FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY AND ALLERGY DRUGS
ADVISORY COMMITTEE

Tuesday,
November 23, 1999

Versailles Ballrooms I and II
Holiday Inn-Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

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C O N T E N T S

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P R O C E E D I N G S (7:47 a.m.)

DR. SESSLER: Good morning. I'd like to welcome everybody to the Pulmonary and Allergy Drugs Advisory Committee meeting. My name is Curt Sessler and I'll be chairing the meeting. As I mentioned yesterday, I think my two goals are to engender meaningful discussion and to stay on time, as much as we can.

The issue for discussion for today's meeting is the committee will discuss the safety and efficacy of the New Drug Application 21-077, Advair Diskus in three strengths for the maintenance treatment of asthma as a prophylactic therapy in patients 12 years of age and older. The sponsor is Glaxo Wellcome, Inc.

The agenda I think everybody has a copy of. I'll review that briefly. We'll have some introductions and welcomes by myself and Dr. Meyer, and Dr. Jenkins when he arrives. This will be followed by the sponsor presentation and questions by the committee. We will have a break at about 10:15 or so. There will be an FDA presentation to follow that with additional questions. The afternoon session after lunch will consist of committee considerations of agency proposed questions. If we get through the agenda early, we'll certainly start on the afternoon session before lunch.

I missed the public hearing. That actually

will be the first item at 8:00 a.m., the open public hearing, if there are public speakers.

For all the speakers, I've asked you to please speak into the microphone. The proceedings are being recorded.

What I'd like to do is ask the committee members and FDA personnel to introduce themselves, and perhaps we could start with Dr. Ford and go around the table.

DR. FORD: I'm Jean Ford. I'm a pulmonologist from Columbia University, Harlem Hospital Center in New York.

DR. VOLLMER: Bill Vollmer. I'm a statistician and epidemiologist with the Kaiser Permanente Center for Health Research in Portland, Oregon.

DR. APTER: Andrea Apter, allergist-immunologist, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pennsylvania.

DR. FINK: Bob Fink, a pediatric pulmonologist at Children's National Medical Center in Washington, D.C.

DR. GROSS: I'm Nicholas Gross. I'm professor

of medicine at Loyola in Chicago.

DR. JOAD: Jesse Joad. I'm a pediatric pulmonologist and allergist at the University of California at Davis.

DR. SESSLER: Curt Sessler, professor of medicine, Pulmonary and Critical Care Division at Medical College of Virginia, Virginia Commonwealth University in Richmond. I have to say that for my president, the Virginia Commonwealth University. I have to add that.

(Laughter.)

DR. CERNY: I'm Igor Cerny, executive secretary, advisory committee staff, FDA.

DR. KELLY: Bill Kelly, clinical pharmacist, University of New Mexico Health Sciences Center, professor of pharmacy and pediatrics.

DR. DYKEWICZ: Mark Dykewicz, associate professor of internal medicine and director of the training program in allergy and immunology at St. Louis University School of Medicine in St. Louis.

DR. NIEDERMAN: Mike Niederman, pulmonary and critical care at Winthrop University Hospital in Mineola,

New York, and professor of medicine at the State University of New York at Stony Brook.

MS. CONNER: Brenda Conner. I'm a nurse educator with Matria HealthCare in Atlanta, Georgia, and I'm the consumer representative to the committee.

DR. MEYER: I'm Bob Meyer. I'm the division director for the Division of Pulmonary and Allergy Drug Products at CDER.

DR. SUSAN JOHNSON: Susan Johnson, medical reviewer, Division of Pulmonary and Allergy Drug Products.

DR. SESSLER: Thank you.

Dr. Igor Cerny will read the meeting announcements and the conflict of interest statements.

DR. CERNY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in

firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), a full waiver has been granted to Dr. Michael Niederman. A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, we would like to note that Dr. Curtis Sessler consulted with Glaxo Wellcome at the American College of Chest Physicians' Liebscher meeting regarding Advair. Further, Dr. Mike Dykewicz received an honorarium from Glaxo Wellcome for his attendance at a

consultants meeting. He was also a sub-investigator in a Schering-Plough-funded study unrelated to their competing product.

Although the interests of Dr. Sessler and Dr. Dykewicz do not constitute financial interests in the particular matter within the meaning of 18 U.S.C 208, they could create the appearance of a conflict. However, it has been determined, notwithstanding these interests, that it

is in the agency's best interest to have Dr. Sessler and Dr. Dykewicz participate in the committee discussions concerning Advair.

Further, two of our committee participants have had interests relating to Advair that we believe should be disclosed. The FDA believes it's important to acknowledge these participants' involvement so that their participation can be evaluated objectively. Dr. William Kelly previously served as a consultant to Glaxo Wellcome regarding the Advair/Seretide worldwide launch. Dr. Michael Niederman's employer previously studied Advair. Dr. Niederman's only role in the study was supervisory in nature.

With respect to FDA's invited guests, Dr. Jean Ford has reported interests that we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Ford would like to disclose that he is a member of the Glaxo Wellcome and Merck speakers bureaus.

In the event the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants

are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. SESSLER: Thank you.

I'd like to open the session entitled "Open Public Hearing" and invite any speakers to make a public statement. We have none listed previously.

(No response.)

DR. SESSLER: Seeing no speakers, I would like to move to the sponsor presentation. The introduction will be given by Richard Kent, M.D., chief medical officer, Glaxo Wellcome, Inc.

DR. KENT: Good morning, ladies and gentlemen. I'm Richard Kent, chief medical officer for Glaxo Wellcome. On behalf of Glaxo Wellcome, I would like to thank the agency and the advisory committee for this opportunity to present the clinical information supporting the use of Advair Diskus in the management of patients with asthma. During the next few minutes, I'll provide some background

information on Advair Diskus and the rationale for its development. I'll also introduce the speakers who will be presenting our data supporting the use of Advair Diskus in the treatment of asthma.

Advair Diskus represents a milestone in the maintenance treatment of asthma. Advair Diskus is not only the first combination product in the U.S. for asthma, but it's the first product which treats both components of this disease, both inflammation and smooth muscle dysfunction. Advair Diskus combines two compounds you are familiar with, the inhaled corticosteroid fluticasone propionate, or Flovent, and the long-acting beta2 agonist salmeterol, or Serevent, in one device.

Flovent has been available in the U.S. since 1996, and Serevent has been available since 1994. Worldwide exposures to these drugs is estimated to be 7.7 million patient years for Flovent, and 8.8 million patient years for Serevent.

Flovent and Serevent are used in the regular treatment of asthma, both given as twice daily regimens. Flovent is indicated as prophylactic therapy for the maintenance treatment of asthma. Serevent is indicated for the maintenance treatment of asthma and the prevention of bronchospasm. Based on how these drugs are currently used, and with the understanding that they address different

components of the disease, we will present our rationale for developing these drugs together in a single device.

The watershed study by Greening and colleagues, published in the Lancet in 1994, changed the paradigm of asthma management. This slide shows the improvements in peak expiratory flow over 21 weeks of treatment with salmeterol plus beclomethasone dipropionate, shown in blue, versus beclomethasone alone, shown in yellow. The study demonstrated that adding salmeterol to a moderate dose of beclomethasone was significantly more effective in improving lung function and controlling symptoms than using 2.5 times the dose of beclomethasone alone.

This finding was not unique to beclomethasone and has subsequently been confirmed with both fluticasone and budesonide at various doses in at least 10 published studies involving over 4,600 patients. These clinical observations helped define an important new treatment option for patients with persistent asthma, and were also the foundation for revisions to the NIH guidelines for the management of persistent asthma.

As shown in this slide, the classification of asthma has changed somewhat from the first guidelines issued in 1991. Low doses of inhaled corticosteroids now

have an earlier and more prominent role for patients with mild persistent asthma. However, in the context of today's

discussion, important changes have also occurred for patients with moderate or severe persistent asthma. Whereas past NIH recommendations for these patients focused primarily on increasing the dose of inhaled corticosteroids, it's now recognized that these patients can also be effectively managed by adding a long-acting beta2 agonist to a lower dose of inhaled corticosteroid.

The NIH guidelines also set forth goals of asthma therapy. These goals include no sleep disruption, maintenance of normal activity levels, including exercise, maintenance of normal pulmonary function, prevention of acute episodes of asthma, and no requirement for emergency room care due to asthma, as well as minimal side effects from well-tolerated medications.

It would be expected that the availability of effective treatment options and guidelines for their use would lead to realization of these important goals and decrease patient morbidity due to asthma. However, many

patients remain under-treated, and the hoped-for improvements in asthma morbidity have not been realized.

This was clearly demonstrated by the results of the Asthma in America Survey, one of the largest and most comprehensive surveys of knowledge, attitudes, and behavior toward asthma ever conducted. This survey, conducted in 1998, included more than 2,500 asthmatic patients in the

United States, identified from 42,000 randomly dialed U.S. households. Patients were asked detailed questions in 30-minute telephone interviews, including questions involving their current asthma symptoms, need for acute medical care for their asthma, and impact of asthma on their daily lives.

As is evident in these results from the Asthma in America Survey, the goals of asthma therapy are not being met. As you can see, nearly one-third of all patients reported having their sleep disturbed at least once a week in the previous four weeks, and nearly one-third missed school or work in the previous year. Nearly half of all patients reported being unable to fully participate in recreational activities due to asthma, and

nearly one-quarter required emergency room care for their asthma during the previous year.

In addition, the survey demonstrated that most patients with asthma overestimate the level of control of their underlying disease. As shown in this slide, 61 percent of patients who, when asked, described symptoms consistent with moderate persistent asthma mistakenly believed that their asthma was well or completely controlled in the previous four weeks. Of even greater concern, 32 percent of patients who described symptoms consistent with severe persistent asthma also mistakenly

believed that their asthma was well or completely controlled in the previous four weeks.

The fact that patients over-estimate their level of asthma control serves as an impediment to improving asthma control in these patients, since they accept suboptimal symptom control as normal. Thus, there is a potentially significant patient population which could benefit from improved control of their asthma. Advair Diskus provides a new treatment option in these patients

for whom combination therapy is appropriate.

This slide shows that significant populations of patients exist as potential candidates for Advair Diskus therapy. Currently, approximately 12 percent of treated asthma patients are on an inhaled corticosteroid and salmeterol, and usage of these drugs together has nearly doubled in the last two years. For these patients, combination therapy may offer the advantage of increased convenience and simplification of therapy.

In addition, results from the Asthma in America Survey clearly demonstrate that there is a significant population of patients whose asthma is under-treated. This includes patients inadequately controlled on a single control or medication and those patients on short-acting beta2 agonists alone who, in fact, have moderate or severe persistent asthma.

In the United States today, there remains a significant population of patients for whom asthma control is inadequate. The development of Advair Diskus, a combination of two drug classes with complementary roles in the management of asthma, represents a logical approach to

therapy, one which is increasingly used in clinical practice and is consistent with the NIH guidelines. Equally important, by providing effective maintenance treatments for both components of the disease in a single device, a more simplified and convenient way for patients to treat their asthma is available. This provides an opportunity for patients to enhance their disease control.

Three strengths of Advair Diskus have been developed: Advair Diskus 100 micrograms, 250 micrograms, and 500 micrograms. Each strength contains 50 micrograms of salmeterol, and either 100, 250, or 500 micrograms of fluticasone per dose. This allows flexibility of dosing with the inhaled corticosteroid component. Advair Diskus is a breath-actuated inhaler which is administered as one inhalation twice daily. The diskus device contains 60 individual doses and provides medication for one month's therapy.

The diskus was designed to assure that a consistent dose is delivered over a wide range of inspiratory flow rates, enabling patients with even severe

airway obstruction, with inspiratory flow rates as low as 30 liters per minute, to obtain a full dose. The diskus device is already available in the U.S. as Serevent Diskus.

The clinical information we will now present supports the proposed indication for Advair Diskus. Advair Diskus is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older where combination therapy is appropriate.

The order of our speakers today and the information they will present are as follows.

Dr. Malcolm Johnson will review the scientific and clinical evidence which demonstrates that for the treatment of asthma, the use of inhaled corticosteroids and long-acting beta2 agonists together provides greater clinical and disease control than the use of these agents alone.

Dr. Tushar Shah will present the results from the clinical trials conducted with Advair Diskus and our recommendation for its appropriate use in the maintenance treatment of asthma.

Dr. Homer Boushey will provide a physician's perspective on why a combination of an inhaled corticosteroid and long-acting beta2 agonist in a single device is a significant advance in the management of asthma.

I will then return and conclude our presentation with some summary remarks.

Dr. Johnson.

DR. MALCOLM JOHNSON: Thank you, Rick.

Good morning, ladies and gentlemen. I am Dr. Malcolm Johnson, director of respiratory science for Glaxo Wellcome.

The rationale for combination therapy is that it should be scientifically sound and justifiable on therapeutic grounds. There should be a significant contribution from each component, and the combination should show superior efficacy over each component alone. Finally, there should be no disadvantages or adverse interactions in combining the components of the combination.

Research over the last 20 to 30 years has illustrated that the underlying pathophysiology of bronchial asthma involves smooth muscle dysfunction and airway inflammation. Smoothness or dysfunction leads to bronchoconstriction and bronchial hyperreactivity, and there is evidence that smoothness leads to hyperplasia and increased release of inflammatory mediators from smoothness of cells.

Acute and chronic inflammation involves

inflammatory cell infiltration and residency in lung

tissue, and the subsequent activation of these cells leads to mucosal edema, cellular proliferation, epithelial damage, and thickening of the basement membrane, and these processes are both independent and interdependent.

It is becoming increasingly clear that in order to achieve optimal asthma therapy, it is necessary to adequately treat this underlying complex pathophysiology in order to control symptoms and exacerbations, and in order to do so, more than one drug type is required. Of the combination therapies that have been evaluated clinically to date, that between long-acting beta agonists and corticosteroids appears to have the greatest effectiveness.

Long-acting beta2 agonists have long-lasting direct effects on airway smooth muscle. They prevent bronchospasm and reduce bronchial hyperreactivity by a functional antagonist effect. They reduce acutely mucosal edema, and there is experimental evidence that they inhibit smoothness of cell hyperplasia and inhibit the release of inflammatory mediators from smoothness of cells.

Corticosteroids, on the other hand, are potent

topical anti-inflammatory agents. They inhibit inflammatory cells, they reduce mucosal edema in a chronic sense, they inhibit cellular proliferation, epithelial damage, and there is some evidence that they reduce basement membrane thickening. As a result of these

activities, they clearly have an impact on bronchial hyperreactivity.

Despite the profile of the long-acting beta2 agonist and the corticosteroids in their own right, the clinical efficacy data show there are significant benefits when these two agents are combined. A possible explanation for that is shown on this slide, that there are fairly complementary modes of action between these two. The long-acting beta2 agonists have long-lasting effects on smooth muscle, and the corticosteroids are potent topical anti-inflammatories.

There is emerging evidence that these drugs may also have complementary mechanisms of action, and I'd like to review some cellular data from both in vitro and in vivo studies that looks at the possible interaction between

long-acting beta2 agonists and corticosteroids.

The first level of this interaction has been known for some time, that corticosteroids increase the synthesis of beta2 receptors. This is an in vivo study from Dr. Baraniuk and colleagues and showed that intranasal administration of BDP over a period of three days increased the density of beta2 receptors in the respiratory mucosa by a factor of approximately two-fold.

The second level of interaction is a more recent finding. In resting cells, the glucocorticoid

receptor, which is an intracellular receptor and normally held in an inactive form, is found predominantly in the cytosole of the cell, only a small amount being detected in the nucleus. A corticosteroid like fluticasone propionate binds to this receptor to form an active receptor complex, and this receptor complex then moves or translocates from the cytosole into the nucleus, where it binds to a target gene to invoke anti-inflammatory activity.

In this particular study, a small concentration of fluticasone causes partial translocation of the receptor. There is a diminution in the density of receptor

in the cytosole, and an enrichment in the nucleus. However, when combined with a long-acting beta2 agonist like salmeterol, which in its own right had very little effect in this system, there is now complete translocation of the receptor from cytoplasm to nucleus. This phenomenon is a result of protein kinase-dependent priming of the glucocorticoid receptor induced by the long-acting beta2 agonist, and the prime receptor is more sensitive to steroid-dependent activation.

Are there any biological and possible therapeutic consequences of this level of interaction between long-acting beta2 agonists and steroids?

In the eosinophil, which is thought to play a key role in airway inflammation, corticosteroids induce the

phenomenon of eosinophil apoptosis, or programmed cell death, and by doing so reduces the survival of eosinophils within airway tissue. Fluticasone alone has an EC50, which is the concentration required for a 50 percent effect on eosinophil apoptosis, of approximately 0.3 nanomolar. Salmeterol in this system has a much weaker effect, but the

combination of the corticosteroid and the long-acting beta2 agonist increases the effect of the steroid by a factor of approximately three-fold.

If we look at the second example, now turning to the T-cell, the T-cell again is thought to be a key element in chronic inflammation in the airways. T-cell proliferation is a system that is responsive to inhibition by both corticosteroids and beta agonists. In this particular experiment, a low concentration of the corticosteroid dexamethasone and salmeterol produced about a 30 to 40 percent inhibition of the house dust mite protein-induced T-cell inhibitory response. However, when these agents are combined, there is an increased level of inhibitory activity and an additive effect against T-cell proliferation.

There are a number of other examples of this sort of positive interaction between long-acting beta agonists and corticosteroids at the level of cell cytokine release, cell chemokine release, and at the level of

respiratory mucosal cytoprotection against the damaging effects of microorganisms. However, these effects are

likely to be a specific topical action in the lung, because the concentrations of salmeterol and fluticasone, for example, in the systemic circulation that are required for this interaction are not achieved even after chronic dosing.

So the scientific rationale for the combination product. The combination product has a complementary mode of action, long-acting beta2 agonists with long-lasting effects on airway smooth muscle, and corticosteroids that have potent topical anti-inflammatory effects.

Now the possibility of complementary mechanisms of action. Corticosteroids increase beta2 receptor synthesis, and long-acting beta2 agonists prime the glucocorticoid receptor for steroid-dependent activation.

