortality.

DR. KAMMERMAN: Before we get to that, I am a statistician. I am Lisa Kammerman. I am a statistical reviewer. I think just to clarify a little bit what Dr. Schoenfeld was doing, instead of looking at relative risk he is a little bit more interested in looking at the difference in the rates, the proportions of people developing asthma-related deaths, which is where he got the 10 from.

But in calculating any number where you are using person years as the denominator there are always issues involved. One of the major assumptions is that there is a constant risk for asthma-related death over time. So, that needs to be cautioned also.

DR. SWENSON: Dr. Schoenfeld, do you want to reply to Dr. Prussin's question?

DR. SCHOENFELD: I guess not right now because I think that the issue of what clinical trials should be done, or what further we should ask these companies for is sort of a later issue.

The other thing, again, I am asking the asthma specialists here I don't know whether this is a large--I calculate that number. Hopefully, it is right, but I don't have the expertise to know whether this is a big number or a small number in regards to the benefit of these treatments. I mean, there are many situations in which this would be a very small number and there are others where it would be a large number.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I was just going to say I think it is also complicated because one has to ask how representative that denominator is to the type of patients I treat, you treat, or are out there and I don't think we know that either. So, it is a very complicated number.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Just a point of clarification, what is it that exactly we are discussing? Are we opening the discussion very generally or are we answering any of the specific questions? I thought that we were very generally discussing and that is what I would like to intervene upon.

DR. SWENSON: The plan was to move to the specific questions but in this time period there will be the chance for specific recommendations for each of you, if you wish to offer those. Dr. Meyer?

DR. MEYER: I am sorry, I just wanted to take the opportunity to respond also to the 1/700 figure. I think our hope with the SMART study was to try to get data that would either confirm or refute the signal that we had coming out of the SNS study and some of the postmarketing experience in the early years of Serevent being marketed.

I think that the SMART study did go some distance in terms of helping to answer that. I

don't think it provided nearly the kind of precision as to what that risk might be that would allow for us to look at a number for attributable risk with any kind of confidence that that represents a true number. You know, these are rare events and this was a big study but it still didn't, I don't think, give us a kind of precision around what the true difference would be if we were to take that out to the entire population. So, I just wanted to caveat that number a little bit from our perspective as well.

DR. LITTLE: This is Roger Little, GSK. I am Vice President of Biostatistics for GSK. I agree with that very much. I like the idea of going after absolute risk. I think that is a great goal but I think if you think about the way we approach the study, we are trying to be conservative. We have the car accident where that is potentially related to asthma. We have been trying very hard to go after these in a very conservative way. If we want to estimate the absolute risk I think you would look to other kinds

of studies. You would look to the epidemiological study. If there was a signal nearly as strong as the one that has been mentioned we would see that in many other places. So, I don't think this is the type of study to really address that. This isn't the primary efficacy endpoint. We have picked out the one that caused the greatest concern perhaps, which is appropriate, in terms of looking at this study and thinking about the risk but I don't think this is the study to support the absolute risk and the difference between these two treatment groups. Thank you.

DR. SWENSON: I think we won't have any resolution today or even in the very near future, particularly with issues about the imprecision of socioeconomic status and questions about the biology of various forms of asthma. I think we will have to leave it as still unresolved.

I would like now to move to the specific questions. The first question is on the screen here. We are being asked now to provide specific recommendations to the FDA as to any further

actions they should take to communicate or otherwise manage the risk of severe asthma exacerbations seen in the SMART study. I will go down our list in order and ask Dr. Schoenfeld to offer any recommendations you feel strongly at this point on this question.

DR. SCHOENFELD: I don't have any specific recommendations there. I thought the boxed warning seemed to--although I haven't examined it in gory detail, it seemed like a reasonable warning to include in the labeling. I am assuming that that then gets communicated.

DR. SWENSON: Miss Sander?

MS. SANDER: I would have to agree.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I think this might lend itself to a medication guide or other kind of direct patient information that is dispensed with the medication because it is an opportunity to educate people about the ancillary issues, and also to assist people in knowing what are the drivers that may signal exacerbation or other problems that

would get them earlier perhaps to care. So, I think that I would recommend some form, either in a med. guide or patient package insert, of direct communication to the patient about these types of risks that includes recommendations for what might be done to minimize them for individuals.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I also don't at this point that there is any specific change to recommend, but part of that is based on not having good outcome data as to how these communications work. So, I would encourage answers to some of the questions that were brought up earlier, which is to try to understand what outcome occurs with a black box warning. But without any of that information and assuming that, at least on a face value, that seems to be an appropriate way to try to educate people who have to prescribe the medicines I wouldn't recommend any changes right now.

DR. SWENSON: Dr. Gay?

DR. NEWMAN: Excuse me, could I just ask a point of clarification before we go further? I am

sorry to interrupt.

DR. SWENSON: That is fine.

DR. NEWMAN: What warning label are we looking at? You know, on page 34 of the materials in that first section on the SMART study that we got from the FDA is what looks to me like a proposed modification of a warning label. Is that what we are commenting on or is that what it is at this point? Have all those deletions already been made?

DR. SEYMOUR: There is a copy of the product labels under separate tabs in the back that are the current product labels. The review may contain different language as the changes in the label progressed throughout the years but the current labels are included in both briefing books at separate tabs.

DR. NEWMAN: So, I guess my question is there is a proposed warning label change that comes from the FDA that is in this packet. Are you asking for comment on that?

DR. SEYMOUR: No, that has been resolved.

We are asking for comment on the current product label that is in the back of the briefing books under separate tabs.

DR. NEWMAN: Thank you.

DR. SWENSON: Dr. Gay?

DR. GAY: I would recommend a few changes. First, I believe that we should put greater emphasis not only on the fact that there does seem to be a difference between ethnic populations, but also that there does seem to be some early difference with greater severity of disease in asthma for those patients with peak expiratory flows less than 60 percent predicted. So, there should be some attempt to make a warning as well for patients as they have greater severity of asthma.

In addition, we have debated to some extent the role of this package insert. If it is to clearly attempt to make the drug as safe as possible, the data is not quite as strong because from the SMART data we clearly don't have enough information about the use of inhaled

corticosteroids in that population. But much of the other data presented to us for combination therapy would seem to suggest to me that we should in some way change the wording from "the use of an inhaled corticosteroid should be considered" to something more along the lines that the use of an inhaled corticosteroid should be strongly recommended, or the use of long-acting beta agonists as mono or individual therapy in patients with asthma should be discouraged and should require the use of some type of anti-inflammatory medication.

DR. SWENSON: Dr. Moss?

DR. MOSS: I think I am going to end up reiterating what a few other people said, but I have four comments about the warnings. Number one is that I think the warning box should be left on the salmeterol. I think it is important that it should also be kept on the Advair since that compound is also in Advair.

I think it is important not to stress a race thing, a race angle, but to state that there

are subpopulations that may be at increased risk of adverse events from this medication because I think that gets back to the beta receptor issues and probably other snips that we are just not aware of yet.

As Dr. Gay said, I think it is important to stress the role of inhaled corticosteroids, reiterating what I said earlier, I don't think that is the whole effect but, getting back to what Dr. Schoenfeld said, if people are treated properly it might make that attributable risk more favorable or better by dropping the numbers in both groups down from 13 to 3 to maybe 6 and 2 or something. So, I think it important that people realize, as Dr. Gay stated, that this medication should be used in conjunction with inhaled corticosteroids.

Again, I think the FDA needs to re-thing about how they are going to disseminate information to physicians and the public. I am not sure changing product labels that I don't think a lot of people spend a lot of time reading is an effective way of communicating information to the public, to

physicians and to the medical community.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I really have nothing more to add beyond what Drs. Gay and Moss just said. I completely agree with that. I would also agree with the idea of considering supplemental information for patients. This gets very complicated very quickly. I do believe that our patients do a good job of understanding the limits of medical knowledge if we explain it clearly enough and we tell them what we know and what we don't know. I think a more direct reach in that way to patients would be something worth considering.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I agree with my colleagues. I would like to make a point that I believe is floating around in the community--and my hope is that it will be picked up after this meeting--the impression that has been floating around in the community that these drugs, and specifically Serevent, are bad for African Americans, and I

think it is critical that that message not go forward because it is likely that it will be far more harmful to the African American community if they avoid these types of drugs in the future. I think that is a real message that really needs to be considered strongly. I absolutely agree with the agency taking that out of the black box warning area.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Notwithstanding my agreement with what my colleagues have said, I would like to add just one more point that I referred to before, and I think it is an issue that is coming up I think very clearly from the data that we have observed. I will briefly repeat what I said before with respect to this issue.

I think there may be two dimensions to asthma morbidity that until now were considered as highly correlated within individuals. In other words, asthma control, meaning the everyday presentation of symptoms, cough at night, wheezing, wheezing with exercise, and the likelihood of

having severe asthma exacerbations. In fact, I think that it is almost implicit in the guidelines, as they are stated now, that if you adequately consider how much a person is controlled you in some way, because of this implicit supposed correlation between this and exacerbations, you are also considering exacerbations, so much so that exacerbations are not part of the algorithm to determine asthma severity today, at least in the American guidelines.

I think that what is emerging from this data that we are observing here, and not only from this data but from several other data that I will not mention here, is that these two dimensions, although correlated, are not equivalent; that there are individuals in the community whose control with these medications, particularly with combined medication, is significantly improved as compared to treatment with only inhaled corticosteroids or with no medicine or with beta adrenergic agonists of short duration by themselves. However, there are individuals in whom either there is control but

there is still a very high risk for severe asthma attacks, or who don't have problems of control, who have something called brittle asthma, but are at very high risk of developing severe asthma exacerbations.

All that I see without yet, I agree, definitive proof seems to indicate to me that long-acting beta agonists as a group may have a negative effect on the control of severe asthma symptoms in the latter group, in what I have called the brittle asthma group. I don't have definitive proof, as nobody else here has, but I think the data is clearly indicating that this is what may be going on, and the scientific community, the FDA, and particularly industry needs to be very worried about this because we are going to discuss next what is it that we need to do next with this class of medicines. And, we would not like, I think, not to pay attention to this possibility which could make it difficult for these medicines to continue to be used in the population as a whole because of a small group that is at high risk when they

provide significant relief of symptoms to a very large part of the population.

So, this idea that is relatively new because it is not there in the guidelines I think needs to be seriously considered in evaluating results of any clinical trials in the future. To summarize, there may be a population of subjects with asthma in whom the main issue is not day-to-day control of symptoms for which combination therapy is the best we have today, but in whom the main expression of the disease is severe attacks that are not only not controlled by these medications but may be rendered worse by these medications.

What are the biological bases for this? I propose one, which is the data that Steve Liggett had proposed but there may be others. Careful consideration to this possibility perhaps would allow us to understand better the results we are seeing.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: I agree with most of the

statements that everyone has made already. Management of asthma is an incredibly complex problem that I think we in general tend to underestimate. Today we have incomplete knowledge of asthma phenotypes, as I think Fernando is alluding to, and even less understanding of the genetic basis of asthma, which makes the optimal management even more difficult. Until we have those data it makes giving a definitive answer on what we should do with each specific class of medication difficult, if not impossible.

So, I am not sure that I can recommend any specific changes in the way to communicate, although I do like the idea of perhaps reiterating these messages to both the medical and the patient community. The only caution I would have, which was alluded to, is that virtually every adherence or compliance study on asthma, particularly with the use of inhaled corticosteroids, would indicate that patients under-adhere to those medications and any message that we send that might be alarmist or hinder the use of what are appropriate medications

for the majority of the population would be a disservice to that community, while we try to understand for whom certain medications are a risk factor.

DR. SWENSON: Miss Schell?