Turning, then, to the clinical rationale for the combination product. As Dr. Kent said, we have now 10 clinical studies in over 4,600 symptomatic patients in which the combination of a long-acting beta2 agonist and an inhaled corticosteroid consistently shows higher efficacy and provides better overall asthma control both from the physician and patient perspective than at least doubling the dose of the corticosteroid.

What I'd like to do is to focus on eight

studies in which the long-acting beta2 agonist salmeterol has been combined with BDP or FP fluticasone and compared in clinical studies with at least doubling the dose of the corticosteroid. The BDP studies from Greening, Woolcock, and Murray consistently showed a superiority for the combination in increasing lung function and decreasing symptoms and bronchodilator use over the higher dose of the steroid, and there was equivalence in terms of impact on exacerbations.

A similar profile was shown with a combination of salmeterol and fluticasone here in these five studies, and the objectives of asthma management, increasing lung function, decreasing symptoms, and decreasing bronchodilator use were all in favor of the combination over the higher doses of steroid, and again, the impact on exacerbations was equivalent.

Taking some specific examples, in this study, over 24 weeks in more than 400 patients, the combination of salmeterol and a dose of fluticasone 88 micrograms twice daily produced a superior increase in peak expiratory flow over that of the higher dose of the steroid 200 micrograms twice daily. This effect was already observed within the first four weeks of treatment, and was sustained over 24 weeks.

The pattern on symptom control is very similar.

Again, within the first four weeks of treatment, the combination produced a significant increase in the number of symptom-free days over that achieved with the higher dose of the steroid. By the time of the end of treatment here at 24 weeks, there was a 30 percent increase in symptom-free days with the combination, compared to 15 percent with the higher dose of the steroid.

However, perhaps the most significant effect in combining a long-acting beta2 agonist with a corticosteroid has been the impact on asthma exacerbations. The FACET study by Professor Pauwels and his colleagues, published in the New England Journal, was the first study in which asthma exacerbations was the primary outcome of the study. The study showed that if the dose of budesonide, in this case the corticosteroid, was increased from 200 micrograms daily to 800 micrograms daily, there was the expected decrease in asthma exacerbations.

But importantly, the study also showed that the addition of a long-acting beta2 agonist, in this case formoterol, to either the lower dose of the steroid or indeed to the higher dose of the steroid, produced a

significant and important further increment in decreasing exacerbations. The lowest level of exacerbations in this study was with the higher dose of the steroid in combination with the long-acting beta2 agonist.

This data on exacerbations has been extended in U.S. studies. In this first study, again over 24 weeks, the combination of salmeterol and 88 micrograms twice daily of fluticasone was compared to the higher dose of 220 micrograms. The study showed a trend towards exacerbations being reduced in the combination study over the higher dose of the steroid. The total number of exacerbations in this study was quite small. When the study is combined with a replicate study carried out in the U.S. at the same time with patients with the same spectrum of disease severity, now the patient numbers have increased here, and now there is a significant decrease in patients with at least one exacerbation in the exacerbation rate, and a trend toward reduction in the duration of exacerbations here.

A further recent analysis of the FACET study has addressed an important issue, and the issue is that if you combine a long-acting beta2 agonist with a low or

moderate dose of an inhaled steroid, is there a possibility that deteriorating asthma could be disguised?

This study from Professor Tattersfield's group in the United Kingdom and recently published in the American Journal has addressed that issue. Looking at either morning or evening peak flow, or asthma daytime or nighttime symptom scores, they compared the profile with low-dose budesonide alone, the higher dose of budesonide,

and in each case the combination with the long-acting beta2 agonist formoterol. The results of the study showed that there was no difference in these profiles in the 14 days prior to the exacerbation here, or indeed in the 14 days after the exacerbation. So the addition of the long-acting beta2 agonist does not disguise the detection of deteriorating asthma.

Now, a number of other studies are addressing a second and equally important issue, and the issue is if you combine the long-acting beta2 agonist with a corticosteroid, despite the obvious clinical benefits, is there an opportunity that airway inflammation would

actually be increasing?

An analysis again of the FACET study in which sputum eosinophils, the numbers of the cells, and their activation status were the markers of inflammation did not show any significant effect between low-dose budesonide in combination with formoterol and the high dose of budesonide.

This study from Professor Walters' group in Australia compared the addition of placebo here, salmeterol, or 100 micrograms of fluticasone to a median dose of 400 micrograms of inhaled steroids in patients who were symptomatic, and the study progressed then for three months. At the end of the three-month period, there was no

evidence of airway inflammation, as evidenced here by the increasing eosinophils in the lamina propria for the combination group compared to the higher dose steroid group. Indeed, there was a significant reduction in the eosinophils in the lamina propria in the combination group compared to baseline.

The second study, from Professor Holgate's group in the United Kingdom and recently presented at the

European Respiratory Society meeting, took a slightly different approach. They studied subjects who were symptomatic on low doses of fluticasone, 200 micrograms, and compared the profile over a course of three months with the addition of salmeterol to this low steroid dose or increasing the steroid dose to 500 micrograms.

Those patients who were symptomatic over the three-month course of this study showed evidence of increasing airway inflammation. There was a small increase in mast cells, and a significant increase here in CD4-positive T-cells. This was not observed in either the combination group or the high-dose steroid group. Indeed, there was now a significant reduction in the mast cells when the low-dose steroid was combined with the long-acting beta2 agonist.

So I think we can say from this kind of evidence that the combination of long-acting beta2 agonists

and inhaled steroids does not increase or mask airway inflammation, and it does not disguise deteriorating asthma.

So in summary, then, asthma is a complex airway disease involving both smooth muscle dysfunction and chronic airway inflammation, and the treatment of this pathophysiology requires more than one drug. Long-acting beta2 agonists and corticosteroids have complementary modes and mechanisms of action that lead to a broader and greater control of the underlying pathophysiology of asthma. Combined therapy with long-acting beta2 agonists and corticosteroids leads to a greater clinical efficacy and better overall asthma control than either agent alone.

Thank you for your attention, and I'll now turn to Dr. Tushar Shah, who will take you through the clinical efficacy and safety data for Advair.

DR. SHAH: Thank you, Malcolm.

Good morning, everyone. My name is Tushar Shah. I'm the director of U.S. respiratory clinical development for Glaxo Wellcome.

In the next 35 minutes, I'm pleased to be able to review results from the Advair Diskus clinical program. The three main objectives of this program were to demonstrate the superior efficacy of Advair compared to the individual components, the comparable efficacy of Advair to

the administration of salmeterol and fluticasone from two separate inhalers, which I'll refer to as concurrent therapy, and finally the comparable safety of Advair to the administration of its two components used alone or concurrently.

We realize that the availability of a combination product containing a long-acting beta2 agonist and an inhaled corticosteroid in the U.S. represents a new approach for the treatment of asthma. I'll share with you the guidance we propose to provide physicians within the label, and patients within the patient instruction leaflet to ensure the appropriate use of Advair.

In addition to demonstrating its efficacy and safety, combination drug products must fulfill several regulatory requirements for approval. These are shown on this slide. The development of Advair Diskus was done in consultation with the FDA and fulfilled these regulatory requirements.

The first requirement was achieved by demonstrating the superior efficacy of Advair and comparable safety of Advair relative to its two individual components. I'll review this in greater detail later in my presentation.

The dosages of Advair Diskus were based on the dosages of the individual components, which have been shown

to be safe and effective. Furthermore, we obtained FDA agreement on our selection of doses for Advair prior to initiating the clinical trials. Dr. Kent reviewed that there exists a significant patient population who could benefit from concurrent therapy. This approach is consistent with national treatment guidelines.

We conducted four clinical pharmacology studies in healthy volunteers to support the development of Advair. I'll not be reviewing the clinical pharmacology results in detail. However, they are included in your briefing document. These results demonstrated that pharmacokinetic or pharmacodynamic interactions between salmeterol and fluticasone were not seen. This means that systemic exposure and effects with Advair were similar to salmeterol and fluticasone used alone or concurrently.

We performed five clinical studies in patients 12 years of age and older for the development of Advair. Three studies -- SFCA3002, SFCA3003, and SFCB3019 -- one at each strength of Advair, were performed to meet U.S. regulatory requirements demonstrating the superior efficacy of Advair over the individual agents. These were the pivotal studies supporting the development of Advair for the U.S.

There were two additional studies, one with Advair 100 and one with Advair 250, whose objectives were

to demonstrate that Advair provided comparable benefits to concurrent therapy. These studies were performed to support the development of Advair outside of the U.S.

SFCB3019, the study with Advair 500, also included a concurrent treatment limb, and thus supported both study objectives.

In each study, all treatments were administered twice daily.

The three pivotal studies are described in greater detail on this slide. SFCA3002 and SFCA3003 were studies of 12 weeks in duration and were performed in the U.S. SFCB3019 was 28 weeks in duration and was performed outside of the U.S.

The patients in the Advair 500 study were considered to have severe asthma. The inclusion of a placebo and salmeterol-alone treatment groups was considered inappropriate. In each study, we involved patients with asthma severity appropriate for the dose of

fluticasone they would receive in the combination product. This means that patients with less severe asthma who were receiving either salmeterol or low doses of inhaled corticosteroids at baseline were considered appropriate to receive Advair 100. Patients with moderately severe asthma on moderate doses of inhaled corticosteroids were considered appropriate to receive Advair 250. Finally,

patients with severe asthma on high doses of inhaled corticosteroids were considered appropriate to receive Advair 500.

As I'll review later in this presentation, these medication entry criteria were used as a basis for providing specific guidance within the label on the appropriate strength of Advair patients should initiate based on the dose of inhaled steroids they are receiving.

The two U.S. studies utilized a similar study design. Each trial included a two-week placebo run-in period where patients' previous salmeterol or low-dose inhaled corticosteroid therapy was continued. The purpose of this period was to ensure patients' asthma stability and adherence to study procedures. Patients were then

randomized to 12 weeks of treatment with either Advair 100 in 3002 or Advair 250 in SFCA3003, Flovent Diskus 100 or 250 according to the study, Serevent Diskus, or placebo. Patients' baseline therapy was discontinued at randomization.

Patients completed daily diary cards for collection of efficacy and safety data. Pulmonary function tests were performed at clinic visits throughout the period. This included 12R serial pulmonary function tests following the first dose, and first and 12 weeks of treatment.

SFCB3019 study design was similar and included a two-week run-in period where patients continued their high-dose inhaled corticosteroid therapy. They were then randomized to either Advair 500, fluticasone 500 alone, or salmeterol and fluticasone 500 administered concurrently. Efficacy data was obtained during the first 12 weeks of this trial. Patients were treated for an additional 16 weeks to obtain safety data, for a total of 28 weeks.

Patients had to be 12 or older and had to

demonstrate a need for additional therapy by evidence of airway obstruction and reversibility on baseline therapy. In the U.S. trials, patients had to have an FEV1 between 40 and 85 percent of predicted, and at least 15 percent reversibility on their baseline treatment.

In SFCB3019, patients' morning peak flow during run-in had to be between 50 and 85 percent of their peak flow measure after 400 micrograms of albuterol.

In the U.S. studies, the primary measures of efficacy were the probability of remaining in the study without withdrawal due to worsening asthma and pulmonary function results. The latter included both change from baseline in morning pre-dose FEV1, at endpoint, and serial FEV1 area under the curve, abbreviated as AUC, at treatment week 1. Mean change in morning peak flow over weeks 1 to 12 comprised the primary efficacy measure for SFCB3019.

The selection of these primary measures had been agreed on with the agency prior to initiating the clinical trials.

Additional measures of efficacy included pulmonary function, symptoms, rescue inhaler use, night awakenings due to asthma requiring Ventolin, and asthma

quality of life using the AQLQ instrument developed by Professor Juniper.

In the two U.S. studies, patients treated with inhaled corticosteroid therapy at baseline were being switched at randomization to placebo and salmeterol therapy. This is an important design feature that explains the lack of significant benefit observed with salmeterol in these studies. Due to this reason, pre-defined withdrawal criteria for worsening asthma were utilized to identify patients whose asthma was deteriorating. These criteria are shown on this slide and consisted of lung function, rescue albuterol use, and night awakenings. They are commonly used to assess asthma control in clinical practice. Physicians also had the discretion of withdrawing patients for clinical exacerbation.

The impact of using these criteria was that many patients, especially in the placebo and salmeterol treatment groups, withdrew early. Data from withdrawn patients were absent from analysis at later visits in order to adjust for this bias of withdrawals, and endpoint

analysis defined a priori was used. Endpoint analysis uses the last evaluable observation. Thus, the endpoint analysis includes the last visit for FEV1 data and last visit of diary card data regardless of whether they completed or withdrew from the trial. This allowed us to include nearly all patients who received study drug in our efficacy analysis.

I'll now share with you the efficacy results from these trials. Due to time constraints, I will only review the primary results from each trial. Results from the secondary measures were similar to the primary measures and can be found in your briefing document. Within each study, baseline characteristics were similar between treatment groups. I'll first review the results from the pivotal studies.

Before reviewing the results from the study on Advair 100, let me quickly orient you to the information on the slide. The Y axis represents the probability of remaining in the trial. The X axis represents the study day. For all efficacy results that I'll be presenting, the Advair treatment group is represented in purple, the fluticasone group in orange, the salmeterol group in green, and the placebo group in white.

These results indicate that patients treated with Advair 100 were significantly less likely to withdraw

due to worsening asthma compared to the other treatment groups. Since this analysis is based on most of the efficacy measures, these results also indicate that Advair provided much better control of asthma than the individual agents or placebo.

Additionally, the withdrawal criteria were just as useful in identifying patients on salmeterol whose asthma was deteriorating. This indicates that the use of salmeterol did not prevent the recognition of worsening asthma. Since patients were switched from inhaled corticosteroids to salmeterol and worsened, these results also indicate that the level of asthma control is the best method of assessing if patients on salmeterol are receiving adequate inhaled corticosteroids.

Shown on this slide are the morning pre-dose FEV1 results for the study with Advair 100. On the Y axis is the percent change in FEV1, and on the X axis is the study week. Treatment with Advair 100 was associated with a significantly greater change in morning FEV1 compared to the individual agents or placebo. Patients on Advair 100 experienced an approximately 25 percent increase in FEV1 from baseline to endpoint.

The apparent improvement in the placebo and salmeterol groups during the trial is a result of the

survival bias which occurred due to the early withdrawal of

patients with worsening asthma. The endpoint analyses, which include all patients' data, demonstrate that these groups did not significantly improve during the trial. This is what we would expect when discontinuing low doses of inhaled corticosteroids or salmeterol at baseline.

Displayed on this slide are the results of the serial FEV1 AUC on treatment day 1, week 1, and week 12 for the study examining Advair 100. The Y axis represents the FEV1 AUC in liter hours, and the X axis the results of each treatment group during the three time periods that these data were collected. On day 1, treatment with Advair 100 was associated with a significantly greater FEV1 AUC compared to FP and placebo, and similar improvements to salmeterol. However, at treatment weeks 1 and 12, Advair 100 led to a significantly greater FEV1 AUC compared to all treatment groups.

In addition, we had performed a subanalysis for each of the primary efficacy measures by the baseline, salmeterol, or low-dose inhaled corticosteroid therapy. These analyses demonstrated that Advair 100 provided

greater benefits for each patient population. These results are provided in your briefing document.

Let's now look at the results for the study with Advair 250. As before, the Y axis represents the probability of remaining in the trial, and the X axis the

study day. Patients treated with Advair 250 were also significantly less likely to withdraw due to worsening asthma compared to the other treatment groups, and thus had better control of asthma.

Since the withdrawal criteria was useful in identifying patients on salmeterol whose asthma was worsening, this trial also confirmed the findings from the Advair 100 trial. It clearly shows that the use of salmeterol does not prevent the recognition of clinical cues associated with worsening asthma. Hence, the level of clinical control is a good method of determining if patients are receiving enough inhaled corticosteroids while on salmeterol.

Displayed on this slide are the morning pre-dose FEV1 results for the study on Advair 250. Once again,

on the Y axis is the percent change in FEV1, and the X axis is the study week. Treatment with Advair 250 was associated with a significantly greater change in FEV1, approximately 23 percent increase, compared to the individual agents or placebo. As before, we see the impact of the high withdrawal rates in the placebo and salmeterol groups. The endpoint analysis, shown on the right, adjusted for this bias, demonstrates that these groups did not improve when moderate doses of inhaled corticosteroids are discontinued at baseline.

Shown on this slide are the FEV1 AUC results for the study examining Advair 250. The Y axis represents the FEV1 AUC in liter hours, and the X axis is the results of each treatment group during the three time periods that these data were collected. On day 1 and treatment weeks 1 and 12, Advair 250 led to a significantly greater FEV1 AUC compared to all treatment groups.

I'll now review the results for the primary efficacy measure for this study in Advair 250. If you'll recall for this study, morning peak flow was the primary measure of efficacy. The Y axis represents the mean change

in morning peak flow from baseline in liters per minute, and the X axis represents the study day. As before, the Advair treatment group is in purple and the FP group is in orange. We've also now included the results of the concurrent therapy group, which is displayed in yellow.

Treatment with Advair 500 was associated with a relatively rapid and significantly greater increase in morning peak flow compared to the 500 FP group. As we would expect, Advair 500 provided a comparable increase in peak flow to concurrent therapy. During the course of the trial, there was a further increase in peak flow with Advair 500, with no evidence for a diminution of effect with time.

In summary, for all three studies, treatment

with Advair was associated with greater improvements than the individual agents for all primary measures of efficacy.

I will now review the results of the primary efficacy measure for the trials comparing Advair to concurrent therapy.

In addition to the trial with Advair 500 which

I reviewed earlier, two additional trials comparing Advair to concurrent therapy were performed outside of the U.S. SFCB3017 compared Advair 100 to concurrent therapy, and SFCB3018 compared Advair 250 with concurrent therapy. All patients were required to be treated with inhaled corticosteroids at baseline. As before, patients symptomatic on low doses of inhaled corticosteroids were enrolled in the Advair 100 trial, patients on moderate doses were enrolled in the Advair 250 trial, and patients on high doses of inhaled corticosteroids were enrolled in the Advair 500 trial. These trials had similar inclusion criteria and study design as the trial with Advair 500 which I reviewed earlier.