MS. SCHELL: I agree with everyone has said but I would just like to add that I think it is very important that the process include education not only to the caregiver but to the patient, and many of the patients that I work with at bedside haven't an idea what the medicine is, let alone if they read the label about the warning. So, I think the dilemma for me is how to get this information to them that they clearly deserve, but to put it in a message that they can understand. So, when you put it into fine print into the insert, most of them can't even read it, and if you put it on the box with the label, are they going to be educated by the caregiver? I would like a clear understanding of the education available to the patient when it is dispersed to them, with the risk involved, also what the medication is for, in a

language they understand. A lot of patients just don't understand what they read when it gets into the complications of the risk. So, that is my dilemma when I look at it, how do we get that information to the people that deserve it in a clear message?

DR. SWENSON: Dr. Prussin

DR. PRUSSIN: I would agree with Dr. Gay's comments on trying to strengthen the language on monotherapy, discouraging its use. This drug is already primarily being used in moderate to severe asthmatics, and those are the groups that we talked about being at risk. So, I am not sure if trying to point out about subpopulations in the package label is going to go much beyond what populations are already being treated, in practical terms.

Lastly, I was struck primarily by the original text, by a whole block of text. Basically your eyes glaze over and all the numbers fade out. You might consider either putting a table or one single figure to try to graphically display the relative risk data that we have been talking about.

I think somebody seeing a graph or a table, they are going to gravitate to it much more than to a text box. So, you may want to consider that. I was originally thinking of that when I saw these huge paragraphs of text, but maybe less so with what you have now.

DR. SWENSON: And my comments echo much of what has been said but I would like to state them very briefly, and that is that the FDA really consider a much stronger sanction of long-acting beta agonist use in combination with inhaled corticosteroids, and that monotherapy be highly discouraged. I don't know whether this could be done in some consensus with the respiratory organizations and the agencies that have promoted these guidelines, but to have possibly a convergence of guidelines that are out there by highly respected bodies match exactly what is in the warning.

To the question of whether there is a very, very small subset of patients that might be adversely affected, i.e., these people with very

brittle asthma, consideration being given to warnings that might suggest that patients that have had very rapid onset of asthma leading to respiratory arrest or need for intubation without warning, that this class of drugs may be potentially considered adverse. That is obviously something that is going to have to evolve but at least for agency consideration as maybe these warnings change over time.

At this point we will move on to the second part of question one, which is the vote. Again, I will reiterate that your vote should be based on what we presently know and not on what we might know three or four years down the road with many of the studies that, hopefully, will go to completion and provide answers. I will start in just the opposite order and ask--

MS. SANDER: Excuse me--

DR. SWENSON: Question, Miss Sander?

MS. SANDER: Excuse me. You know before we go to the vote, if I might just add a little bit from a patient perspective, I think some really

wonderful insights have been shared around the table. If you are considering any types of changes in any of the labeling, I would just encourage you that when you are communicating with patients or physicians we have to be careful what we say, and how we say it, and when we say it because it does have impact on what patients will wind up doing about their disease with regard to this drug. For example, we know from within our organization that patients will often use Serevent to treat acute symptoms because they don't see themselves in rescue situations, warranting a rescue use of albuterol. And the word "rescue" has a certain meaning to them that is very different than what we have talked about today around this table. So, you know, while I think it is good for us to think about what we are telling patients, it would be nice to have a guide. It is also very important for us to be careful about how we communicate. I just wanted to echo that statement.

DR. SWENSON: Okay, if there are no further comments, Dr. Prussin, your vote?

DR. PRUSSIN: Yes, should be continued.

DR. SWENSON: Miss Schell?

MS. SCHELL: Yes.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: Yes.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Yes. May I justify my yes--

DR. SWENSON: Certainly.

DR. MARTINEZ: --or is it only yes or no?

DR. SWENSON: No, be brief but you may.

DR. MARTINEZ: I will try to be as brief as possible. I think the agency and industry--and I thank them both--have presented very interesting and important information. I would like to summarize the way I see that information. We have been presented with two large what I would call surveillance studies, both coinciding with the same type of result, which would indicate and increased risk of asthma-related deaths in individuals who are being treated with salmeterol without regards to what other medicines they are receiving.

Dr. Beasley has several times mentioned an epidemiologic study which I think is the strongest study which shows that no such effect exists in a type of different surveillance study, in which all individuals who died with asthma are compared with matched controls. In this case, controls in that study were matched for the hospital in which the subject had died or had been treated and for age.

I would like to warn, however, that that study is completely different not only in methodology but also in many other aspects to the ones that were presented and are prospective studies. Subjects in that study were much older; 42 percent of them had a specific diagnosis of COPD. And, I would suppose that, for example, in the SMART study any SMART doctor would not have included subjects with COPD because what they were asked to include were subjects with asthma. So, we may be talking about two different things. When you have 42 percent of subjects with COPD in one study and perhaps not as many in the other study, perhaps the results could be interpreted

differently.

I think we may have here a true signal. As Dr. Schoenfeld has many times told us, here the only way in which we can truly assess the signal of risk is in terms of benefit. My evaluation today is with respect to the patients that I see in my clinic and the patients out there with asthma in this country in general. It is still justified to keep this medicine in the market. However, I say that with a conditional, which is that there has to be very, very accurate follow-up of the increased risk that has been observed in these patients on salmeterol in the future, and particularly better understanding needs to be there if this risk is or is not decreased by steroids. I do not think that the data, as I see it today, justifies saying that this risk is decreased by steroids. I am not saying that it is not decreased by steroids. There is no clear data to say either thing.

I am worried that the concept may get out there that there is strong data, suggesting that if you just give steroids this effect is not going to

be there when we don't have strong and definitive data in that sense either. So, in that sense I vote yes but with the strong conditional that a very accurate follow-up for this issue needs to be part of the FDA task in the future in collaboration with industry.

DR. SWENSON: And I think most members would agree with that. Dr. Brantly?

DR. BRANTLY: Yes.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Yes.

DR. SWENSON: Dr. Moss?

DR. MOSS: Yes.

DR. SWENSON: Dr. Gay?

DR. GAY: Yes, and I would like to state that these drugs do seem to have a clear and profound impact on morbidity and mortality overall in a very positive sense. We have seen the overall declines in some of the data presented here for the occurrence of exacerbations and on morbidity and mortality. There does seem to be a true signal present but we cannot disregard the other things

that may contribute to this signal in these subpopulations. This does include access to healthcare. This does include the use of inhaled corticosteroids in these populations. This does include the changes in treatment and management patterns for certain subpopulations and certain under-represented populations. It is going to be extremely important, and I do believe that both companies are making good efforts to attempt to control for those factors in the subsequent studies that they are beginning to perform, and it is going to be extremely important to analyze this data on the basis of those multiple factors to see if we can make any impact on this true signal that does exist.

DR. SWENSON: D. Schatz?

DR. SCHATZ: Yes.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: Yes, with caveats.

DR. SWENSON: Miss Sander?

MS. SANDER: Yes.

DR. SWENSON: And Dr. Schoenfeld?

DR. SCHOENFELD: Yes.

DR. SWENSON: My vote is yes as well. I think that we have a unanimous vote here but, clearly, the warning is there that none of us feels 100 percent yes. I think that possibly I am stating the obvious but wish to have it for the record.

We will now move then to the next question which now turns on formoterol. Here the question is the label for formoterol an formoterol-containing products at this point does not include warnings comparable to the warnings that are present in the salmeterol products and, based on currently available information, should the label for formoterol-containing products include warnings similar to those to the salmeterol label?

This will be a yes/no vote, but I think we have enough time here if people wish to say very briefly why they voted one way or the other.

DR. SCHOENFELD: May we comment first so we can communicate with each other before we have to vote?

DR. SWENSON: That is a reasonable request I think if we could limit to five to ten minutes for those that wish to make it an open discussion here, and I suspect you wish to lead off.

[Laughter]

DR. SCHOENFELD: Well, first, again a back-of the-envelope calculation and, again, if anybody who has better data wants to contradict the calculation, but as I understand it, formoterol had the same risk as salmeterol we would expect, based on the number of patient-years of follow-up, 0.23 events--0.23, and this is based on 527, multiplied by 16/52 to get 162 years of follow-up, and then multiplying that by the event rate and dividing that by 700 we get 0.23. So, the chance of not seeing any event is roughly 80 percent, which is good power actually for not seeing anything. So, I think the fact that at least in clinical trials we didn't see anything is not surprising because if the risk was exactly the same in the two drugs the chances of not seeing anything would be 80 percent. That is the point I wanted to make.

Now, the issue as to whether a warning should go across the class depends upon, I guess, how similar with think things are in the class, which is beyond the level of my expertise. They apparently both work similarly. One drug works faster, which may be an advantage in terms of preventing these problems. But if anybody has any comment--I guess there has been a comment by the industrial representatives but if anybody on the panel would like to make a comment to the extent that this is a class, I would love to hear that.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I will hold until maybe someone can answer his question.

DR. SWENSON: Dr. Gay, do you care to comment?

DR. GAY: Certainly. Every other drug that works at this receptor has shown effects with the arginine/arginine subtype of receptor of negative outcomes. We have seen it with albuterol. We saw it with other shorter-acting forms of beta agonist, and we have seen it with salmeterol as

well. Because of this concern that with certain genotypes or phenotypes of this receptor we have seen this effect, I have significant concern that it is a class effect. We have not seen a study yet that has been powered appropriately and designed appropriately to look at whether or not this is potentially the case win formoterol. However, with the fact that every other beta agonist, both short-acting and long-acting, has similar effects at the receptor, I have concerns that until proven otherwise we have to make ourselves believe that formoterol may act the same way.

DR. SWENSON: Dr. Gardner?

DR,. GARDNER: I appreciate what the question is trying to get at but I want to raise another one. In looking at the formoterol insert, given the data that we saw today related to children, I don't think that what we saw is very well communicated in the insert as it stands, and I would like to suggest that in addition to the question we are addressing, which I think probably has mostly to do with class labeling and black

boxes, I would like to suggest that more attention be paid to communicating what may be a heightened risk in children and then, of course, update it as more data become available.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I guess I would like to get some clarification from FDA people regarding what the standard is for class labeling. If, for example, you have a signal from one drug in a class and no adequate data in the other to say yes or no, is that typically an indication for a class warning? And, would you only not have a class warning if that other drug had adequate data to show that the signal did not exist?

DR. CHOWDHURY: I want to first clarify that the question is actually specific to formoterol, not necessarily all long-acting beta agonists. So, you can't probably use the term class labeling. The specific question is on formoterol.

DR. SCHATZ: Yes, but I would like to understand the meaning of the class label, my point

being that if one assumes one has to have a class label until you can prove the drug doesn't do something, then I think everyone would agree we have different types of studies. We don't have a study that shows that formoterol doesn't do this. But I think this issue of class labeling--what that means, and we are talking not clinical; we are talking about regulatory recommendations. So, I think I need to understand the regulatory environment better.

DR. MEYER: Right. I think that your recommendation has to be informed by the degree that you do, in fact, feel, as Dr. Gay pointed out, that this in fact does represent a class effect because, as you say, we do not have data one way or the other. Obviously, many drugs have idiosyncratic effects that will not be represented by other members of their class. On the other hand, there are situations where we can feel fairly confident from the pharmacology as we understand it, or other mechanisms as we understand them, that this would extend to other members of the class. I

mean, you can take certain adverse events with ACE inhibitors for instance where you know it is a direct result of its pharmacology.

So, I think we would defer to your expertise in that regard but I think you would need to feel personally convinced that this probably does represent a class effect and, therefore, it is only fair to put it in formoterol's labeling. On the other hand, if you thought that the observation, the signal that has been seen in the SNS study and the SMART study could be due to other considerations of the way salmeterol itself interacts at the beta receptor that might not apply to formoterol, then if that is a significant unknown for you, I would think your recommendation would be I don't think this should be extended. But the bottom line is we do not have the data one way or the other. If the SNS and the SMART study did not exist for salmeterol, we would be in a situation of having really no idea at all about this. We have those data for salmeterol; we don't have them for formoterol. So, you know, it is just

an unknown whether formoterol would have similar findings or not. So, again, we are deferring to your expertise, and I hope I gave you enough of an explanation there.