The primary objective of these trials was to demonstrate equivalence between Advair and concurrent therapy. If equivalence was achieved, the 90 percent confidence intervals of the treatment difference for mean change in morning peak flow over weeks 1 to 12 resided within plus or minus 15 liters per minute. Displayed on

this slide are the mean changes in morning peak flow, the treatment difference in morning peak flow, and the

corresponding 90 percent confidence interval for each of the three trials comparing Advair to concurrent therapy. In all trials, treatment with Advair and concurrent therapy was associated with improvements in morning peak flow over weeks 1 to 12. In each trial, treatment with Advair provided slightly greater improvements in concurrent therapy.

The treatment differences favored Advair and are negative because they are calculated as concurrent therapy minus Advair. I'd like you to focus on the last column. For the Advair 250 and 500 trials, the pre-defined criterion for equivalence was achieved. For each trial, the 90 percent confidence interval for the treatment difference in morning peak flow was within plus or minus 15 liters per minute. In the Advair 100 trial, the 90 percent confidence interval fell just outside the criterion for equivalence. However, these differences were small in magnitude and were unlikely to represent a clinically significant change.

Additionally, Advair 100 and concurrent therapy provided similar changes for secondary efficacy measures in this trial. This analysis indicates that for all three strengths, Advair provided comparable benefits to

concurrent therapy.

One of the advantages of a combination product containing a long-acting beta2 agonist is this rapid onset of effect. I will now review some of these results from the trial with Advair 100. Similar analyses and findings were observed with the Advair 250 trial and can be found in your briefing documents.

Displayed on this slide are the 12-hour serial FEV1 results on day 1, shown on the left, and treatment week 12, shown on the right. The Y axis represents the percent change in FEV1, and the X axis represents the time in hours following dosing. At day 1, treatment with Advair 100 was associated with a relatively rapid onset of effect. Most patients achieved a 15 percent increase in FEV1 within 30 to 60 minutes following the first dose. At treatment week 12, shown on the right, patients treated with Advair 100 had an increase in their pre-dose FEV1 of approximately 27 percent from baseline, which is represented by the dotted line.

After receiving their dose, they experienced a further increase in FEV1 during the 12 hours after dosing at week 12. Patients treated with Advair 100 in this trial had an approximately 40 percent increase in FEV1 for baseline during those 12 hours after dosing at week 12. No single maintenance therapy currently available has been

shown to provide this magnitude of improvement in FEV1 with chronic dosing.

In addition to FEV1 results, diary card data such as morning and evening peak flow, symptoms, and Ventolin use were also examined to assess Advair's onset of effect. Shown on this slide are results of the mean change in morning peak flow in the Advair 100 trial. The Y axis represents the change in morning peak flow in liters per minute, and the X axis represents the day of treatment. Treatment with Advair 100 was associated with a significant increase in morning peak flow beginning one day after initiating treatment, which increased further during the course of the trial. Similar onset of improvements were seen with the other efficacy measures.

In summary, Advair Diskus at each strength was found to provide superior efficacy to the individual components, and comparable efficacy to concurrent therapy. These results also indicated that Advair Diskus had a rapid onset of effect, with the clinical benefits improving over time. The subset analyses of patients by baseline therapy indicated that Advair 100 provided greater benefits than

the individual agents in patients on salmeterol or low doses of inhaled corticosteroids at baseline.

I would like to now share with you some of the safety results from the Advair Diskus clinical studies.

The safety information is provided in greater detail within the briefing document.

A total of approximately 1,800 patients were enrolled in the five Advair Diskus clinical trials; 644 of these patients received treatment with Advair Diskus. Approximately half of these patients were female, 8 percent were adolescents, and approximately 7 percent were greater than or equal to 65 years of age. The majority of patients in these studies were Caucasian, with approximately 5 percent of patients being of African descent.

This slide shows the percent of patients with adverse events, drug-related adverse events, withdrawn due to adverse events, and serious adverse events from the two U.S. studies. For ease of presentation, safety results for the Advair, the FP, the salmeterol, and placebo treatment groups from these two trials were combined for this analysis. Just as the higher withdrawal rates in the

placebo and salmeterol treatment groups impacted the efficacy results, they also affected the safety analyses. Patients treated with Advair had a higher duration of exposure to treatment compared to the other treatment groups, especially the salmeterol and placebo groups.

Since patients with a longer duration of exposure are more likely to experience adverse events, this difference in exposure needs to be considered in

interpreting the adverse event data. Despite the greater duration of exposure, treatment with Advair 100 or 250 was not associated with a greater frequency of these adverse events compared to the individual agents. The incidence of withdrawals to adverse events and serious adverse events was low and similar between treatment groups, including the placebo groups.

Displayed on this slide are the adverse events results for the Advair 500 trial. Since safety data was obtained over 28 weeks in this trial, this had a significantly greater duration of exposure in these trials than the U.S. studies. Treatment with Advair 500 was

associated with a similar percentage of patients experiencing various categories of adverse events compared to concurrent therapy and FP administered alone.

This slide summarizes the pharmacologically predictable adverse events that were observed during the Advair 100 and 250 trials. Once again, for ease of presentation, we have combined the results from the two U.S. trials. Differences in duration of exposure presented earlier needs to be considered in comparing results across treatment groups. In general, a low frequency of patients experienced these events. Advair treatment was associated with a similar frequency of these events compared to the individual agents.

Displayed on this slide are the results of the Advair 500 trial. A similar percentage of patients experienced these adverse events in the Advair 500 treatment group compared to concurrent therapy or FP administered alone.

Serious adverse events occurred infrequently, and for the most part they were isolated events which were scattered across the various treatment groups. Displayed

on this slide are the serious adverse events that occurred in the Advair treatment groups. None of these events were considered drug-related by the treating physician. We had two deaths which occurred in the Advair studies, neither of which was considered by the treating investigator to be drug-related. A 72-year-old male patient developed status asthmaticus following elective cataract surgery and stopping Advair 500 micrograms preoperatively. A 61-year-old male developed bronchial carcinoma while on salmeterol and FP 500 concurrent therapy.

We performed extensive cardiovascular monitoring in the Advair clinical program. This included assessments of cardiovascular adverse events; pre-, during, and post-treatment ECGs in the U.S. and non-U.S. studies; as well as 24-hour Holter monitoring in a subset of patients in the two U.S. studies.

The results of the cardiovascular monitoring

are summarized on the following slide. The frequency of cardiovascular adverse events such as palpitations and heart rate were low and occurred at a similar rate between

Advair and the individual agents. The frequency of ECG, including QTc abnormalities and Holter abnormalities, was low and similar across all treatment groups, including the placebo group. Thus, there was no evidence that treatment with Advair was associated with greater cardiovascular risk compared to the individual agents or placebo.

HPA axis assessments were performed by measurement of morning cortisol concentrations in most trials, short ACTH stimulation tests performed in the trial, in Advair 250, and 24-hour urinary cortisol excretion corrected for creatinine performed in the trial on Advair 500. The results of the HPA axis analysis indicated that there were no differences in HPA axis results between Advair and the individual agents as assessed by morning cortisol, short ACTH-stimulated cortisol in the trial with Advair 250, and mean 24-hour urinary cortisol adjusted for creatinine in the trial with Advair 500.

Additional safety analyses included assessments of vital signs, laboratory tests, subsets based on gender, age, ethnic origin, subsets based on concurrent use of albuterol, methylxanthines, and intranasal fluticasone

propionate, and adverse events with long-term use. These analyses were also reassuring. They indicated that treatment with Advair was not associated with greater abnormalities compared to the individual agents or placebo.

The results of the safety analyses can be summarized as follows. There were no differences in safety results between Advair and the individual agents, or between Advair and concurrent therapy.

We realize that Advair Diskus is the first combination product in the U.S. containing a long-acting beta2 agonist and an inhaled corticosteroid. As such, Glaxo Wellcome is committed to promote its appropriate use in the management of patients with asthma. During the final few minutes of my presentation, I'll review some of the ways that we intend to accomplish this. This includes a proposed indication for the appropriate patient populations and dosing recommendations, some of our guidance to physicians in the label and to patients in the patient instruction leaflet on the appropriate use of Advair, and our guidance within the label to physicians on the management of deteriorating asthma while on Advair.

The results from the clinical program I have just reviewed support the following proposed indication. Advair Diskus is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age

and older where combination therapy is appropriate. This indication is consistent with decisions physicians need to make and are making every day in initiating medical therapy. Physicians are unlikely to initiate therapy with a combination product in patients with mild asthma in whom they believe a single medication will achieve control of their patient's disease. In these patients, combination therapy would be inappropriate.

However, in patients with moderate or severe asthma, even if currently being under-treated with short-acting bronchodilators alone, it is medically appropriate to initiate treatment with combination therapy. This is currently occurring in clinical practice and is supported by guidelines. Furthermore, clinical data has shown that in these patients, the use of these two classes of drugs together provides better asthma control than the individual agent.

Hence, appropriate patient populations for Advair Diskus can include patients not adequately controlled on bronchodilators alone where combination therapy is appropriate, patients not adequately controlled on inhaled corticosteroids alone, or patients receiving inhaled long-acting bronchodilators and inhaled

corticosteroids concurrently. The use of Advair in these patient populations can be supported by clinical data and

is consistent with how physicians are using the individual products today and recommendations for their use by guidelines.

The proposed dosing in the label for patients 12 years of age and older is shown on this slide. For patients inadequately controlled on bronchodilators alone in whom combination therapy is appropriate, the recommended starting dose is Advair 100 twice daily. For patients inadequately controlled on inhaled corticosteroids alone, the recommended starting dose is Advair 100, 250, or 500 twice daily, depending on the baseline dose of inhaled corticosteroids they are receiving.

For patients receiving long-acting bronchodilators and inhaled corticosteroids concurrently, the strength of Advair Diskus should be selected according to the dose of fluticasone propionate that corresponds to their current inhaled corticosteroid dose. In order to ensure that patients on inhaled corticosteroids are

initiated with the appropriate strength of Advair Diskus, specific guidance is provided within the label. It indicates which strength of Advair to use according to their current dose of inhaled corticosteroids.

For Flovent, recommendations are provided that patients should be transferred to the strength of Advair with the same dose of fluticasone. For patients on other

inhaled corticosteroids, recommendations are provided in the label based upon the entry criteria used in the Advair clinical trials. Patients on low doses are recommended to transfer to the low dose of the Advair 100. Patients on moderate doses should receive Advair 250. Patients on high doses should receive Advair 500.

Examination of U.S. product use data indicates that nearly all patients on inhaled corticosteroids are covered by these dosing recommendations. Based on the entry criteria used in these clinical trials, an analysis of the product use data, Advair 100 will meet the needs of a majority of patients in the U.S. Our rationale for doing this is to help ensure that patients do not receive more medication than needed to optimize control of their asthma

with Advair.

Specific recommendations for dose titration are provided within the label. For patients in whom asthma stability has been achieved, recommendations are made to titrate to the lowest effective strength of Advair. On the other hand, for patients who do not respond adequately to the starting dose after two weeks, recommendations are made to replace the current strength of Advair with a higher strength.

Additionally, guidance within the label for physicians and the patient instruction leaflet for patients

is provided on how to recognize deteriorating asthma and what actions to take. Physicians and patients are advised not to exceed recommended doses and to treat acute symptoms with an inhaled, short-acting bronchodilator, not Advair.

Dr. Johnson and I demonstrated that greater clinical control with the use of these drugs together resulted in a low percent of patients with deteriorating asthma. Both Dr. Johnson and I presented information which indicates that treatment with a long-acting beta2 agonist

does not prevent the detection of deteriorating asthma. The best method of determining if patients on Advair are receiving enough corticosteroids is by assessing their level of asthma control. Patients whose asthma is not adequately controlled while on Advair Diskus can be identified by the use of usual clinical assessments, and appropriate change in therapy can be instituted.

We realize that increasing the number of inhalations with a single strength of Advair Diskus is not recommended due to the increased potential for side effects from higher doses of salmeterol. The guidance within the label advises physicians not to increase the number of doses during deteriorating asthma, but rather to consider one of the other options. In addition to using higher doses of short-acting rescue therapy, physicians have the option of increasing the strength of Advair or adding

additional inhaled or oral corticosteroids. These are options which many physicians are using currently.

However, in the event that patients use extra doses of Advair against medical advice, there exists considerable clinical data on the safety of using higher

doses of salmeterol, which is reassuring. At least seven clinical studies in 2,600 patients has compared salmeterol 50 and 100 micrograms twice daily. These studies range from one week to six months in duration, with the majority of patients receiving inhaled corticosteroids concurrently. Side effects that are observed in these trials included predictable dose-dependent effects of beta adrenergic agonists such as tremor and palpitations. However, there was no increased incidence of serious adverse events or death attributed to the higher dose of salmeterol, and no clinically significant effects on blood pressure, pulse rate, ECGs, or laboratory tests at the higher dose of salmeterol.

These data were used to support the approval of salmeterol at a dose 100 micrograms twice daily, equivalent to doubling all strengths of Advair Diskus, in more than 20 countries worldwide. Thus, deteriorating asthma can be managed with alternative treatments rather than using extra doses of Advair. In the event that some patients against medical advice take more than the recommended doses of

Advair, the safety information on higher doses of salmeterol are reassuring and indicate that serious consequences should not occur.

In summary, I have shared with you results from our clinical program which achieved the regulatory requirements for combination products. We demonstrated that Advair provided substantial clinical benefits compared to the individual components. These clinical benefits with Advair were not associated with any evidence of a greater safety risk. I also shared with you the information we plan to provide within the label to help ensure appropriate use of Advair Diskus in the management of patients with asthma.

Thank you for your attention. I would like to now introduce Dr. Homer Boushey.

DR. BOUSHEY: Well, thank you, and good morning. I am Homer Boushey, professor of medicine and chief of the Asthma Clinical Research Center and of the Division of Allergy and Immunology at the University of California in San Francisco. During the next few minutes I'd like first to outline why I'm here this morning, at the invitation of Glaxo Wellcome, to discuss what I believe are some of the important factors determining a major problem in asthma treatment, patient non-compliance with treatment, and then to discuss what I believe this new combination

therapy offers for dealing with this important problem.

I have spent my career as a clinician and clinical researcher, with a special interest in asthma. I served on the executive committee of the National Asthma Expert Panel, which produced the 1997 Guidelines for the Diagnosis and Management of Asthma. I'm also one of the principal investigators for the NIH-supported Asthma Clinical Research Network, or ACRN. This network, the ACRN, has conducted many studies. Two of our recent studies examined the place of long-acting beta agonist inhaled corticosteroid therapy as monotherapy and in combination in the treatment of moderately severe asthma. I believe the results of these studies are pertinent to today's discussion.

From my involvement with these trials, I believe I have some understanding of what this new therapy brings to the treatment of asthma and how it will impact the kinds of patients I see regularly in my own clinical practice.

There are many products available for the management of asthma, and guidelines have been developed on how to use them, including these 1997 revisions of the National Asthma Expert Panel's guidelines. Despite the publication of these publications as outlined and reviewed

by Dr. Kent, asthma treatment in the United States remains

suboptimal. For example, although regular treatment with an anti-inflammatory agent, particularly with an inhaled corticosteroid, was urged as the cornerstone of therapy for mild persistent, moderate persistent, or severe persistent asthma in these guidelines, this class of drugs is still under-used by both patients and physicians in the United States.

Some of the possible reasons for this under-use are highlighted on this slide. One of the reasons for the under-utilization of inhaled corticosteroids is or may be that patients do not sense rapid symptomatic improvement on inhaling them. Thus, patients often resort to using only short-acting beta agonists, which do cause rapid symptomatic improvement when their symptoms of asthma worsen. Additionally, both patients and physicians appear to have safety concerns about inhaled corticosteroids, especially if taken at higher doses for prolonged periods of time.

There are, however, other factors that are equally germane to the problem of medication non-compliance

in asthma. Specifically, many patients require treatment with multiple medical therapies with medications of different classes. I believe that among the patients I see in my own practice, the more complex the medical regimen, the more likely is the patient to be confused about the

purposes and use of the medication, and the more likely they are to adhere poorly to the prescribed treatments.

I am especially worried that once a patient with poorly controlled asthma has had the asthma brought under control by the addition of a long-acting beta agonist inhaler to an inhaled corticosteroid inhaler, the patient will decide to discontinue one or the other of the inhalers for purposes of saving on convenience or expense, and will, often without even discussing the question with his or her physician, selectively discontinue the inhaled corticosteroid because it does not produce a rapidly perceptible change in condition.

That this approach to therapy is inappropriate was proven by one of the studies conducted by the Asthma Clinical Research Network examining inhaled corticosteroids

and long-acting beta agonist therapy in the treatment of asthma. These studies were presented at the American Thoracic Society meetings last spring.

Our first study showed that in patients with asthma well controlled on a moderate dose of an inhaled corticosteroid, switching to monotherapy with salmeterol or placebo was associated with a significantly higher rate of exacerbation than was continued therapy with the inhaled corticosteroid. I should say that we have no evidence that these exacerbations were harder to detect, were more

severe, or were less responsive to treatment than those that occurred in the patients who continued on the inhaled steroid or who were switched to placebo.

In saying this, I'd like to note that our second study, that of patients with asthma poorly controlled on an inhaled corticosteroid therapy, the addition of salmeterol improved asthma control and enabled a 50 percent reduction in the dose of steroid without loss of this gain in control.

These findings of the ACRN study suggest that a combination therapy like Advair may have an important place

in the clinical management of patients with asthma. As a preparation that contains both an inhaled corticosteroid and a long-acting beta agonist, it treats both components of asthma with a single medication, both the smooth muscle dysfunction and the airway mucosal inflammation as reviewed this morning by Dr. Johnson. It also has a high clinical efficacy and so far has raised no new safety issues, as you have just heard from Dr. Shah.

There is evidence, as confirmed by the second of the ACRN studies, that combination therapy may enable maintenance therapy with a lower dose of the inhaled corticosteroid.

Although greater efficacy is important, we should not underestimate the additional benefits of

combination therapy for patients with asthma, particularly I think in enhancing compliance with therapy or adherence to therapy. First, the addition of the long-acting beta agonist means that the use of the therapy will be associated with rapid improvement in symptoms, reinforcement of the benefits of taking therapy, and

thereby enhancing adherence. Because the drugs are provided together, patients will not be able to selectively discontinue their inhaled corticosteroid therapy, and thus be maintained inappropriately on monotherapy with a long-acting beta agonist.