DR. SWENSON: I will ask Dr. Schoenfeld then for his vote.

DR. SCHOENFELD: Again, I am sort of voting beyond my expertise in a way because I know this 80 percent chance but I don't really know the biology of these drugs. But I think the prudent thing would be some sort of warning, boxed label, on formoterol that says that this effect has been seen in another member of the class and it is unknown whether it would apply to this member, but at least to warn people that this could be an effect either of the class of drugs or of the way patients act when they are, in fact, on these drugs, which is another possibility.

DR. SWENSON: Before I ask directly for your--

DR. SCHOENFELD: So, the answer is it shouldn't be--

DR. SWENSON: Wait one minute.

DR. SCHOENFELD: Sorry.

DR. SWENSON: One can abstain if you feel so uncertain as to whether you should vote one way or the other. An abstention is perfectly fine.

DR. SCHOENFELD: In other words, I believe it should be marketed but I believe it should have some kind of warning pointing people in the direction that this has been found with other drugs in the class.

DR. SWENSON: Miss Sander?

MS. SANDER: When I read this question, we are talking about a similar warning label as the one when we are looking at salmeterol. Is that right? I don't know all the similarities. I do know that there is information on this in the package insert that I do think should be brought forward, and there may be some other information that should be made more prominent as well that we have learned today. I don't know if I know how to vote on this one so I think I may have to abstain. I think there is information that should come

forward; I don't know that it needs to be the same information as with Serevent. So, if that is a yes or a no, I am not sure.

DR. SWENSON: I think we will count it as an abstention.

MS. SANDER: Okay, thank you.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I guess I would have to say, based on what we saw today, my answer would be no, although I would like to comment that I agree with Dr. Schoenfeld that some wording pointing at what is known about salmeterol would be useful until we have more data.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I really don't like the idea of making such and important decision with such little information, and I definitely intended to abstain but I guess it is one of those situations where something has to be done. I think that in the absence of being able to say that it is not a class effect, I am leaning, and I will therefore, vote yes, that labeling to say that it has been

shown in a drug of its class; it is not known whether it is a class effect--I am not even convinced the effect--I see the signal. There have been mentioned other reasons for that that may also not even show that the drug does it. So, I am not even convinced there, but in the sense of letting people know what exists so they can made the best decision, I think I am in favor of having it say that another drug of the class has shown this signal and it is not clear whether it extends to the other class.

DR. SWENSON: Dr. Meyer?

DR. MEYER: I just wanted to perhaps point out-- and maybe this will help Dr. Schatz although I guess he eventually came down on a yes recommendation--that one of the implications of having one label that has these boxed warnings and one that does not to a patient or a practitioner may be, well, if this one is unsafe then my patient will be better off on this other one. I guess that is the other thing you need to consider as well. Is that disparity something you are comfortable

with?

DR. SWENSON: Dr. Gay?

DR. GAY: For the reasons I have already stated, I will vote yes.

DR. SWENSON: Dr. Moss?

DR. MOSS: I would like to reiterate what Dr. Meyer said because I think it is important. If we sat here today and the SMART study only had 2,000 people in it, I think people would have totally different conclusions. We would have two small underpowered studied that maybe didn't show anything. I think it would be a bad message to send to the industry that if you terminate studies earlier that can be potentially beneficial for you. I am not saying that Novartis did that for that reason, but I think it is very important that if we don't know the information and there is a possibility that it is a class effect, I think it is very reasonable to have a warning on formoterol that says that a similar class of drug has shown adverse events. It is not implicating that drug per se but it is just, again, relaying the

information that there is the possibility that there are subpopulations that may have adverse events to this class of medication. So, I would say yes with that reasoning.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: My answer is yes. I would just like to give you a little bit of my basis for it. I think that Dr. Schatz said it very well and I would underscore it with a little more emphatic yes. We know that there are similarities in the chemistry, the pharmacology and mechanisms of action. We know that clinicians will use these two drugs rather interchangeably. And, I think that Dr. Schoenfeld used the key word, which is "prudent." Sometimes in the absence of as complete medical information and scientific information as we would like, we have to recommend something that we think is the medically prudent thing to do. So, that is my basis, given all the caveats of the uncertainties of the data.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Yes, I vote for a black box

warning for formoterol.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Yes.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: Yes.

DR. SWENSON: Miss Schell?

MS. SCHELL: My vote is yes. I would just like to state that I think that it is necessary for the patient to have that information so they can make an informed decision.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: Yes, with the caveat that it has been shown in another member of the class but hasn't been shown for this specific drug.

DR. SWENSON: And my vote is yes as well, with that same caveat in all fairness to formoterol that it be explicit that this has not been established for that drug but of its class.

DR. GARDNER: Mr. Chairman, I want to change my no vote to yes, given that my colleagues also have expressed the caveat that caused me to vote no. So, I agree with what you have said as

long as there are caveats so yes.

DR. SWENSON: Okay, fair enough. The vote on this then was 12 yes and 1 abstention.

We move to the vote on the last question on the slide, that is, based on currently available information, do we agree that formoterol should continue to be marketed in the United States. I will ask Dr. Prussin to start the vote.

DR. PRUSSIN: Yes.

DR. SWENSON: Miss Schell?

MS. SCHELL: My vote is yes. Again, I would like to reiterate with patient and physician education as an important part of that.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: Yes.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: Yes, with the caveats and conditions expressed before.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: Yes.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Yes.

DR. SWENSON: Dr. Moss?

DR. MOSS: Yes.

DR. SWENSON: Dr. Gay?

DR. GAY: Yes.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: Yes.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: Yes.

DR. SWENSON: Miss Sander?

MS. SANDER: Yes.

DR. SWENSON: And Dr. Schoenfeld?

DR. SCHOENFELD: Yes.

DR. SWENSON: And my vote is yes as well. So, that is a unanimous yes to that question.

We now move to recommendations to the agency with ideas and opinions and recommendations toward how we might further improve the understanding of the nature and magnitude of the risk of salmeterol first and then we will turn to formoterol. I think that possibly much of what has already been stated is contained in this but I think I will go down the list to give people one

more opportunity to emphasize just these points here with specific recommendations. Dr. Schoenfeld?

DR. SCHOENFELD: I guess I really don't know because, clearly, if you have what you consider as a problem what you want to do is figure out how to prevent the problem. So, I am not going to suggest that big trials or studies would be done to sort of determine the extent of the problem. It seems to me that what is necessary is to try to figure out how to prevent it and I don't think with the study we really know what the problem is. And, I am not really sure I know enough about this to suggest ways that you could study the prevention of this problem, whether this is an issue of patient education or something else.

DR. SWENSON: Miss Sander?

MS. SANDER: My feeling is that the overall question is what we do now and how we do measure risks, and do we see greater risks in certain populations of people, whether it is ethnic or gender specific, or otherwise, or age related;

you know, effects on children versus on elderly people or other groups. I think that we need to look at things long-term. I made a few notes here and I am trying to put them all in a capsule here, but the challenge is that we are always going to have questions about these medications, particularly when I don't believe we are doing enough to study what is happening when patients go to the doctor in the first place to get the medication, what kind of information they are being given, and does that information empower them to use the product properly at home, at school and on the playground.

We just hear every day from families who get their medications, go home, and have a zillion questions that they don't seem to be able to get answered in a manner that--well, I just think that we could be doing a better job and I think that whatever studies we do approach, we do need to make certain that patients do have the information necessary to use these drugs safely so that they do know that Foradil and Serevent and Advair are three

different drugs and the instructions for using them are going to be different. You know, I would hate for patients to be left with the idea that they are the same and that they are used the same.

One of my concerns is that patients are going to use Foradil more frequently than they should because of what they think when they hear that it treats, you know, the breakthrough symptoms as well as preventing symptoms. So, I think we just need to have education included in these studies. Anyway, I won't preach too much, except to say that the language of asthma is very important. What we say to patients must be said within their hearing and their ability to follow through whether it is a study or not.

DR. SWENSON: Well taken. Dr. Gardner?

DR. GARDNER: I think that the studies that GSK described to us go a long way to helping to answer some of our questions. The one thing I have become concerned about is that they be encouraged to stay on task and get these studies done and reported to us in a timely fashion. We

are aware that these products are moving toward a patent expiration and there may be motivation not to finish things as quickly as we would like. If there is a way for the agency to encourage that they, in fact, be completed on time and reported in a way that we can use the data, that would be my interest.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: We are trying to consider both science and practicality in terms of the methodology. I think I would actually suggest something fairly specific, which would be a case-control surveillance design where one, in fact, would involve hospitals with linked pharmacy databases and actively be looking for those patients who have these rare outcomes in a large enough net that it doesn't take forever to have those, to be able to match then sort of real time with other decent controls, appropriate controls, perhaps hospitalized and not intubated, perhaps emergency department. And, I think in so doing you have a chance to get both phenotypic information of

the type that we would like to have and even genotypic information. It is different than a case-control study in the way I mentioned. Without giving this a huge amount of thought, I would put that on the table to be considered and, of course, the advantage of that is that that would be one study that would be essentially done for both of these types of medicines, as well as any other factors that could, in fact, be associated with these very severe and important but very uncommon outcomes.

DR. SWENSON: I am going to step in here simply because I want to follow on with what Dr. Schatz had said. One recommendation I might have is that another system with a broad database be considered as a source for this particular improvement information. That would be the VA, the Veterans Administration. They are leading the way in information management so this might be another valuable source, akin to the state Medicare analysis.

The other possibility would be, if we are

talking about a potential class effect, is to consider that both companies merge efforts here, if possible and practical, to look at this by expanding numbers and resources to get at this issue. Dr. Gay?

DR. GAY: I believe both companies at this time, with a number of the studies that they have commented on here today, are making good efforts toward running the appropriate studies to help us evaluate some of the questions we have brought up as a committee. I would be hopeful that both companies, with the fact that they either have available or have in development combination long-acting beta agonists and inhaled corticosteroid formulations of their medications, would look to do similar studies with those medications to help to standardize for the lack of inhaled corticosteroids in a number of these studies, and to help us further evaluate where we are in terms of some of the signals that we have seen currently with the SMART study.

DR. SWENSON: Dr. Moss?

DR. MOSS: I think it is important to remember that asthma is a heterogeneous disease, and I think the answer is not to just to do an even larger clinical trial. I think we would be sitting here with probably having the same discussions. Not to sound too NIH appropriate, I think it is important to look at this as a translational research project and to take the idea that there are specific subsets of patients that may not respond properly to this long-acting beta agonist therapy; identifying a basic science laboratory with a translational approach to what these specific populations are, whether they are genetic or acquired traits, and then study those populations to see if there are truly harmful outcomes in these smaller studies. I think that would be a better way to go than just enrolling 60,000 people, or whatever, and I think the NIH would like that too.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: I wish I could roll back the clock because I guess what I really want is for the

SMART study to reach its stopping point that was set forward and really get to that point so we would have something more complete. But I can't have that now. That being said, I would underscore the things that were said here. I don't have a whole lot to add, except that as we go forward with these additional studies and we become more interested in both the clinical phenotypes of asthma, as well as the genotypes of asthma, I would encourage the sponsors not to ignore something that we all know, which is that while the genes are important and it is a heterogeneous disease, there are also major environmental factors that are going to affect an individual's risk of having severe exacerbations and I haven't heard that really discussed here.

People look conventionally at tobacco. That is important. But we know that many cases of asthma, especially in adults, have their onset in adulthood due to occupational and environmental factors other than tobacco smoke being involved. I think that those ought to be weighed in when you

are designing studies that look at the genetic factors. We have to understand the somewhat more complex interactions and confounding effects, as well as true attributable risk related to environmental factors added to the understanding of the genetics.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: I would echo Dr. Moss' belief about pursuing subgroups. But I think that one of the keys to trying to understand about this small group of people who die is that we need to find their phenotype. One approach to doing that is obviously pursuing exactly what that phenotype was at time of death, and to couple that, for instance, with a VA study in which we actually are able to forensically dissect what those patients were like at that time would be a very valuable thing. I would encourage the sponsors to consider partnering specifically with the VA to approach that and perhaps capture that death phenotype that we are seeing. It may open up a wide array of possible mechanisms which we might be able to look

at in the future.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: I fully agree that at the present time further assessment of the potential existence of this increased risk, although interesting, shouldn't be the center of the attention. My general assessment of the data that has been presented to us is that there is a signal here, and I think the main objective will need to be to understand what the signal is and in which way it could be prevented.