Because the drugs are delivered together, therapy is simplified. Patients find it easier to comply or adhere to simple treatment regimens. Finally, the drug is delivered in a device that is quite simple to teach patients to use. Taken together, these benefits suggest that a single treatment that is easy to use, that provides symptomatic perceptible improvement will enhance the adherence to treatment, and thus address an important problem in the treatment of asthma.

Now, the benefits derived from this combination have raised concerns, and the principal concern is that the addition of a long-acting beta agonist to an inhaled corticosteroid will interfere with the detection and management of worsening asthma. As you've heard from Dr.

Shah and Dr. Johnson, there is no evidence from the studies conducted so far that treatment with a long-acting beta

agonist prevents the ability to detect worsening asthma. We also found this in our own ACRN study, that the fall in peak flow was no greater at the time of disease worsening or exacerbations among the patients taking salmeterol than it was among the patients taking inhaled steroids or placebo, no evidence that treatment with a long-acting beta agonist prevents the ability to detect worsening asthma, nor did it impair the response to treatment.

Finally, treatment options are available for managing worsening of asthma even in patients taking a fixed combination therapy without much modification of current practice.

I'd like now to speak to where I would use this drug in my own practice. First of all, as an author of the expert panel's treatment recommendations, I hope it's redundant to state that my habits of practice conform to what I recommended. I use the combination of a long-acting beta agonist and a low to medium dose of an inhaled corticosteroid in patients with moderate persistent asthma. I use a long-acting beta agonist in combination with a moderate to high dose of an inhaled corticosteroid in patients with severe persistent asthma.

I also use these drugs together in patients who

present with symptoms or pulmonary function consistent with moderate or severe persistent asthma even if they have only been taking beta agonists on an as-needed basis, often very frequently, up until their first visit to see me.

I therefore believe that the indication is appropriate that this combination therapy is appropriately recommended for patients for whom combination therapy is appropriate.

In summary, based on my experience as a clinician and a clinical researcher, I believe that Advair will fill a medical need in the treatment of asthma. It will provide a single maintenance medication that is highly efficacious, that enables the prescription of a simple treatment regimen delivered by a device that is easy to use. The availability of this drug will, in my opinion, help overcome one of the major obstacles to the successful treatment of asthma, the difficulty that many patients have in adhering to treatment.

I'd now like to turn things back over to Dr. Kent for his concluding remarks.

DR. KENT: Thank you, Dr. Boushey.

In closing, I'll summarize a few of the key points which emphasize the value of Advair Diskus in optimizing asthma therapy.

There is a strong scientific rationale for

combining these two classes of medications, and greater clinical benefit has been repeatedly demonstrated when these drugs are combined. Advair Diskus has been convincingly demonstrated to be superior to the individual agents and comparable to the two drugs administered concurrently. This efficacy is achieved without any additional safety risks.

Advair Diskus will be the first combination product for asthma in the U.S., and Glaxo Wellcome is committed to ensuring it will be used appropriately. Detailed guidance is provided in the product labeling and patient leaflet and will be reinforced through physician and patient education programs. We will provide specific guidance in labeling and education for the management of deteriorating asthma in patients taking this product.

Let me first remind you that the exacerbation rate with Advair Diskus is expected to be low, and data presented today indicate that exacerbations that do occur will be recognizable through the usual clinical cues. However, if patients do experience deteriorating asthma, it can be managed by prescribing a higher strength of Advair

or, as is common practice, prescribing additional inhaled or oral corticosteroids.

The patient population suitable for Advair Diskus are those patients in whom combination therapy is

appropriate, as shown in this slide. These patient populations are supported by the Advair clinical program and are also consistent, as you have heard, with the NIH guidelines.

There are additional advantages to patients when a long-acting beta2 agonist and an inhaled corticosteroid are combined. This should not be underestimated. Patients perceive rapid benefit and recognize the therapy as working. This improvement encourages patients to continue their therapy and not selectively discontinue their inhaled corticosteroid.

Advair Diskus also provides a real opportunity to simplify asthma therapy. It will enable many patients to use a single twice-daily medication in an easy-to-use device as the only maintenance treatment necessary for their asthma control. This may improve patient adherence.

In summary, Advair Diskus is an advance in

asthma therapy. It is a highly effective maintenance treatment for both components of the disease in a single device. Advair Diskus provides an opportunity for patients to enhance their disease control and improve overall morbidity due to asthma.

Mr. Chairman, that completes our presentation. Before taking questions, I'd like to point out that in addition to Dr. Boushey, we have with us Dr. Romain

Pauwels. Dr. Pauwels is professor of respiratory medicine at the University of Gent in Belgium. He was chairman of the GINA executive committee from 1994 to 1998, and is currently chairman of the GOLD initiative on COPD. He has extensive clinical experience and involvement in major clinical trials on the management of asthma, including the FACET study, which was presented earlier.

We welcome your questions.

DR. SESSLER: Thank you.

I'd like to open the session for questions from the committee on the sponsor's presentation.

Dr. Fink?

DR. FINK: This I guess is a two-part question. In all of the studies, the 100, the 250, and the 500, what were the number of 12- to 16-year-olds included in each study?

Secondly, in those 12- to 16-year-olds, did you look at Tanner staging for prepubescent status, and did you look for increments in growth velocity?

DR. SHAH: Yes. Can I have the slide that just reviews the total number of subsets, patients that we had in the clinical program?

This slide just reviews the number of patients in the various subsets that we had in the program. Specifically, the answer to your question about Tanner

staging, we did not do that because these were three-month studies and we weren't specifically looking at growth in the context of this trial. Additionally, as you know, it's very difficult to do growth studies in adolescent patients when the effect of puberty is involved and the complexity that introduces in assessing growth in this setting.

But, as you can see, we had about 152 total patients in the 12- to 17-year-old age group, and we did do

subset analysis for both the efficacy results and the safety results for this subset. Essentially, what we found was the results were comparable to the overall results, that Advair provided greater benefits than the individual agents in this subset of patients, as well as the safety appeared to be comparable, again recognizing that the number of patients in some of the subsets were small, so you couldn't make any major conclusions, but the trends were all in the same direction as the overall results.

DR. GROSS: (Inaudible.)

DR. SHAH: This is all the patients -- there were about 152 patients that were 12 to 17 years of age.

DR. GROSS: (Inaudible.)

DR. SESSLER: Dr. Gross, could you use the microphone, please?

DR. SHAH: No, these were the subsets. There were a total of about 1,800 patients in all the program.

DR. SESSLER: Dr. Joad?

DR. JOAD: I found it interesting that part of the way the combination works is through enhancing the

effectiveness of the steroid dose, which brings up a bunch of concerns that I hadn't really thought of before. It reminds me of the TAO days, where TAO interfered with the metabolism of the steroids, and really it was the increased steroid effect that we were seeing.

That brings out a bigger concern long term, especially with safety and the issues Dr. Fink was bringing up in adolescence. So I wonder if you have any sort of estimation about when you're looking at efficacy, how much of it is because you have an increased effectiveness of the steroid, versus how much is the separate bronchodilator effect of the salmeterol?

DR. SHAH: No, we clearly had examined the effects, if there was evidence of any systemic interactions, both in the clinical pharmacology studies as well as in our clinical studies. We looked at, in the clinical pharmacology studies, assessments of the various beta agonist effects, such as tremor, heart rate, cardiac, blood pressure, and so forth. In assessing the effects potentially systemically of the inhaled corticosteroid, we look at HPA axis effects in many different manners, looking at urinary cortisol, ACTH stimulation tests, plasma

cortisol, both morning values as well as, in the clinical pharmacology studies, 24-hour plasma cortisol profiles.

What these studies consistently showed was that there was no evidence that there was any systemic interaction occurring between the use of these two drugs together. I think the reason this is really occurring is related to what Dr. Johnson had mentioned in his presentation, that the concentrations that we're delivering, especially of salmeterol, are so low that we're not able to get enough concentrations peripherally to achieve some of the systemic interactions that he is showing in in vitro models and some of the in vivo models of inflammation.

So we believe that most of the effects that we're seeing of these interactions are topical in the lungs, and there is no evidence yet that we have seen in any of the clinical studies we've done to date that there is systemic interactions that are occurring with these drugs used together.

DR. JOAD: Because I wasn't looking for it at the time I was reading your application, were you even able to show a dose response between 250 and 500 in your systemic measurements of corticosteroids?

DR. SHAH: Yes.

DR. JOAD: I'm just wondering if your study

would have even shown it.

DR. SHAH: Well, we haven't done a dose response to assess systemic interaction across strengths of Advair in an individual study. But clearly for FP, we have looked at the systemic effects in terms of dose response and have shown in individual studies, as you'd expect with all inhaled steroids, there's a dose-related increase in systemic effects with FP.

In the program that we did conduct with Advair, we compared the systemic exposure of FP to Advair across the strengths, and what we found was that there was no increased systemic exposure with Advair versus FP administered alone. So both the pharmacokinetic as well as the pharmacodynamic results between Advair when the individual products were identical, there was no systemic evidence of an interaction occurring with these drugs used together.

DR. JOAD: I guess it just seemed to me like the 24-hour cortisols and your various measures of HPA axis seemed to not show enough results with the numbers that you had to be able to make a good comparison. Or did you think your numbers were high enough to really say much? It seemed like a sort of sporadic event that it would be --

not sporadic, but a very low frequency occurring event to really say something strong like that, like there was none.

DR. SHAH: Actually, these studies, the clin pharm studies have been shown previously at the numbers of patients that we used to be able to pick up differences between FP and other treatment groups. So there were enough patients in these studies so that if there were significant differences between groups, they would have been able to show those. So the studies were designed and powered to show a certain percent of differences that have previously been able to be shown in these studies. So if there was a clinically meaningful difference, these studies would have demonstrated those differences.

DR. SESSLER: Dr. Dykewicz, and then Dr. Gross.

DR. DYKEWICZ: I had a question about labeling, and it has to do, first of all, with the proposed patient populations for treatment with Advair. I think what we're seeing essentially could be summarized as looking at two management strategies. One would be patients who are currently receiving inhaled steroids in a long-acting

bronchodilator and essentially just converting them over to a product that would contain both components. The other strategy, consistent with NAEPP guidelines, would be if you step up therapy, patients who are currently not controlled on inhaled steroids or who are currently not controlled on beta agonists alone.

But, of course, as part of NAEPP guidelines,

you not only step up, but you consider stepping down after control has been achieved.

Now, part of the step-down considerations are addressed by the product labeling, and that would be that you would reduce the steroid component to the lowest effective dose of the Advair that would control the patient. However, the other question that would come into play would be a patient who is well controlled on Advair, shall we say on the Advair 100, and then considering tapering off of the salmeterol component, thinking that a patient who, for instance, is going to end up having mild persistent asthma really would not need the salmeterol component.

What in the product labeling do you propose to

address that type of consideration?

DR. SHAH: In the current proposed label, we don't have specific guidance that patients can step down from low strength of Advair to FP alone, or inhaled steroids alone, but clearly I think that would be, as you said, the clinical practice that is occurring and would be consistent with what we would certainly advocate physicians should do if they felt the patient's severity warranted that type of a change in therapy.

DR. DYKEWICZ: I guess I'm just questioning whether that should be something in the labeling in terms

of being complete if you're talking about stepping up with the drug, and also considering stepping down, so that there would not be a large portion of the population with mild persistent asthma who would be receiving two component therapy, whereas really it would only be necessary for them to receive the inhaled steroid component.

DR. SHAH: I think clearly that kind of a change is consistent with medical practice and is not anything that we would find controversial.

DR. SESSLER: Dr. Gross?

DR. GROSS: I have a number of questions. I wonder if you did any biopsy studies with Advair specifically to look at the histologic effects of these agents.

DR. SHAH: Let me ask Dr. Johnson to address that question.

DR. MALCOLM JOHNSON: Malcolm Johnson, Glaxo Wellcome.

Yes, the biopsy studies that I showed you was with concurrent therapy from Professor Holgate's studies and from Professor Walters' studies. We are in the course of doing biopsy studies with Advair to look for the long-term consequences at the level of airway inflammation with the Advair product itself, but I think the concurrent therapy biopsy studies are very reassuring that when you

combine a long-acting beta2 agonist with a corticosteroid, there is clearly no increase in the inflammation compared to the higher dose of the steroid, and in some studies there may even be a small reduction in inflammation.

I think your question is well taken, that the

longer-term effects on airway inflammation with the product itself is something that we are currently considering.

DR. GROSS: Maybe I missed it, but did you report any growth studies in children, or are you planning to do that?

DR. SHAH: Yes. Can I have the pediatric slide? We actually did perform one pediatric study with Advair 100 to register Advair in Europe for pediatric. I'd be more than happy to review these results quickly since I realize that's of interest to the panel.

This was a study that, again, the primary objective in Europe was to compare the Advair to concurrent therapy. Again, this study was very much focused around efficacy and relative safety of this treatment approach. So it was a study looking at demonstrating equivalence between the Advair and the concurrent therapy treatment groups, and it was of 12 weeks duration. Patients had to be symptomatic on inhaled corticosteroid therapy at baseline for inclusion.

Next slide.

As we'd expect, when you receive either Advair or concurrent therapy in these patients, they had a rapid improvement in their morning peak flow, which, as we've consistently shown with the use of these two drugs together, improves further over time, with no evidence that the treatment diminishes in benefit with time.

DR. GROSS: Can I interrupt you? I think you missed it, I didn't get my question straight. I asked about growth studies in children.

DR. SHAH: Right. We have not done any growth studies with Advair yet. We're in the process of developing a formulation for the U.S., which would be containing a lower strength of fluticasone, because as you know, in the U.S., fluticasone in children is down to 50 and 100 twice daily. We anticipate having that available next year. We have submitted a proposal for a pediatric program to the FDA and are waiting for their comments. As part of that proposal, we have included plans to do a one-year growth study to look at that question.

DR. GROSS: And could you just remind me of the equivalence between the Diskus version of fluticasone and the MDI version, because I know that the strengths are sort of comparable. The three strengths almost match up. But take fluticasone 50, for instance, by Diskus. Is that equivalent to 44, or what is the equivalence? Because it

will help us to determine the relative risks of the steroid dose in your Advair combination.

DR. SHAH: The difference between the MDI and powder nomenclature-related dose is really the way we -- the doses in the meter dose is described as X-actuated dose, meaning it's the amount that actually comes out of the plastic device; whereas the X-valve dose for Flovent MDI is really 50 micrograms. So, as you correctly surmised, the 50 that comes out of the Diskus is actually the amount in the blister. The amount that comes out of the mouthpiece is comparable to the MDI, which is about 44 micrograms. So those two are corresponding to each other.

Now, because the MDI is administered at two inhalations twice daily, and the powder can be administered as one inhalation twice daily, the numbers don't directly match up, but you can get to essentially the same place by using different strengths of either the Diskus or the MDI.

DR. GROSS: So, basically, if a patient went from fluticasone 44 by MDI to fluticasone 50 by Diskus, you would expect comparable --

DR. SHAH: That's comparable, correct. And we've shown that in clinical studies.

DR. GROSS: All right. I just have one other question about safety. I notice that you have one death

due to exacerbation of asthma, and I notice that that

patient had recently been discontinued from their asthma therapy because there was surgery planned or something like that. That just raises the question of the problem of patients discontinuing the therapy. I know, of course, you mentioned this in your package inserts for the currently available medications, that patients should not withdraw their steroid medications suddenly, and now your presentation makes a strong case that the combination is actually more effective than the steroid alone. So one wonders whether withdrawing the combination would actually be more dangerous than withdrawing the single agent.

DR. SHAH: That particular incident was a patient with severe asthma, and the investigator really had withheld the morning dose of that treatment for the surgery that was planned that day. And he -- I'm making an assumption that it was a he, but the investigator determined that in that event, that it was unrelated to withdrawal of that treatment.

Additionally, we did look at the post-withdrawal of Advair. In the European studies, there was a

follow-up period where patients were switched from Advair to other appropriate therapy at the discretion of physicians, and we monitored if there were any serious consequences that occurred during that period, and essentially we saw no evidence of patients having serious

exacerbations or worsening of their asthma with that change in therapy that occurred in that context.

So I think that case was an isolated event related to a severe asthmatic who had his morning dose withheld, which is unlikely because the benefits are relatively long term, because you have both the FP and the salmeterol component, to explaining what occurred. I think that was just coincidental, and that's the way the investigator judged the event as well.

DR. GROSS: I have no more.

DR. SESSLER: Dr. Apter, and then Dr. Niederman.

DR. APTER: I have a couple of questions related to compliance/adherence, because I agree that that's a big problem in asthma and a point to be addressed

by this medication.

First, in your trials, how did you measure compliance? And in the ones where there was concomitant therapy compared with Advair itself, did you have enough data to look at the difference? Would you review that?

DR. SHAH: Of course. All the studies were very controlled studies, and adherence was monitored with the dose counter that exists on the Diskus. So we were actually able to track adherence by looking at the dose counter numbers. What we showed, as we expected to see in

a clinical trial setting, which is fairly controlled, is that adherence across all treatment groups was over 90 percent, on average.

So the differences that we see in clinical results, at least in the trial setting, cannot be attributed to differences in adherence between treatments.

In the rest of the world studies, they were double-dummy studies, meaning everybody had two inhalers, and again adherence was monitored by looking at the dose counter. Again, adherence in those studies was relatively high in both treatment groups. We just haven't had an

opportunity in the clinical trial setting yet to really look at the question of the impact that a product that has simplification and advantages in that regard would offer in terms of improving adherence. But clearly, we believe that it will, and we are committed to looking at that question once the product is available and where you can really assess that in a more real-life situation.

DR. APTER: And then one more question. Another influence on adherence, of course, is cost of medication. So where will Advair be placed compared to the individual components or other drugs of these two classes?

DR. SHAH: We haven't really determined the pricing for this product yet, so it's hard for me to speculate at this point on how that's going to be

determined and what it will be.

PARTICIPANT: What's the comparison price?

DR. SHAH: Dr. Fuller?

DR. FULLER: Thank you. I'm Rick Fuller, the director of therapeutic development and research based in the U.K. It's on the market now throughout Europe. It's

difficult to give you an exact cost because the cost varies per country, as you would expect. But essentially it ranges from parity to a discount for the combination compared to the two components separately, as you would imagine.

DR. SESSLER: Dr. Niederman?

DR. NIEDERMAN: Yes, I have three questions. First I wanted to clarify in relation to the questions about adrenal suppression. In the high-dose Advair studies, there was no comparison done with placebo. So particularly when we talk about using the high doses in children, we have no reassurance from any of this data that there is no adrenal axis suppression in the high doses. Is that correct? You showed comparability to concurrent therapy but not to placebo.

DR. SHAH: That's correct. But again, we have identified the effects of FP alone in terms of dose response on the HPA axis effects, and clearly, at that dose of 500 twice daily, there are no measurable effects on the

HPA axis, which is in our package insert.

DR. NIEDERMAN: But in the way that this study

was done, you couldn't at least exclude the possibility of an additive suppression with the combination compared to placebo, because you showed statistical equivalence to concurrent therapy. But maybe if the comparison had been done to placebo, it might be even more dramatic than concurrent therapy.

DR. SHAH: I think those are very important questions. Clearly, this is an interest I recognize from the panel, so let me ask my clinical pharmacology colleague to maybe come up and address some of the analyses that have been done in the clin pharm data that I think might help allay some of the concerns that you're raising.

DR. DALEY-YATES: I'm Dr. Daley-Yates, clinical pharmacology at Glaxo Wellcome.

Perhaps if we look, first of all, at the data from the high-dose clinical study, which is shown on Slide A10. The question is quite right, that we didn't actually include a placebo group.

The next slide, please.

But we did look at the systemic exposure to fluticasone in all three groups. That's the Advair group, the concurrent therapy, and also fluticasone alone. We showed equivalent systemic exposure in the three groups.

So we have a similar comparison in healthy volunteer studies, which again showed no difference between these three groups, although in the patients we actually show about 50 percent lower systemic exposure to fluticasone compared to healthy volunteers, and that was seen in this study for fluticasone, and it's been seen previously.

DR. NIEDERMAN: Could you explain what that's graphing again? That's plasma?

DR. DALEY-YATES: This is the plasma concentration of fluticasone measured over the dose interval at steady state to 12 weeks. So just to clarify, this is the steady state plasma concentration time profile of fluticasone in a subgroup of patients, 45 patients, in the high-dose clinical study.

DR. NIEDERMAN: So you're showing lower fluticasone levels, a trend with the Advair compared to concurrent therapy?

DR. DALEY-YATES: There was no significant difference between these three groups here, but if we compare back to the data that we did in healthy subjects, shown on Slide A07 --

DR. NIEDERMAN: But in terms of a biologic interaction, you have no information in terms of comparing the combination to placebo and adrenal effects. Is that correct?

DR. DALEY-YATES: Yes, you're right, there was no placebo group in the clinical study in terms of effects on cortisol. This is the healthy volunteer study. Again, this is the systemic exposure to fluticasone, and it showed higher, greater effects on cortisol than in the study comparing to placebo. Does that clarify?

DR. NIEDERMAN: Yes. So the conclusion would be that the high dose would cause some adrenal suppression compared to placebo by extension of your observations on fluticasone alone.

DR. DALEY-YATES: That's correct. We would expect normally the exposure we see from 500 twice a day fluticasone in patients is borderline for the effects on cortisol. So in something above 1 milligram a day, you do see measurable effects on cortisol. Below a milligram a day, you see very little effect. So this is just about on the borderline of showing measurable effects on cortisol.

DR. NIEDERMAN: The second question I had related to a statement that you made that the combination therapy is not associated with a masking of deterioration, or I think the comment was made that it doesn't make the

deterioration any worse. But do you have any information on that latter point? In other words, for the patients who deteriorated on any of the doses of Advair and, say, even ended up in the hospital, what was their management like?

How were they compared to patients who deteriorated on the other regimens? Is there a possibility that patients on the combination therapy who did deteriorate in spite of combination, even though the numbers may have been lower, had a more severe exacerbation and needed more medications, stayed in the hospital longer? Any of those data?

DR. SHAH: In the U.S. studies, there were no patients in the Advair groups that had an asthma exacerbation that would warrant that kind of treatment approach. We had patients who had worsening asthma according to our criteria, who were then appropriately -- therapy was instituted by the treating physician.

In the placebo group in the U.S. study and the salmeterol group, we did have one individual patient who had a severe exacerbation of asthma which required hospitalization, emergency care type of treatment.

In the rest of the world studies, clearly we

have not seen that evidence either, that treatment with Advair, patients who had exacerbations did not have more severe exacerbations.

Let me also have Professor Pauwels comment, because he's done a lot of work in understanding the use of these two drugs.

DR. NIEDERMAN: Let me go back, though. The U.S. studies didn't involve the 500 dose, correct?

DR. SHAH: Correct.

DR. NIEDERMAN: So the most severe asthmatics were not treated in the U.S. studies, the ones that would be likely to end up in the hospital.

DR. SHAH: Correct.

DR. NIEDERMAN: So in the European data, for specifically patients in the clinical trials who got the higher doses, some ended up in the hospital?

DR. SHAH: I think in the European studies we had one or two patients who had severe exacerbations that required hospitalization. But there was no evidence that that occurred at a greater incidence in the Advair group

than --

DR. NIEDERMAN: I guess with one or two observations, you can't make any comment that having received the combination therapy in this manner did anything to make the exacerbation different from any other out-patient therapy.

DR. SHAH: Correct. But let me also clarify, we have a lot of experience with these two drugs given together, and let me have Dr. Pauwels maybe comment on that experience, which speaks to the question you're asking.

DR. PAUWELS: Romain Pauwels from Gent in Belgium.

The question that you raise has been raised

several times, and that is does the addition of the long-acting beta agonist in fact change the pattern of exacerbation or the treatment you have to give for the exacerbation. I think there are several pieces of evidence that they don't, and the first one is derived from the Tattersfield publication, where we have looked at the pattern of exacerbation and the treatment needed to be given for severe exacerbations. These were all so-called

severe exacerbations because the clinician had decided to start an oral corticosteroid course.

If you look at, for example, the quantity of beta agonist that was needed to treat the exacerbation, there wasn't any difference between the people on the long-acting or without the long-acting, and there has been a recent publication by McFarland looking at the people treated in the emergency room with or without treatment with salmeterol, and there was no difference at all with regard to the need for short-acting or the dose for short-acting, or the dose of oral corticosteroids.

So I think that overall the data are very reassuring in that perspective.

DR. NIEDERMAN: Are there data there about the duration of the exacerbation?

DR. PAUWELS: Yes, and the duration was exactly the same.

DR. NIEDERMAN: And I guess the last question that I had related to a question that was raised -- but, Dr. Boushey, you felt that one of the major advantages of

this drug was that patients typically discontinue one component related to the expense of using two, but I haven't heard how this product would address the compliance, where if patients were likely to stop one component because of expense, it doesn't sound like this product is going to address that issue.

DR. BOUSHEY: What I said is that we believe that patients may stop one or the other of two therapies because of expense, because of convenience, or the prescriptions are out of phase, they run out of one halfway through the month, and then the other one is good until the end of the month, so they'll decide to simplify their therapy on their own, without conferring with a physician.

Dr. Fuller said that in Europe, the combination device is a little less expensive than the two independently. So there is some savings with the combination.

DR. NIEDERMAN: But there's no reason to be necessarily optimistic that patients would continue. It still may be a lot cheaper to take one rather than a cheaper combination, correct? It sounds like that's going to be the situation, that taking fluticasone alone is going

to be cheaper than taking Advair.

DR. BOUSHEY: That's right, and this therapy is indicated for patients in whom combination therapy is recommended.

DR. NIEDERMAN: I understand. But as you said, patients often don't do what's recommended, and one of the driving forces is cost. So it doesn't sound like this preparation will address that compliance issue.

DR. SESSLER: One of the concerns for using any product, and particularly I guess combination products, is the potential for misuse and the use of extra doses, particularly when, as in this case, it's a combination of a drug that you'd like to keep in a fixed dose and another one that you'd prefer to be able to titrate. So patients may do that on their own volition, certainly, and you did present some data with the 200 microgram BID dosing for salmeterol, and I'd like to come back to that just a little bit.

In the briefing document I think is the series of about seven or eight publications dealing with the higher dose of salmeterol, and one of them did include Halter monitoring. Certainly cardiac arrhythmias is one of those side effects of excessive doses of salmeterol we're concerned about. Could you elaborate on the findings of this study? It was the Dahl study in 1991.

DR. SHAH: We've looked at Halter monitoring fairly extensively with salmeterol as part of its development, and even in that study there was no evidence on Halter monitoring of any serious dysrhythmias associated with salmeterol at the higher dose compared to the lower dose, and that's something we've seen consistently with salmeterol. Clearly there will be effects on heart rate, which you would expect, but there are no disrhythmias that seem to be occurring at increased incidence at the higher dose.

DR. SESSLER: How about hypokalemia? Were there any differences there? Certainly that's important potentially for patients that might not have been captured in the well-structured clinical trials. I guess the first question along those lines is did you see much difference in the clinical trials? Then I'd like to broaden both the hypokalemia question as well as the arrhythmia question to the broader experience with salmeterol, perhaps used at higher doses in other studies, and perhaps including European studies as well as U.S. data.

DR. SHAH: The hypokalemia, we did not see any evidence of that in our clinical trials. We actually looked at it very carefully because we collected dose, pre-

dose, and about an hour and a half after dosing throughout the studies in the U.S. to assess that specific question.

I think those data are included in your briefing document. There were no differences between Advair and the individual treatment.

But additionally, in terms of higher doses of salmeterol, we really don't see much of an effect on hypokalemia with use of up to 100 dose. You have to get up to much higher doses before you start seeing effects on potassium with regards to use of salmeterol.

DR. PAUWELS: In some European countries, the two times 100 is allowed as a dose. So in some of the patients with the most severe asthma, we use that, in fact, in combination with the high dose of the inhaled corticosteroid just to avoid and for getting on to oral corticosteroids. What you see is the predictable side effects like tremor and palpitations in a few percentages of the people, so then you reduce the dose. But there hasn't been a problem with things like hypokalemia.

In fact, there is one publication that looked

at the dose dependency of the hypokalemia when increasing the dose to a very high dose of salmeterol, and actually what you see is that there is a hypokalemia that occurs at five times the recommended dose, something like 250 micrograms, and it's almost a leveling off of the effect. So it's even not there, a clear dose-response curve, and that has been documented. That's published in the blue

journal.

DR. SESSLER: As a final follow-up to this line of concern, I know there is experience in the COPD population as far as formal clinical trials, and then I'm sure there is also data from patients who have coronary artery disease and maybe an otherwise higher risk, say they have preexisting cardiac arrhythmias. If you could comment on worldwide experience as we know it in those areas, that would be helpful.

DR. SHAH: Clearly, we haven't designed clinical studies specifically to look at that question because those are difficult studies to do, but we have included in clinical studies, as well as now with the drugs being available for many, many years, patients with all

types of concomitant illnesses and diseases have used these drugs. What we have seen in clinical trials with these patients have been included, especially in the COPD studies, where, as you can surmise, these are very ill patients who are elderly, many of them have been smoking and have additional concurrent illnesses related to smoking, and we have not seen that the use of salmeterol, either at the 50 or the 100 twice daily dose -- both have been studied in that patient population -- was associated with any higher incidence of serious consequences.

Actually, one of the studies that's in the

briefing document was a COPD study specifically looking at that question in those patients.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I have a couple of questions. One refers to a comment that was made earlier. Maybe Dr. Boushey might be able to answer it, because I know the ACRN group has a lot of experience taking moderate patients off of drugs. Two of the issues about compliance, one is if you get a rapid effect, you may improve compliance. But

also, if you get a rapid offset of effect, that might make the patient understand that they're getting an effect from their drug.

Is there any data on offset of effect? I know there's a lot of data on offset of effect when you take them off of inhaled steroid and you leave them on salmeterol, but is there offset effect data on combination?

DR. BOUSHEY: Actually, I can't answer that. We've done studies of offset effects of inhaled steroids and of salmeterol, and the people who are kept on inhaled corticosteroids then switch to salmeterol, then the salmeterol is stopped. So it's steroids, monotherapy, well-controlled monotherapy with salmeterol, and then stopped, as opposed to a longer continuation of an inhaled corticosteroid and then switched to placebo, so they were stopped. And the offset is very similar in terms of rate

of return of symptoms.

I was disappointed by this. I had thought that the "disease modifying effects" of corticosteroids would mean people would have symptoms return much more slowly than after you stopped a long-acting beta agonist, and one

of the surprises of these studies is when you stop inhaled corticosteroids, bronchial hyperreactivity, symptoms of unstable pulmonary function return much more quickly than I had anticipated. I thought it would be weeks. In fact, it's days before it starts to come back. So it's not that different than treatment with a long-acting beta agonist.

But we haven't specifically looked at off effect from combination therapy. I'd better turn this back to Tushar.

Did you? You did mention that there's no evidence of rebound when you switched people back to their former treatment from the combination therapy.

DR. KELLY: You have not included any follow-up data in which you've taken the patients off after they completed the clinical trial?

DR. SHAH: Well, they went back to their usual therapy after they were stopped from the clinical trials in Europe, and we monitored after that switch occurred if there was any evidence of the withdrawal effect, and we didn't see that in those clinical trials. But we didn't

specifically design the study to look at the off effect of the response treatment.

DR. KELLY: An issue about the package insert and the recommended starting doses. It's pretty impressive, actually, when you look at the data in terms of improved control and being able to significantly improve control instead of doubling the dose. Then there's the ACORN study which shows that if you start salmeterol, you can half the dose of the inhaled steroid. Yet, what you're recommending is that when you start the combination, to start them on the higher dose of inhaled steroid that they're already on.

I can see that if they're already on fluticasone, but why not just recommend that everybody gets started on the lowest dose?

DR. BOUSHEY: You may know, Bill, that in the guidelines there are two recommended approaches to treatment. One is to creep up -- that is, if the patient's symptoms are not controlled by the lowest compatible level of therapy, you then go to a higher level -- or overtreat and back down, get them under control and back down. The guidelines are constantly being reviewed by the committee that prepared them, and increasingly the sense of the guidelines committee members is that the treat high/back down is a better approach to therapy, both because it

demonstrates to the patient that their disease can be controlled, and also it seems to be easier to back down than to creep up to bring a disease under control.

So as I understand the package insert, it's to start the therapy and then back down on the dose of fluticasone as is appropriate to maintain control, and then to switch them when they're on the lowest dose to fluticasone alone.

DR. KELLY: I guess I'm concerned based on some anecdotal things that have happened with children being started on the highest doses of fluticasone and their primary care physicians never backing down after they've started them. That's a major concern.

DR. SHAH: Actually, we share that potential concern with you, and what we have done in this context is actually provide very specific guidance in the label as to which strength of Advair to use if you're on inhaled corticosteroids. It's in the label.

Can I have the slide, I think it's C2, on the dosing for what we're proposing in the label? What you'll see is that we're recommending Advair 100 to be the most common dose that would be appropriate for the U.S. What we have done is, if you will recall, we had inclusion criteria according to baseline inhaled steroids for all of these

various steroids in our clinical trials in the U.S. and in

Europe. In each study, we showed -- these were patients symptomatic on these doses of corticosteroids -- that the use of Advair was associated with significant improvement in asthma control.

Based on this inclusion criteria and the clinical benefits observed in the clinical trials, we constructed a table to recommend which strength of Advair these patients should use. If you look at this table, what you see clearly is that other than for budesonide at the highest dose, and clearly fluticasone at the highest dose, the Advair 500 is not recommended for patients on flunisolide, for patients on beclomethasone, and patients on triamcinolone at the doses that these drugs are recommended to be used in the U.S., because that would be, as you would surmise, much more than they would need in order to get the benefit.

So we feel by providing this guidance, we're trying to ensure that physicians pick the right strength of Advair right from the beginning and avoid the potential for using more medicine than is probably needed to control the

patient.

DR. KELLY: My very last question is a clinical pharmacology question. It has to do with that area under the curve or exposure of fluticasone in patients versus normals. Do you have any evidence that that's a delivery

difference from the device, or whether it's an absorption difference and that the delivery is the same in normals and in patients but for some reason there's a significant difference in the way it's handled once it's delivered to the lung?

DR. SHAH: Let me ask Dr. Daley-Yates to answer that.

DR. DALEY-YATES: We looked at this issue in more detail with fluticasone as a single agent, and it appears that it could either be due to a lower lung position or due to a difference in the rate at which the drug is absorbed from the lungs, and the evidence really points to it being a lower deep position related to lower lung function in asthmatics.

DR. SHAH: I think what we know about lung

delivery is that the particle size is a critical determinant in where in the lung a drug is going to go. For drugs that deliver very small particles, you get very peripheral deposition down in the alveolar region, whereas you can imagine, due to the surface area and the blood flow, you get substantial absorption systemically from that.

What we have shown in patients versus healthy volunteers, we've done several studies looking at this question and have clearly shown that patients with airway

obstruction get much more central deposition. They don't deliver drug as peripherally. Because of that, the systemic absorption that occurs in these patients is much less, on the order of about 50 percent in patients as what we see in healthy volunteers.

So you have to be careful when interpreting the safety data on healthy volunteers for inhaled steroids, because it exaggerates the systemic effects we would see in patients where you have air flow obstruction and the drug isn't able to get down as peripherally into the lungs.

DR. PAUWELS: Maybe I can add to that. There

has been a comparison looking with the same dosing in healthy volunteers and asthmatics with regard to the area under the curve for the plasma cortisol over 24 hours, and what you see from the levels of the drug actually is applicable to the suppressive activity on the cortisol excretion also, that in asthmatics, for the same dose, you have less suppression of the cortisol secretion than in healthy volunteers. I will fully support what has been said, that we have to be very careful in translating data from healthy volunteers to asthmatics.

To your previous question, I wanted to add something. The combination has been on the market for about a year, and what you see is that it is mainly used in people with moderate to severe asthma, and in fact only a

small percentage is transferred from bronchodilators only to the combination therapy. So it's really in the more severe ones that it's mainly used at this time.

DR. SESSLER: Dr. Vollmer, then Ms. Conner.