I completely agree with Dr. Brantly that trying to define the phenotype and perhaps the genotype of these subjects is a great objective that I think needs to be pursued. This will have an additional advantage--in Spanish there is a saying that not all bad things come to harm--which is to better understand brittle asthma. I think this is a good opportunity to understand who are the subjects who have this severe form of the disease who probably represent a significant proportion if you think about it, of mortality for

this disease which is relatively low.

My recommendation also, since I have been doing some genetic studies for the last ten years in this disease, is that more than the more common polymorphisms expressed in any of these potential candidate genes, rare polymorphisms may be the crucial factors here. Therefore, the approach of doing this by genotyping for common polymorphisms found in the general population may not be successful. Perhaps a better approach could be a more profound re-sequencing of individuals who have this phenotype to try to determine if rare polymorphisms are present in them that are not present in the population as a whole. I don't see that methodological approach mentioned and I think it would be very important. It is more expensive but, at the same time, it could give very interesting results because polymorphisms that are present, say, in 1/1,000 or 3 or 4/1,000 are not going to be detected in linkage to equilibrium--I am sorry to give such a complicated answer but in linkage to equilibrium with the common ones. They

will have to be found specifically in each subject who has these polymorphisms which perhaps are increasing the risk in the way we are talking about.

So, I strongly recommend to the industry to search for different approaches both in genetic and phenotypic studies to determine who the subjects are and to ensure that in that way we can have some sort of preventive strategy.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: I agree completely with what Dr. Moss, Dr. Brantly and what Dr. Martinez just stated quite elegantly, that we are clearly moving into an era of one size does not fit all for asthma therapy, and pharmacogenetics is really going to be what will direct us to effective and safe therapy, and it is only through identifying those high risk phenotypes that we will be able to do that. So, I would agree completely with what they said.

DR. SWENSON: Miss Schell?

MS. SCHELL: I would just like to make a

couple of statements. When we look at asthma, as a practitioner at the bedside, there are many components and asthma is very individualized on the patient. And, when you look at the components of asthma management, clearly, medication is one of the components that we look at. But I also would like to see a study that would look at factors that could affect how much medication you are giving, including the environmental factors, the factors of education and compliance, all those things that patients are not very well at doing yet and how is that affecting how much medication you are going to have to give them. So, basically looking at all parts of asthma management on an individual basis I think is important to include in a study.

DR. SWENSON: Dr. Prussin?

DR. PRUSSIN: I think it is important to remember the public health impact of the question we are debating. Asthma is an incredibly common disease. Combination long-acting beta agonists and inhaled corticosteroid therapy is the primary therapy for moderate to severe asthma. As an

example of that, Advair is I believe the number one drug for GSK. So, these are problems that deserve the input of some resources.

I am not an epidemiologist; I am a translational researcher. So, just the opposite of Dr. Schoenfeld, I really can't think about study design in a way that really is going to make sense. But I am concerned that the small-scaled studies that we are looking at, these translational studies, are all very good for understanding the biology but not for answering real-world questions. You know, they are fine for the future and for projecting ourselves forward and they are important. It is the kind of work I do. But I would like to step back and say, five years from now or three years for now, are we going to have answers to the questions that we are talking about today? And, I am not clear that these are going to do that. Again, I don't know how to; that is beyond my expertise.

I think, clearly, one of the questions we should be addressing is looking at combination

therapy versus inhaled corticosteroid alone. Is the safety signal that we saw here with salmeterol alone still present when you have an inhaled steroid on board in all of the patients? I think that is a study that could be done.

The other concern I have, just in terms of long-term studies, that has not been addressed is the issue of monotherapy. Again, we have talked about it but, you know, how do we get a grasp on it? Both companies are selling long-acting beta agonists and I don't think we have any handle on patients that are taking this as monotherapy and that is a public health problem that presumably also is a safety problem. At least we should have a handle on the magnitude of that problem, what percentage of patients using these drugs are using them as monotherapy and that could be addressed as well.

So, these are some of the issues I see as far as what studies could be done. Again, how you answer the specifics on those studies I don't know but I am hesitant just to look at mechanistic

studies, thinking that those are going to answer real-world questions that we need addressed that patients and practitioners would like addressed.

DR. SWENSON: We will move to the last question, and I think it mirrors so much the former question that this may go quickly but we should at least allow for discussion relevant in particular to formoterol.

I will start just so I don't have to have Dr. Prussin go again initially. I think the comments that I mentioned in regards to salmeterol hold equally for formoterol and they are in the record. Dr. Prussin?

DR. PRUSSIN: This is in terms of question four?

DR. SWENSON: This is in terms of Novartis.

DR. PRUSSIN: I think really basically the same issues are involved. I think there is a safety signal and, obviously, the numbers need to be greater but I think roughly the parallel issue to what I mentioned for number three.

DR. SWENSON: Miss Schell?

MS. SCHELL: I will stand by what I said earlier. Thank you.

DR. SWENSON: Dr. Kercsmar?

DR. KERCSMAR: I think the same issues apply to this drug as well.

DR. SWENSON: Dr. Martinez?

DR. MARTINEZ: The same issues.

DR. SWENSON: Dr. Brantly?

DR. BRANTLY: The same issues.

DR. SWENSON: Dr. Newman?

DR. NEWMAN: Actually I have more a question than even a comment. Based on what we discussed earlier about kind of a within class warning that we would put with this drug based on the SMART study and leave the question unanswered for Novartis' product, why wouldn't we be saying here today that there should be a SMART study equivalent, only smarter, for formoterol? Right? I mean, why wouldn't we be proposing that? Otherwise we are going to be proposing what is really kind of a watered down "well, another drug

in the class; may have some problems and so we put it on this label but we don't know about this drug." Well, don't we need to know about this drug and its safety profile based on what we have heard today?