DR. VOLLMER: Let me first off compliment you on a very well put together packet and a wonderful

presentation. It's been very helpful for me in digesting it. I'll also reassure you that I don't have any killing statistical questions about the basic analysis.

DR. SHAH: Thank you.

(Laughter.)

DR. VOLLMER: Shucks.

(Laughter.)

DR. VOLLMER: I do have a couple of questions. One is that I want to follow up on a comment that Dr. Apter made about compliance out of the clinical trial setting and just in an observational setting. You do have experience with this drug in England, and I'm wondering whether you have looked there at just general compliance issues and continuing people on this product versus the separate combination therapy.

DR. SHAH: Maybe I can again have Dr. Fuller provide that perspective.

DR. FULLER: Yes, I can almost help you with that question, because it's been on the market in the U.K.

since March, and we are tracking it in the GPRD database. In reality, we don't have enough data to compare with the

pre-data to actually answer your question. We have looked extensively at the issue of when you put people on Serevent, what then happened to their subsequent compliance in terms of prescription filling to the other medication, which was an issue when Serevent was first brought on the market.

That data was reassuring, that there wasn't wholesale stopping of the other medication in that group, probably because they had more severe asthma, and therefore more incentive to continue treatment. But we are tracking it, and hopefully sometime within the next year we should have some real data for you.

DR. BOUSHEY: But it wouldn't be hard to improve on our current compliance figures. David Stemple's studies in Seattle with a large prescription database shows that it's only around 20 percent of patients prescribed an inhaled steroid by a primary physician who renew it even once, and it's only around 30 percent prescribed an inhaled corticosteroid by a specialist who renew it even once, and this is way below what we would expect from our guidelines. So it's a low hurdle for us to improve on those figures.

DR. VOLLMER: I would agree with that wholeheartedly.

My biggest concern here, and I'm speaking as a non-clinician but somebody who is trying to grapple with this, is in the acute exacerbation, you make it very clear in your instructions that you're not to take additional product here, but it seems to me that it limits somewhat the options one has. Either you're carrying oral corticosteroids and you're going to go that avenue, or you're going to have two different doses of the Advair product to be using. If it's the latter, it just seems a bit cumbersome.

The big advantage, and I agree with you that it's a compelling advantage, is having one product used rather than a separate salmeterol and an ICS preparation, but yet that seems to be negated somewhat by the necessity of having the ability to modify your ICS dose, and I'm wondering if you could speak to that a little bit and how you see that happening in practice.

DR. BOUSHEY: We have a nurse on the panel who can speak to this because nurses are so good at patient education. When people have two inhalers, a steroid and a long-acting beta agonist, and you say, "Okay, when you have an exacerbation, you're to increase this one, the burnt umber one, that's the fluticasone, or the white one, the triamcinolone, but not this other one, the salmeterol," people do get confused about what you mean.

I actually think it's probably no more difficult to say, "This one with the 100 on the label, that's what you use regularly. When your symptoms are flaring or you get a cold, I want you to start on this one with the 250 or the 500 on the label, one puff twice a day for four, five, or seven days, or until your symptoms improve, and then call me." I actually think this is going to make it easier.

The more inhalers, the more people are likely to get confused, even though you would think that would give them flexibility to increase one rather than the other. People get very confused, even with color-coding and time spent on the visits.

DR. SESSLER: Ms. Conner?

MS. CONNER: What a perfect segue. Thank you, Dr. Boushey. My question is along those same lines. The information in the briefing documents as well as the presentation gives one a feeling of safety, and also that you recognize the need for additional education for clinicians and physicians, as well as nurses and patients. I've had the opportunity to do patient education programs

and clinician education programs enough, even recently, to realize that there is still terrible confusion about the role of salmeterol and how it's used and when it should be used, and don't take it with you, and leave it with the

toothbrush.

There's just not a real clear understanding of that. You've mentioned that you do recognize the need for programs to help this. I'm wondering what gimmicks have you come up with for physician education, realizing that the majority of the physicians who are going to be prescribing this medication are not specialists, they're not in this room. They're the physicians out in the rural areas in communities who don't have a lot of time and don't have a lot of time to educate their nurses, who do this education. So what magic gimmicks have you come up with that are going to make this clearly understood?

DR. SHAH: As Dr. Boushey clearly identified, we've been trying to do this with salmeterol currently, and the same issues are relevant with salmeterol as we're discussing with the Advair. The advantage of Advair is that patients will get an inhaled corticosteroid if they

take that dose. So they can't misuse the salmeterol without getting the anti-inflammatory therapy, which is really critical for that acute attack of asthma.

I think we don't have a magic answer, unfortunately, as to how to best educate the nurses and physicians on how to use any medication. It is a challenge. I think what I can tell you is that we are committed to working and continuing to build on the

experience we have with salmeterol and take that further along. We clearly will provide very clear instructions in the patient instruction leaflet on how to use the product appropriately and what not to do when you have worsening asthma.

We will clearly do physician education programs. We will also do patient education programs with the help of nurses and other supporting groups, allied health groups, in the context of delivering that. Clearly, if we do any DTC or direct consumer advertising with this product, that appropriate use will be a key component of what we will be emphasizing, as we do with all products,

because it's in no one's best interest if products are misused.

MS. CONNER: As salmeterol was a new concept when it came into the market, this combination is also a new concept and a new approach to the therapy of asthma, and I can't emphasize strongly enough -- I mean, I'll get on my soapbox, but I'll try to avoid that. The majority of practicing clinicians out there are going to need substantial education and reinforcement on the appropriate indication for this therapy.

DR. PAUWELS: I would actually agree with you. In the most recent GINA guidelines, which is the 1998 edition, the preferred therapy as it's outlined is the

combination of the inhaled steroid and the long-acting bronchodilator, the long-acting beta agonist. This has caused, as you say, a paradigm shift again that is needed for the clinician who was used to increasing the dose of inhaled corticosteroids depending on the severity of the disease.

But I think one of the advantages of the Advair and any fixed combination is that it helps you for the

teaching, because you avoid that people treat this type of asthma without the inhaled corticosteroids, so that you always have the combination of the two. So I think it's an educational tool that you can use for that.

DR. BOUSHEY: Sorry to prolong this, but I want to join you on your soapbox. Again, as an author of the guidelines, as one of the executive committee members, we were kind of frustrated at the slowness with which habits of practice were changed. And you're right, 70 percent of people with asthma get their care from a primary care physician, not from a specialist.

I would say that actually the pharmaceutical industry in general has been quite responsible in helping promulgate those guidelines through CME activities. We think the version we wrote was too long. We've made a shorter version. We've made a highlights version, and we're trying to get it into a wallet-sized card.

(Laughter.)

DR. BOUSHEY: We're working on it. But glacially, it's happening. Some of the signs that it's

happening is that mortality has stopped increasing despite increases in prevalence. It happened first in Sweden, and now it's happening in the United States, which is evidence that there's better treatment of severe asthma. There is an increase in long-term control of therapy. So the guidelines may be cumbersome. It may be like turning the oil tanker, but it does seem to be being turned. It is happening. It's going to take a lot of work from the medical, nursing, educating communities, and probably voluntary health associations as well.

DR. SESSLER: Before we leave the patient and physician education rollout sort of questions, I'd actually like to get the early experience in the U.K. as far as how this drug has been rolled out and how Glaxo has actually positioned it in terms of helping the clinician and patient use the drug properly. What sort of things have you done so far?

DR. FULLER: Well, I think that we have no magic over on the other side of the Atlantic either. It's essentially concentrated on the sorts of activities that have been outlined here, carefully stressing the appropriate patient group. I think we have been

successful, at least in the early uptake.

We are tracking it in detail in Sweden, the U.K., and in the Netherlands on a regular basis, and looking at the sort of patients where Advair is being used. As Professor Pauwels said earlier, essentially it's being used in moderate and severe asthmatics. When we ask about use in patients who were previously on short-acting beta agonists, which is I guess your concern, if you look at the overall population of the doctors that we're asking, roughly 20 percent are on short-acting beta agonists alone. But when we actually look at the patients where they're using Advair, only 3 to 5 percent had only short-acting beta agonists as their previous treatment, which would be consistent with the sort of numbers of people with moderate to severe disease who are inappropriately treated.

So certainly not evidence in Europe that it's being used widely in inappropriate population groups, but that's clearly something we keep an eye on because, as Dr. Shah said, it's not in their interest or anybody else's for this combination to be used inappropriately.

DR. SESSLER: Dr. Ford?

DR. FORD: I think most of the questions that I had regarding the educational issues that are implicit with the introduction of this new device and combination, some of these questions have been raised. I have a couple of

questions nevertheless, one regarding the subpopulations.

First of all, in regard to patients with low peak inspiratory flow, in Dr. Shah's presentation, you mentioned that patients with flows as low as 30 liters per minute do get the drug. So that would suggest that, at least in terms of airway deposition, there is no problem in terms of delivery. Is there any difference looking at subgroup analyses of efficacy in terms of very low flow versus much higher peak inspiratory flow patients? I would not suspect, a priori, that that would be a problem, considering the mechanisms of action of the drugs, but I think it might be worthwhile looking at that.

DR. SHAH: I think that's a good point. We haven't specifically looked at the question in the Advair clinical program in terms of whether patients with very low inspiratory efforts are having less clinical benefit. What I can share with you is what we do know about the Diskus device, which is that it's a low resistance device, and thus it doesn't require a great deal of effort for patients to administer a dose.

Where we've looked at various severity of patients' ability to generate that peak inspiratory flow of 30 liters per minute, including patients with severe COPD

with airway obstruction of approximately 20 to 30 percent of predicted, and in children as young as 4 years of age,

all of those children that we've studied thus far have been able to generate at least a 30, if not more, liters per minute inspiratory effort to get that dose.

So I think we feel fairly comfortable, based on the evidence we have available with the device, that most of the patients who would use this product will be able to generate the inspiratory effort needed to get a dose, and I think the clinical results certainly support that conclusion.

DR. FORD: I guess this is more of a comment than a question. I think that this drug is going to present certain challenges in certain populations. Particularly, we've talked about cost and educational approaches. That is, we have a new device, it's taken us a long time to teach a lot of primary care providers about appropriate use of an MDI, and now we're going to be trying to teach patients to inhale fast with one and inhale slowly with their rescue medication. So I just want to underscore

once again a point that has been made by several people here.

DR. SESSLER: Dr. Apter?

DR. APTER: I want to pick up on what Ms. Conner mentioned. It's my experience with fluticasone that patients confuse the doses even though the numbers are there because of the colors being so similar. You showed

us a picture of Advair, and it was lavender. Is it going to be lavender, and are the strengths going to be different in color?

DR. SHAH: The color will be purple or lavender. I always get shades of colors mixed up. But clearly, we have a need for patients to be able to distinguish Advair from other products, and I think most people would agree that the selection of purple will clearly achieve that objective.

We also have a need, as you clearly identified, to ensure that patients and physicians can clearly distinguish between strengths, and there are many ways to address this issue. You can change colors of devices, but we find that it's helpful for patients and physicians to

have one color which they then know is Advair, versus another product. What we then are committed to doing is working with the FDA looking at different stripes on the label, big numbers that clearly identify the three strengths. We are committed to ensuring that this is as easy as can be for physicians and patients, because we realize that that's an important need.

DR. PAUWELS: Can I add something which is from a practical point of view, and that's the discussion about what has been going on. What I personally found the most effective is to use a different device for the maintenance

treatment than for the rescue medication. So if you use, for example, a powder inhaler for the maintenance treatment, and a PMDI for the rescue, that is much more educational than any color difference, because patients don't recognize the color differences, and I think that's the way to handle that problem.

DR. APTER: Yes, but when patients go from one physician to another, which they do for primary care and their asthma specialist, they don't know what drug they're

on.

DR. SESSLER: We're about out of time, but what we have is three more questions here. If you could make your questions and responses very brief, please, Dr. Joad.

DR. JOAD: This question is probably for Dr. Boushey because of his role in the guidelines. The guidelines do say that we should titrate the steroid dose to the lowest possible dose.

DR. BOUSHEY: That's right.

DR. JOAD: Yet with this Advair, we won't have that kind of fine-tuning that we can do as far as steroid dose. There are just going to be three, and I wonder what your thoughts are with regard to that.

DR. BOUSHEY: Well, I don't see it as a problem. I mean, the high dose, 500 twice a day, is equivalent to four puffs of 220 twice a day, and the low

dose, 100, is equivalent to two puffs of 44, the lowest maintenance dose of fluticasone. So I think we have the same range of doses.

DR. JOAD: No, I think the range is there, but the gradations within the range are not going to be there.

DR. BOUSHEY: Yes. It's 500 twice a day to 250 twice a day to 100 twice a day.

DR. JOAD: What are we losing and what are we gaining that makes Advair worth it, since we will lose -- according to the guidelines, moderate and severe asthmatics should be going to an asthma specialist who will know they should titrate the dose to the lowest achievable good control dose, and yet that fine-tuning we're going to lose.

DR. BOUSHEY: I don't think we're going to lose a lot in fine-tuning because they do have the three steps.

Also, I'm impressed that there may be an interaction at the level of the airway. That means that people on higher doses of steroids will end up on lower doses because they're taking it in combination with long-acting beta agonists. So that's a gain. And I don't think this loss of titration is very important, because it does have the three strengths over a pretty wide range. I guess you've lost 44, and they are proposing to develop that for pediatrics within the next year, so we'll have another step at the low end, which is where I think your concern would

be, within a year's time.

DR. SESSLER: Dr. Niederman?

DR. JOAD: Can I just ask one more question? With regard to the guidelines, your package insert doesn't use any guideline terminology, and that seems strange to me. There's no controller wording, reliever, action plan. All the words we're trying to teach to our patients and other physicians are not part of the wording in your package insert suggestions.

DR. SHAH: Clearly, I'm probably not the only one to comment, and maybe the agency can comment on this as well, but I think historically the package inserts have not used the guidelines as a way of defining how the treatment should be used, and the definition of treatment has been very much based on the clinical trials and the programs that have been done supporting that particular product.

Maybe Dr. Boushey can comment on the value of having guidelines that potentially can be changing as they're used.

DR. SESSLER: Perhaps at another time.

DR. SHAH: Yes.

DR. SESSLER: Dr. Niederman?

DR. NIEDERMAN: I would like to get a little more clarification. I know you have this information in your package on some of the secondary endpoints. In other

words, all the data we've seen here relate to lung function. Maybe you could make some comments on the different studies and doses, sort of an overview of how these lung function abnormalities correlate into better symptom control, rescue medication, quality of life measures, which I know you've looked at.

DR. SHAH: Yes. Again, because of time, I think I probably won't have time to show you the slides on that, but what I can share with you is that the secondary measures are very comparable to what we saw in the primary. We saw improvements in quality of life, we saw improvements in control of symptoms, rescue albuterol use, and night awakenings with Advair. For most of those measures, the improvements with Advair were significantly greater than the individual agents. For one or two of those events, it didn't quite achieve statistical significance, but in all cases, numerically they were much better with Advair.

DR. NIEDERMAN: And it was true at all dose ranges?

DR. SHAH: That's correct.

DR. SESSLER: Dr. Fink?

DR. PAUWELS: Maybe I can add something to that, which comes out of the many studies on the combination product. That is, the combination, or adding a

long-acting beta agonist to an inhaled steroid dose, is

very effective in controlling lung function symptoms and the number of asthma-free days. The only thing that is remarkable is that increasing the dose of inhaled corticosteroids is more effective than adding the long-acting beta agonist on the number of severe exacerbations, and that's a difference that might be important for titrating your treatment, depending on the characteristics of your patient.

DR. FINK: The FDA analysis of your data states that only six patients under the age of 17 were in the 500 microgram study, and based on six patients, do you think it's reasonable to ask for an indication in 12- to 17-year-olds for the 500 microgram Advair?

DR. SHAH: I think we have to realize that the development of this program is intricately linked with the individual products, where we do have substantial long-term data in terms of efficacy and safety. Clearly, I share your comment about the adequacy of six patients in the context of this clinical program being adequate, but I think we do have data on the individual products at those

dosages in large numbers of patients, and I think that's the key point that we need to remember, that the higher dose of fluticasone should really be used in the most severe patients in whom the alternatives are systemic corticosteroids.

When you do that kind of a risk/benefit analysis, then I think clearly the use and value of high-dose inhaled steroids has been shown to be consistently appropriate. I think what I would share with you is that we have data on those strengths individually, and I think that would be our supporting evidence for the use of the product in these patients.

DR. VOLLMER: Time for another one?

DR. SESSLER: Dr. Vollmer, a quick one, please.

DR. VOLLMER: Perhaps more of a comment than a question. I'm puzzled, in looking over the 3002 and 3003 trials, actually at the inclusion of a placebo arm in that. I know there are other people here who are disappointed that we didn't have one in the 500. All of these trials involved people who were on regular maintenance therapy

and, from the descriptions I could read, appeared to be poorly controlled. They certainly had very poor lung function. I understand that you did exclude those who were most severely uncontrolled during the run-in, but I wondered why the necessity -- and maybe this is an FDA requirement, and, Dr. Meyer, you can speak to that -- but why the necessity for a placebo?

I mean, particularly in the 250 group, these people were on regular steroids, and the early dropouts of these individuals attest to the fact that it's an

inappropriate therapy for them.

DR. SHAH: I think clearly that is a concern that we had, and we designed the criteria that we had used previously in the development of Flovent, where we have a great deal of experience in a similar context. Because of the use of these criteria, we ensure the protection of the patients' conditions, such that if they are deteriorating, we identify those patients who are deteriorating and we allow appropriate institution of change in therapy.

As to exactly why we include placebo, I think maybe that's a question I'll reserve for the FDA to address

later.

DR. MEYER: For a combination product, the requirement is that they beat the single components. So, quite frankly, you would not necessarily need a placebo in this kind of design. I think the placebo group does offer some information, but I think what I would stress is that we feel comfortable in the manner in which Glaxo proceeded in terms of protecting the patients, that if there was a signal that they were deteriorating, they would declare it as not well controlled and taken out of the study. So I think we were comfortable that that adequately protected the placebo patients.

DR. VOLLMER: I'd just add, then, my one statistical comment from that, that the result is that many

of your outcome analyses that would like to look at 12-week data are really forced to look at the endpoint data, because you note the obvious bias in getting a survivor population. It's impressive to see that despite that bias, you're still getting significant differences, but it does greatly complicate the analysis.

So if there's not a lot of scientific rationale for having that population in there, then I would suggest that you look closely at the inclusion of them in the future so that you satisfy yourself that there's good rationale, good scientific benefit and value to be gained from having them in. That's my only comment.

DR. MEYER: I think that debate could go on for a very long time. I appreciate the point.

DR. SESSLER: Thanks to the sponsor for their presentations, and to the committee for their questions.

What we'll do is return at about 10:40 to begin the FDA presentation. Thank you.

(Recess.)

DR. SESSLER: I'd like to welcome you back to the second morning session. This session will be devoted to the FDA presentation.

The sponsor has asked to have a couple of quick minutes to clarify some dosing issues, and we'll go ahead and do that before Dr. Meyer presents.

DR. SHAH: Thank you.

It was brought to my attention that I didn't

clearly communicate the dosing between FP and Advair. As I indicated, we have the Flovent 44, which is the MDI that's administered at two puffs twice daily. So the Advair 100 corresponds to the Flovent 44 dosing that patients would do. The Advair 250 would correspond to the 110 strength of Flovent, because you use two puffs of that twice daily. Then the Advair 500 corresponds to the Flovent 220 in the MDI, which would be two puffs of that twice daily. I hope that clarifies any confusion I might have created in terms of relative dosing between Advair and the individual Flovent component.

DR. SESSLER: Thank you.

Dr. Robert Meyer is director of the Division of Pulmonary and Allergy Drug Products, and he will offer some opening comments, followed by Susan Johnson, Ph.D. and Pharm.D., who will offer the FDA medical review.

DR. MEYER: Thank you, Dr. Sessler.

I did want to take the opportunity to once again welcome the committee and thank them for their participation in this important discussion, particularly on a holiday week. I want to also welcome the FDA staff, the representatives from the sponsor, and the interested audience.

Clearly, I think this is an important product for the sponsor and represents a novel approach in the U.S. for fixed-dose combination. I'd like to acknowledge the sponsor's very well polished presentation of their data, and also I think it's important to note that Glaxo Wellcome and the FDA did have some consultation on the design of this program and these trials, and I think we commend them on their conduct of this program.

I think it's also important to note in terms of that consultation that the FDA has expressed some concerns about how this product may be best used, and more importantly how it's likely to be used in practice, both in our early consultations and as things have gone on. We were not just concerned about the benefit/risk of concurrent fluticasone and salmeterol therapy, as that's something which is already available, and indeed, as the sponsor has shown, is used in practice. But we also have the question of a fixed-dose product and how that impacts on the optimal dosing of these agents and the optimal asthma care.

As Dr. Boushey stated in his presentation, confusion about medications is a very real problem for asthma, and I think this raises several issues with regard to this product that our Dr. Johnson will cover. We've got two Dr. Johnson's presenting today, and I'll call Sue our

Dr. Johnson. But I should emphasize that our questions really are not whether Glaxo Wellcome has met the regulatory requirements for fixed-dose combination, because I think that it's fairly clear that they've shown that the product is safe and effective for its intended use.

But the question in many respects is more that if this product is approved, we want to know how best to assure that it's used according to that intended use.

I would also note that a part of that question that we will not be asking, but I think it may be important for the committee to know this, is that the FDA has not really settled with the company how best to note dosage strength with this product. I think the company has shown Advair 100, Advair 250, and so on. I think we would have some concerns about the message of the salmeterol component given the present naming scheme, but we are still discussing that internally, and we'll have further discussions with the company.

With that, I'm going to turn the presentation over to Dr. Susan Johnson from our division.

DR. SUSAN JOHNSON: Good morning. My name is

Susan Johnson and I'm the primary medical reviewer for the Advair products. As Dr. Meyer just mentioned, the Division has worked with Glaxo Wellcome to design the drug development program that's just been presented. The

Division is very pleased that the clinical data are promising, and we feel that they are generally supportive of approval of the product.

The Division is interested, as Dr. Meyer reflected, in hearing the committee's interpretation of these data primarily in terms of the clinical application of these products. In addition, we're interested in your ideas about how to craft labeling that reflects your vision of the appropriate use of these products.

From the Division standpoint, trials 3002, 3003, and 3019 were the most important investigations included in this development program. While all three trials provided safety and efficacy data, the placebo treatment arm, as we've had a little discussion about by Dr. Vollmer and Dr. Meyer, included in trials 3002 and 3003 did provide an interesting scientific comparison.

In addition, trials 3002 and 3003 included

comparisons of the combination with the individual components of the combination. This design helped to meet the regulatory requirements set forth in the Code of Federal Regulations for new fixed combination prescription products. Specifically, this regulation stipulates that approval of a new fixed combination product is in part dependent on the demonstration of the contribution of each component particularly to the efficacy of the product.

Since these Advair products are the first combinations of inhaled bronchodilators with inhaled corticosteroid in the United States, the Advair products will fill a different niche than the existing spectrum of asthma therapies. Our interest is in how the committee views what place in therapy Advair should take on. We're very aware that it is not the role of the agency to regulate the practice of medicine. At the same time, it is our mandate to protect public health by providing information that helps optimize the use of these medications.

To that end, I'll outline a number of issues on

which we'd like to continue to hear your feedback. These topics are not intended to limit the committee discussion, and we're eager to hear all of your concerns and comments. The sponsor has provided data which address many of these issues, at least in part, and I'll discuss those data where they are available. I also want to emphasize that we are asking you today to render your clinical interpretations of many of these issues that the product development program was not required and did not evaluate.

We would like to hear specific comments on the ability of practitioners to titrate patient therapy effectively with the fixed combination, and also to monitor the effects of therapy, particularly with regard to the

inhaled corticosteroid component. We would also like you to help us describe the appropriate patient population in whom these products should be used, and to tell us whether you feel that the products can be effectively used in asthma, a disease whose clinical course can have enormous inherent variability. Finally, we would like to hear more about your thoughts on the potential benefits of this dosage form vis-a-vis enhanced compliance and convenience

for patients.

One of the major considerations for evaluation of this drug development program is to understand how Advair's use compares to the use of concurrent administration of salmeterol and fluticasone. We all recognize certainly that at present, concurrent therapy with salmeterol and fluticasone is already widely used. Direct comparisons of concurrent and combination therapy were made for all three Advair strengths in trials conducted outside the U.S. during this program; namely, trials 3017, 18, and 19.

The Division agrees with the information that the sponsor has provided, that although there were minor numerical differences between treatments, the clinical data did not establish that there was a statistically or clinically important difference between the safety and efficacy of the Advair fixed combination as compared to

concurrent use of the individual agents. In fact, many of the challenges associated with dosing Advair products are fundamentally the same as challenges posed by the use of

concurrent administration of the two individual agents.

However, the management of asthma therapy with Advair will need to be distinct from concurrent therapy in many regards, and it's the unique challenges associated with the Advair products that are of primary interest today.

Since this fixed combination approach to asthma therapy is new in the United States, it comes with a requisite learning component, as Ms. Conner pointed out, for prescribers, health care practitioners, and patients. Perhaps the most obvious learning would need to be about the use of a single device versus multiple devices. It seems that there may be some theoretical benefit of the fixed combination related to patient convenience in that it may, for some patients, reduce the number of prescriptions to be filled, the number of devices to be maintained, and the number of inhalations used.

However, given that asthma is an inherently variable disease, optimally with continual monitoring, dose adjustments can be frequent. Practitioners and patients will need to learn how to adjust doses in association with the fixed combination. In many instances, dose adjustment

could mean the addition of a second inhaler, and with the need for a second inhaler, the benefit of single device convenience would be lost.

In addition, with the concurrent therapy now available in which patients have two distinct inhaler devices, dosing of either salmeterol or fluticasone can start or stop, and doses of fluticasone can be titrated upward or downward without affecting administration of the other agent. With the combination product, titration of either component necessitates consideration of the other component. Most often, changes in therapy will necessitate not only a change in dose but also a change in the device or devices that are prescribed to the patient, and we would like to know more about your perception of these challenges, particularly because they are distinct for the fixed combination in comparison to the currently available concurrent therapy.

A unique feature of the Advair products is the manner in which titration will need to be handled. Since the dose of salmeterol is not generally titrated in the U.S., we're talking about patients being either on or off Advair with respect to that component. Again, stopping salmeterol therapy would require patients to obtain a new device; for instance, changing to a single ingredient Flovent inhaler. I think this is consistent with Dr.

Dykewicz' comments with regard to salmeterol stopping and starting. I think we had a little discussion about that earlier.

Titrating fluticasone would also require a change in devices. The proposed devices provide a range of 100 to 500 micrograms twice daily of fluticasone, the currently approved dose range for treatment of asthma, and we're interested to hear whether you feel that this range is adequate. In addition, there are limited gradations in dose of fluticasone available with this product. For instance, a dose of 400 micrograms is not feasible. We would ask you to comment on whether the three proposed dosage strengths provide you with adequate flexibility in dosing. Do you perceive that the proposed 100, 200, and 500 microgram doses allow for an adequate number of dose gradations?

Since it's recommended that all inhaled corticosteroids, including fluticasone, be titrated to the lowest effective dose, we'd like to understand your impression of the impact of the availability of a fixed combination on prescribing practices, particularly with regard to titration. Do you think that the combination could have a negative impact on practitioners' awareness

and attentiveness to the need to titrate and monitor the effects of both salmeterol and fluticasone independently?

I think Dr. Kelly raised some concerns specifically related to the effect of the availability of the combination on practitioners' attentiveness to this issue.

Dose titration was not addressed in the clinical trials, and it was not required to be. Dr. Joad asked a question earlier about dose-response trials. Those were also not required during this development program. While each of the proposed doses were studied in separate trials, cross-study comparisons are not appropriate. Patients were discontinued from the U.S. trials if their asthma worsened, so they were not titrated to higher doses. Neither were patients backed off of their assigned dose of fluticasone within a given study.

The subject of titration, then, leads us to a broader question of how to monitor patients' therapy in general. Patient monitoring during Advair treatment is expected to be similar to monitoring patients on concurrent therapy. The intent of monitoring is to be sure that the

dose administered is safe and efficacious, and that we're avoiding underdosing as well as overdosing. Data are available to confirm the general safety and effectiveness of the Advair products, and also to tell something about the consequence of underdosing.

This slide summarizes the primary efficacy outcomes for the two U.S. trials, 3002 and 3003. This is

strictly a qualitative expression of the data based on statistical outcomes and is designed just to reiterate the data that the sponsor has already presented. These two trials differed in two important regards, both dose and patient population. Trial 3002 enrolled milder asthmatics on prior inhaled corticosteroid therapy or on salmeterol therapy. Patients were treated with twice-daily doses of placebo, salmeterol 50 micrograms, fluticasone 100 micrograms, or Advair 50/100.

In trial 3003 involving moderate asthmatics on higher pre-study doses of inhaled corticosteroids, patients were treated with twice-daily doses of placebo, salmeterol 50 micrograms, fluticasone 250 micrograms, or Advair 50/250.

The first primary endpoint is FEV1 AUC at week 1. Again, week 1 was chosen for this endpoint in order to avoid complication, as Dr. Vollmer pointed out, from the relative disparity amongst the discontinuation rates and the complication that that would bring to statistical interpretation of data later in the trial. In both 3002 and 3003, this endpoint showed statistical superiority for Advair relative to all of the other treatments. The other treatments are shown in rank order such that salmeterol was numerically superior to fluticasone, which in turn was numerically superior to placebo.

In addition, in trial 3002, salmeterol was statistically superior to placebo, and in trial 3003 both salmeterol and fluticasone were statistically superior to placebo.

Morning pre-dose FEV1 at endpoint or time of discontinuation is shown in the next row. Again, Advair was statistically superior to each of the other treatments. In contrast, however, to the AUC outcomes, fluticasone therapy tended to be associated with greater effects than

salmeterol. This trend is likely to be related to the relative pharmacologic properties of salmeterol and fluticasone. The bronchodilatory action of salmeterol seems more apparent in the AUC outcomes, while fluticasone's effects on the underlying disease appear more evident in the morning pre-dose values.

In interpreting the morning pre-dose outcomes, I'd like to add an observation from salmeterol trials outside of this application. It's important to note that salmeterol's effects on FEV1 are generally not washed out within an overnight or 12-hour interval. Some residual bronchodilatory effects are seen even after a 12-hour interval and were likely to have been responsible in part for the morning pre-dose outcomes seen in this trial.

Finally, the probability of discontinuing from the trial was lowest for Advair. In both 3002 and 3003,

Advair was statistically superior to both salmeterol and placebo. However, in trial 3002, there was no difference between Advair and fluticasone treatments.

As a general observation on the outcomes of these trials, and in response to a question from the

committee, the secondary efficacy endpoints were supportive of the primary efficacy outcomes. We feel that these data helped to provide meaningful assessments of the expected clinical benefits of Advair and were generally thought to be consistent.

Without highlighting any of the specific data, I'd like to observe that Advair's effects do not appear related to enhanced systemic bioavailability relative to the single-ingredient products.

Finally, let me just summarize with regard to safety of the Advair products. We found no evidence that the combination product was associated with increased or unexpected safety concerns relative to the single-ingredient products. In response to Dr. Niederman's questions about high-dose fluticasone therapy and HPA axis suppression, we have seen in prior work with fluticasone dry powders that the 500 microgram BID dose appears to be the threshold for suppressive HPA axis effects. These effects are obviously expected at high doses of fluticasone, as they are for all inhaled corticosteroids.

Overall, we agree with the sponsor's assessment that these data support the safety and efficacy of Advair.

To continue talking about patient monitoring with Advair, I'd like to remind you of the trial designs for 3002 and 3003 in which patients were discontinued if not adequately controlled on their assigned treatment. This slide just reiterates the specific criteria for discontinuation, including evidence of increasing symptoms or decreasing lung function.

We feel that the discontinuation rate from the trial or the probability of remaining in the trial was a very good overall measure of product performance. A couple of points to emphasize in the results of trial 3002. First, as we've talked about before, the discontinuation rates essentially invalidated the statistical analyses at the later time points in the trial, and that was why the sponsor chose to include this endpoint in their design. So little weight was placed on the outcome for week 12, for example. This slide uses the same color strategy that the sponsor used, with Advair in purple, fluticasone in orange, salmeterol in green, and placebo in white.

Also, even among the milder asthmatics in this development program included in trial 3002, you can see that some of the patients in each group received inadequate treatment. This can in general thought to indicate

underdosing for the purposes of patient monitoring, and we can see that it's detectable even among Advair patients.

Finally, in this population, the outcomes of fluticasone 100 microgram and the Advair combination containing 100 micrograms of fluticasone were indeed very similar.

Just to reiterate for quantitative purposes, here are the number of patients continuing in trial 3002 at day 1, and the beginning of weeks 2, 7, and 12. Again, you can clearly see the disparity in the discontinuation rates.

The probability of remaining in trial 3003 was generally lower for each treatment group than in 3002. Of particular note on this slide is the disparity between fluticasone 250 and the Advair product containing 250 micrograms of fluticasone. While this difference is relatively small compared to the differences seen between Advair and salmeterol, or between Advair and placebo, it does raise some questions. Presumably, the majority of patients who discontinued from single-dose fluticasone therapy were not receiving adequate doses. Yet this same dose of fluticasone, when combined with salmeterol, controlled symptoms to a greater extent.

What we don't know from these data is whether the symptom control demonstrated in combination therapy is

preventing us in any way from seeing the consequence of

underlying and uncontrolled airway inflammation.

Here are the actual patient numbers for trial 3003, which showed the differences among discontinuation rates for the various treatments. This question about not being able to detect corticosteroid underdosing in the presence of salmeterol, perhaps best termed masking, is not specific to Advair and is problematic in patient monitoring during concurrent therapy as well. The same can be said about overdosing, that it is unnecessarily giving high doses of corticosteroids. It's a potential problem with Advair, as it is a potential problem with concurrent therapy, and there were no specific data in the trials in this program that addressed downward titration of therapy.

We ask that you consider potential underdosing and overdosing as part of the whole therapeutic picture for Advair and factor these elements into your overall recommendations on how to best use the fixed combination.

Turning from issues related to patient monitoring, I'd like to please ask you to consider the question of how to define patient populations that should

receive Advair treatment. Some primary considerations here are patients' prior asthma therapy and their asthma stability. But as Dr. Ford pointed out, there are other patient factors that will determine prescribing practices for Advair.

Trials 3003 and 3019 involved patients who were fairly well stabilized on inhaled corticosteroid treatment, and give us information for the Advair products containing 250 or 500 micrograms of fluticasone. Patients enrolled in trial 3002 were also relatively stable but were stratified by prior use of either inhaled corticosteroids alone or salmeterol alone. Patients, in other words, used one or the other prior to coming into the trial.

There were descriptive analyses conducted on these study outcomes, but no further statistical analyses were conducted on these data due to differences in the number of patients in each group. I just wanted to illustrate that here by showing just the Advair and placebo numbers. These are patients who were on prior inhaled corticosteroids and on prior salmeterol on day 1, week 6,

and week 12, and you can see by the end of the trial there were very few patients who had used prior salmeterol remaining in the trial.

Looking qualitatively at the primary outcomes based on prior treatment, there appear to be two trends. The first is very evident in the FEV1 AUC, and that is that patients who used salmeterol prior to enrollment tended to show a greater improvement overall upon entering the trial than did patients who had previously used inhaled corticosteroid. So these tend to be lower than these. The

clinical relevance of this trend, though, is unknown.

For morning pre-dose FEV1, prior salmeterol users also seem to perform better than prior inhaled corticosteroid users overall. In addition, it appears from these data that patients who had previously used salmeterol therapy benefitted nearly as much from being switched to single-agent fluticasone as they did from beginning Advair, and this was not true of the prior corticosteroid users.

Looking at the discontinuation rates for the two groups, again prior salmeterol users seem to benefit nearly as much from beginning fluticasone alone as they did

from Advair therapy. Advair did not apparently have an advantage for these patients. Again, I would stress that these were not statistically analyzed data and the study was not specifically designed to look at this question.

We have not reviewed any data specifically from patients who were switched to Advair therapy following use of short-acting beta agonists alone, and we'd like the committee to consider that patient population as well.