DR. SWENSON: Dr. Moss?

DR. MOSS: I would like to build on that a little bit. I think if Novartis thinks that there are differences between their drug and Serevent, that this is not a class effect, I think it would be prudent for you, guys, to go and figure that out. Right now, since there is not the information and we feel that everything should be lumped together, it might be in your best interest to go and figure out, either doing the large clinical study that Dr. Newman is talking about if you feel that it is worthwhile, or to come up with smaller translational studies that show that there are differences. If that was, indeed, the case then the recommendations of a class warning would be changed based on that. So, that is the only thing I would add.

DR. SWENSON: Dr. Gay?

DR. GAY: I have to agree with Dr. Newman and Dr. Moss. They both stated it very eloquently. I am sure Novartis must have some concerns with the potential addition of a black box warning and I feel that we do need to see the data that it is different and they will have to run some study that shows us the differences that exist with their drug in order to not have it present.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: Well, I may see it a little differently than what has been mentioned. I mean, I think what we have learned from the SMART study is that even a study of this magnitude doesn't answer the question, and I understand the concept of doing it smarter but I am not totally sure it is possible to do it smarter in the way we want and still have it accomplished. So, I would say that we really do need to think of another design. Of course, the one I suggested before I still feel would answer that question because, in addition to other drugs, it would have other issues. So, I

actually don't think another SMART study is the right answer even though I would like to have more information.

But the only other thing I would mention is what Cal mentioned in terms of monotherapy and how prevalent it is. There are some data out there that could look for that. The data like the VA and like Kaiser where they keep track of these sorts of things, I think we could get a handle at least in those populations as to how common monotherapy is. I actually have seen some of that within the Kaiser population and it is reassuringly small in at least that population. So, I do think the answers to some of those questions are there if we look.

DR. SWENSON: Dr. Gardner?

DR. GARDNER: I agree about study design. I think that Dr. Knobil's response to why they weren't able to get more than 30,000 people would signal to us that Novartis starting the same study again wouldn't be able to either, and I think a more productive way to go would be the combination of the Medicaid analyses that are planned, which

will address children, and possibly the VA--encompassing all of them, the HMO research network or Kaiser Permanente databases carefully analyzed by someone who understands their potentials and limitations could help us see the real-world issues and answer some of the questions that we have about both of these products about monotherapy, about combination therapy and so on.

So, I would encourage that if there are going to be more large-scale studies done that they be done with existing databases of real-world data so that we can get a better handle on it.

The only other thing that occurred to me in what we saw today was the unique signal, as I noticed it, relative to children in the formoterol data and I wondered whether there should be pediatric dosing studies or some other attention paid specifically to children since that signal came out of there. So, I would suggest that for this product.

DR. SWENSON: Miss Sander?

MS. SANDER: Well, I have a question first

and that is do black box warning make--on drugs that have black box warnings, are they more likely to wind up on the prior authorization list of state health programs? Does anyone know?

DR. TRONTELL: We don't have that information. Are you talking about state Medicaid formularies or health plans? We don't have that information at the agency.

DR. SWENSON: Perhaps Glaxo might know since they have been living with a black box warning.

DR. WEEN: Generally speaking, the black box warning doesn't have an effect on whether or not your drug is listed on a formulary or not. It is just something that is pertinent to prescribing practice and what-have-you. So, the black box warning is not an a priori reason why you would not be on formulary.

MS. SANDER: I just wanted to make sure because asthma is not a prior authorization kind of disease. So, I just wanted to make certain I clarified that. With regard to the question at

hand, really I think what we are talking about here today is trying to figure out why patients are dying and the data doesn't tell us. But the parents of children with asthma who have died and loved ones, family members whose loved ones have died of asthma do tell us that asthma is a very deceptive disease and I think that is one of the reasons why we are having a hard time getting our hands around, you know, what the data means in the real world. I think that we all need to remember that asthma is a serious condition; that 13 people die of asthma every single day; and how does that fit in with this data up here? I don't really know except that somehow in the information that we provide patients when we are crafting these studies we need to make certain that the terminology and the instructions that we are giving them are extremely clear. I would just encourage that in your studies when you refer to albuterol you do not refer to it as a rescue drug because it is not reserved for what patients feel are rescue situations only. It is to prevent exercise. It is

to be used at the earliest point, earliest sign of symptoms and when we refer to it as a rescue drug patients are waiting too long to use it. I think that it can also cloud some of the answers that you may get from them when you are asking them about rescue medication use. So, that is the only advice that I have.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: Actually, I think that there is place for a clinical trial. Basically, it seems to me, there would be place for a clinical trial comparing the two drugs without a placebo control. The advantage of this would be that the trial could last longer because we don't really know the timing of these events. They may be transitory or they may be something that sort of happens constant over time. So, it seems to me we would learn that as well from a trial that could last longer than half a year and would be a comparison of the two drugs in terms of severe asthma or asthma-related death. I think such a trial would be practical. I think probably that is

the kind of trial that NIH should probably help with, as they have helped with other heads-up trials of commonly used pharmaceuticals.

I think the only thing that would sort of make this less useful would be the situation if there is a large number of other LABAs in the pipeline. Then this would be less useful. But if these are the two drugs, then they should be compared.

DR. SWENSON: Dr. Schatz?

DR. SCHATZ: I would just ask a question though. To power it for the outcomes we are talking about, do you have any sense for what sort of sample sizes would be required?

DR. SCHOENFELD: You would use the statistic of 1/700 per year--

[Laughter]

--and you could come up with a sample size quite easily, but I don't want to do it on the back of an envelope.

DR. SWENSON: You might need a big envelope! With that, I believe we have come to the

end of the meeting. I wish to thank the personnel from both Novartis and GlaxoSmithKline for their excellent presentations, the panel members and the FDA. I think if there are no further points, then the meeting is adjourned.

[Whereupon, at 4:45 p.m., the proceedings were adjourned.]

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