Asthma itself is a naturally fluctuating disease and poses another complicating factor to our understanding of how best to use Advair therapy. This slide invites you to consider the normal permutations of asthma treatment to further consider the role of Advair. Mild and severe asthma exacerbations require different

management strategies, and therefore may affect ongoing Advair therapy or the introduction of Advair therapy differently, as would the development of a respiratory infection, contact with allergen, or the need for additional medication such as oral corticosteroids.

In addition, waning of the disease also needs

to be considered in determining Advair's place in therapy.

To further this exploration of the clinical spectrum, we propose two hypothetical scenarios. In the first, a patient with moderate persistent asthma who has been controlled on Advair 50/100 and PRN albuterol experiences an increase in symptoms. This is similar to the scenario suggested by Dr. Vollmer earlier. In response to such an event, this patient could receive doses of fluticasone of 250 or 500 micrograms in the Advair formulation, or it's possible that single-ingredient Flovent could be added to Advair treatment.

We also have a concern, and would like to hear your thoughts, on whether patients or prescribers can be expected to double doses of Advair, as Dr. Sessler suggested, on their own, and thereby doubling salmeterol doses as well as doubling fluticasone doses.

In the second scenario, a patient with moderate to severe asthma is concerned about continued exposure to high doses of steroids. Is it appropriate to lower this

patient's Advair dose from 500 to 250 micrograms of fluticasone? And if an interim dose is more appropriate,

how should that be arranged, as Advair given with additional Flovent, or perhaps with the use of concurrent medication after discontinuation of Advair therapy?

Finally, we need to consider what is probably the greatest potential benefit of Advair, and that is increased patient convenience and presumably compliance. Unfortunately, in response to Dr. Apter's questions, we don't have data which gives us direct insight into this hypothesized benefit.

Compliance was assessed in the clinical trials based on dose counters in the device and on diary data. Compliance rates were high, over 90 percent, in both trials 3002 and 3003. There were minimal differences among the treatment groups, and, interestingly, a slight trend in the data associated the lowest compliance rates with the Advair treatment. Overall, the available data do not appear to provide us with a mechanism for assessing the impact of Advair on patient compliance, and we would certainly like to hear more of the committee's thoughts on this particular issue.

In summary, the Advair development program provided us with what we considered to be adequate evidence of safe and effective therapy. We need your input to

better understand the role of Advair in the clinical setting. Of particular interest are the challenges that are unique to Advair therapy, such as titrating with the fixed-dose combination. While patient monitoring for Advair may not pose unique challenges relative to concurrent therapy, labeling for use in an appropriate population and conveying meaningful approaches to use with the various clinical manifestations of asthma will be important to this new product.

So, with that, I'd like to go over the specific questions that we've posed for you today.

Given the efficacy data presented for the combination compared to its components alone, and the hypothesized benefit of increased convenience and compliance, do the benefits of Advair as a fixed-dose combination outweigh its risks?

I lost my cursor. I'm sorry. I'm not as good as I should be with this cursor. The questions are actually contained in your blue folders that are on the table here, and I'll just wait a second so you can get that out. While you're doing that, let me see if I can fix this.

DR. SESSLER: Do we have any ex-chief residents in the room?

(Laughter.)

DR. SUSAN JOHNSON: So again, given the efficacy data, do you feel that the benefits of Advair as a fixed-dose combination outweigh the risks? And if you do, what patient population of asthmatics should this product be indicated for?

Do you recommend any additions or changes to the sponsor's proposed labeling on how this product might be best used in practice?

What, if any, Phase IV studies should be required to address safe and effective use of this product in the general population?

If you don't feel that efficacy data were adequately presented to outweigh the potential risks of this product, what additional studies or data would the sponsor need to gain approval of Advair?

We also have posed questions with regard to future development of the pediatric program, and I heard Dr. Gross and Dr. Kelly and Dr. Fink all raise concerns about the pediatric population that I think merit further discussion.

Thank you very much, and with that, I'll take

questions.

DR. SESSLER: We'll take any committee questions for Dr. Johnson or Dr. Meyer.

Dr. Niederman?

DR. NIEDERMAN: I just wanted to go back to the request to use this medication in the mild asthmatics. As the data were presented for the 100 dose for the 3002 study, it really didn't look, as you pointed out, any better than fluticasone alone. Given the issues that have been raised about combination therapy, do you feel that there are -- you've looked at the data in more detail. Are there enough compelling secondary endpoints that would make this a good choice for the milder asthmatic, or should we ask the question that you've asked separately for the different populations? In other words, the risk and benefit ratio may be different for the moderate and more severe asthmatic than for the mild asthmatic.

DR. SUSAN JOHNSON: I think with regard to the secondary endpoints, in general our evaluation was that they were very consistent with the primary endpoints. So in 3002, where there was very little difference between

Advair and fluticasone, the secondary endpoints followed suit. There was a trend in the data which showed an advantage for Advair, but the secondary endpoints did not confirm a greater advantage than the primary. So I agree with your approach to looking at the populations separately. I think that's a very advisable way to do this.

DR. NIEDERMAN: Then I would at least request

that we consider your first question separately for the mild asthmatics compared to the more moderate and severe.

DR. MEYER: I guess the other thing I would add to Dr. Johnson's reply as far as the data we reviewed, it's not entirely clear that we've seen data for patients that would clearly fit the category of mild persistent. The patients on this trial were reasonably mild but were on prior salmeterol. So I guess there's some question about whether they would really fit in that category or not. These trials were very well conducted trials, but they're not really expected to ask these specific questions in relation to the guidelines.

DR. NIEDERMAN: But I think the proposal in the label is that this be potentially used as a therapy for patients who are either not controlled on inhaled steroids or not controlled on salmeterol, and looking at the data in this trial, I think you could agree that if they're not controlled on inhaled steroids, they may benefit from this drug. But if they haven't had a trial of inhaled steroids and they're not controlled on salmeterol, I'm not sure that the combination therapy fits for that population based on the data that were presented.

DR. MEYER: That's certainly the type of feedback we'd like from the committee, from all the members of the committee.

DR. SESSLER: Dr. Kelly, and then Dr. Apter.

DR. KELLY: I have a comment that relates to Dr. Niederman's comment, and that is, looking at both sponsor's presentation of the data and yours, you show the endpoints, but none of the endpoints, as Dr. Meyer just pointed out, are really control of asthma as defined by any group, whether it's the guidelines or anything. It's improvement in FEV1, improvement of deep flow, amount of

symptoms, but there was no a priori definition of asthma control. Am I correct?

DR. SUSAN JOHNSON: I think that what the sponsor designed into their program to approximate that is the discontinuation variable, such that if control appeared to be being lost, that analysis was available.

DR. KELLY: I have a lot of asthmatics who don't discontinue their medication and are completely uncontrolled. So discontinuation out of the trial is dissatisfaction with the trial or control. But if there's no a priori definition of what loss of control is, then can you make any comments about whether or not there was a decrease in asthma control? I guess that's my point.

DR. SESSLER: Dr. Johnson, you may wish to review what the criteria were for discontinuation, if you wouldn't mind.

DR. SUSAN JOHNSON: At the risk of losing the

cursor, let me see if I can get this back.

DR. MEYER: While Dr. Johnson is working on that, I think just to clarify that these were a priori

criteria that were applied. So when patients met them, they were discontinued. It's not that they discontinued the medication. It's that by trial design, they were discontinued from the trial and then treated appropriately as per the investigator's usual asthma care.

DR. KELLY: What they used were similar to what the ACRN has actually used in some of their trials in terms of getting to a really inadequate control. What I was saying more is not completely inadequate control, but what would we define as controlled asthma?

DR. MEYER: I think Dr. Johnson has those criteria. But I think perhaps on the first bullet, one might argue that's pretty bad control when you're using more than 12 puffs on two consecutive days. But I think that two nights awakening or the peak flow criteria really get at lesser amounts of destabilization.

DR. KELLY: These are or.

DR. MEYER: Or.

DR. SESSLER: Dr. Apter?

DR. APTER: I think one dose that I would be interested in and that primary practitioners might be interested in, since presumably they would see the more

mild population than the specialist, would be a dose of Advair 100 at bedtime. Since there's a diurnal variation, they may benefit from the salmeterol overnight, and that would be a way of stepping up from straight beta agonist to the introduction of inhaled steroids, and it might be interesting to know whether that would be useful alone.

DR. SESSLER: Any comments, Dr. Johnson?

DR. SUSAN JOHNSON: I think, obviously, that that would require a new formulation of Advair. The single daily dose would not be consistent with the salmeterol dosing, obviously.

DR. APTER: Yet people do use it that way.

DR. SESSLER: Dr. Gross?

DR. GROSS: I think we should spend a little time talking about the question of flexibility of dosing. There's a lot to be said about this, and I'd just like to raise a couple of points. I think you'll find there's some difference of opinion about this on the committee, too.

I think that the option of three different levels of fluticasone going from 100 to 500 does indeed provide us with some flexibility. I'd like to see the smaller dose. I think that probably the highest dose should not be very much used, except in the really exceptional cases. But I definitely think a smaller dose is needed for pediatric patients.

I think in general that weighing up the advantages with the disadvantages with the slightly reduced flexibility as compared to what we currently have, I think the loss of flexibility is not all that great because, as Dr. Shah mentioned, we do actually cover most of the range that we'll need to use in clinical practice. But I think that the advantages of the combination outweigh the fact that there is some loss of flexibility.

I would also like to say that I think there are two other things we should bear in mind. One is that in actual practice right now, where we have infinite flexibility of dosage, my impression is that there is very, very little alteration of the dose once a patient gets put on a therapy, and in the case of most patients who are not seeing specialists, it seems to be the exception that the dose is ever modified once the patient has been put on it. So we would not lose any flexibility in that group of patients, certainly, because it's all being exploited currently.

I would also say that I think that the place where flexibility is most needed is when the patient's clinical condition changes, when they get much better or much worse, and I think that there is a potential problem

when a patient goes into an exacerbation or at least gets a deterioration in their control. What do you do about

increasing the amount of steroid that the patient is getting? I think that might be a little bit of a dilemma for the clinician if they feel comfortable or knowledgeable about changing the Diskus that the patient is receiving, and then that raises the question of what happens to the one they've been using already. It probably goes into a closet and stays there and gets wasted.

What happens to the new one after two weeks when the exacerbation is effectively treated? Do they throw that away and then re-start on the original one? There's probably going to be some extra cost, some waste involved there, but I think these are relatively minor points as compared to the major one, which is that probably control will be improved by having the combination in the first place. So there won't be too many occasions where the real need to intensify steroid therapy will actually come up.

Let me leave it at that, because I'm sure that

there are plenty of other things that the rest of the committee wants to say about that.

DR. SESSLER: Dr. Joad, and then Dr. Ford.

DR. JOAD: I just had a question about your conclusion that it was safe and effective. Do you feel that the safety, knowing that long-term safety issues are osteoporosis and growth problems, do you feel like they've

addressed that adequately? They were very short studies, no measurements of growth, no looking at long-term effect on eyes, that sort of thing.

DR. SUSAN JOHNSON: I think that in general we agree with the sponsor, that there is a significant body of data available for the individual agents, and without having seen any increase in systemic bioavailability with the Advair combination or any other indications that there would be enhanced safety complications with the combination formulation in particular, we didn't feel that there was a need to have additional safety data such as you're talking about. In other words, the characterization of the drug in previous formulations did supplement what we do know about Advair.

DR. JOAD: And just a comment, that it seems like salmeterol does change the effect of the steroid once it enters the cell and would not be picked up by pharmacokinetics.

DR. SUSAN JOHNSON: And that being an enhanced efficacy probably would not have a negative safety outcome. That would be our expectation.

DR. MEYER: I think I'd also add that those are in vitro data, and until we see some clinical sign that that's actually true either from the safety or efficacy standpoint, I think it remains rather theoretical.

DR. SESSLER: Dr. Ford, and then Dr. Fink.

DR. FORD: I have a question, which is as much a comment, perhaps, in regard to the titration issue. I wonder whether it is possible, in order to give not only coverage of the entire persistent asthmatic population, and also to address the titration issue, to think about concurrent development of a 100 fluticasone-alone Diskus, because that might address the needs for the mild persistent asthmatic population and also might serve as one

of the options in terms of titration in certain situations. I wonder whether this is something that is worthwhile thinking about, and it doesn't change the actual delivery device.

DR. MEYER: I'll take this opportunity to address what -- I'm not sure anybody has really picked up on it, but one of the comparison arms that we were talking about here was fluticasone Diskus, which is not currently available in the United States, but I think the company feels comfortable with me acknowledging that we have seen efficacy data and we feel that, from a clinical standpoint, it's an approvable product. So it's likely that that product will be coming in the not-too-distant future. Of course, the Flovent powder question, there is a rotadisk dose that is comparable to that.

DR. SESSLER: Dr. Fink?

DR. FINK: Is there any data on drug-drug interactions with this combination, particularly looking at the leukotriene modifiers of the macrolide antibiotics?

DR. SUSAN JOHNSON: Not submitted to our application that we reviewed in detail. Perhaps the

company would like to respond to that in terms of other formulations.

DR. DALEY-YATES: Dr. Daley-Yates from Glaxo Wellcome. We have looked at drug interactions of fluticasone itself, and there's some detail in the current labeling. As far as the relevant ones you mentioned, we have looked at an interaction with erythromycin and no interaction was seen. We haven't looked at leukotrienes, but we don't think there's any theoretical basis for interactions of that type. So both salmeterol and fluticasone metabolites by cytochrome P450 3A4, that type of interaction you might expect, and we've seen it with ketoconazole and other known 3A4 inhibitors.

Is that sufficient information?

DR. SESSLER: Thank you.

Now, Dr. Dykewicz.

DR. DYKEWICZ: Actually, two questions. One just to kind of continue on, or maybe one's a comment, one's a question.

To continue on with what Dr. Gross has raised,

and this was the concern about lack of flexibility, if you will, of dosing to the corticosteroid component with fluticasone in the Advair device. I am of similar mind on this, that I don't think it's a major problem, because if we look at the dose responsiveness, the dose-response curves to inhaled corticosteroids, we know that it's not steep, and what we're looking at, then, with the 100 versus the 250 versus the 500 dosing of Advair is a doubling or two and a half-fold increase in the amount of steroid dose, and I think that may be the amount of gradation where you're really going to have to have a change in order to see that there's some clinical impact.

So although it's true that you're not going to have the discrete titration on the basis of number of puffs that you may have with the metered-dose inhaler, let's say, I don't think practically in clinical terms that's of great consequence.

The second point was a question. It may be a little bit of a side-tracking, but it was something that was raised in reviewing the briefing document that you had provided to the committee, and that was looking at the analysis of concomitant use of nasal fluticasone in studies 3002 and 3003. Although there was not a consistent finding, it was a kind of a recurrent finding that there may have been some additional benefit or improvement in

patients who were receiving some concomitant nasal fluticasone. Would you like to review or comment on that?

DR. SUSAN JOHNSON: I don't have slides to show you that represent that data. I think that your characterization is very appropriate. I also would just add that, like the inhaled corticosteroid versus salmeterol prior use data that I showed you, those analyses were very speculative. They were not done with statistical analyses because of the numbers of patients and the way in which patients were stratified. So without using them to define a hard and fast conclusion, your characterization of them is adequate, I think.

DR. SESSLER: Dr. Niederman?

DR. NIEDERMAN: I just wanted to go back to understanding the question I had asked earlier and your interpretation in relation to prior therapy. I'm looking at the sponsor's proposed appropriate populations. There really are no data to support the idea that this product should be used for patients who are inadequately controlled on bronchodilators alone, that this product would be any better than using -- and that population was only studied, I understand, in the 3002 study. In all the other studies, patients were inadequately controlled on inhaled corticosteroids.

25 For one study where inadequate control on

1 bronchodilators was studied, adding fluticasone by itself
2 was really no different than using the Advair. So is there
3 support in the data that this product is better than
4 inhaled corticosteroids alone for the population that
5 they're proposing, uncontrolled on inhaled bronchodilators
6 alone?
7 DR. SUSAN JOHNSON: With regard to your
8 question, let me just clarify that these patients probably
9 can't be characterized as being uncontrolled on their
10 previous therapy. They were relatively stable on their
11 previous therapy. So the entire question of whether
12 uncontrolled patients should be placed on Advair is not
13 really addressed by the trials.
14 With regard to the issue of previous
15 bronchodilator use, the trial 3002 is the only data that we
16 have seen relative to that.
17 DR. SESSLER: Dr. Vollmer?
18 DR. VOLLMER: Two comments. One of them, I've
19 heard repeated the use of the phrase "use of bronchodilator
20 agents alone." That doesn't distinguish between short-

acting beta agonists and salmeterol, and I think that how you would propose this, if you are going to recommend it for one of those two categories or for either one of them, there would be in my mind a clear separation, that I would feel much less comfortable advocating that you jump

immediately to Advair from simply using short-acting beta agonists and taking the salmeterol. Whether you even want to do it in the latter case is a separate issue.

I would ask for a little more clarification. Again, I'm not a clinician, but as I read the eligibility criteria, I would have thought these patients weren't well controlled. Their baseline lung function was extremely low, they were all exhibiting strong variability on lung function, and the indications for kicking you out of the study was severe lack of control, I would have thought. It was more than three or four days a week where you had -- well, that was once you were in the study, right? But there was the criteria for getting you out at the baseline that was separate.

I looked at that and thought you could still be

having quite a lot of symptoms and still be in the study. So I would welcome, as a non-clinician, somebody else's views on the severity categorization or the level of control of this population at baseline.

DR. SUSAN JOHNSON: I guess I would just make the comment that the patients' previous therapy had led them to not have significant exacerbations or significant medical treatment. They had been on stable doses prior to entry into the trial. So the term "stable" might be too gross for this metric, but, in fact, they were not patients

who were enrolled in the trial particularly because they were extremely symptomatic or were having problems with their previous therapy.

I also want to reflect back on your first comment, which I think is extremely important. If you look at the full-blown version of the questions, we do actually ask you to address the long-acting versus short-acting prior therapy question in terms of defining patient population. I think we think that's also a very important issue.

DR. MEYER: I guess one other point I'd make on

your question rather than your comment is that if you looked at the entry criteria, if you enrolled at the extremes of those criteria, you'd be talking about a much different population than what the population ended up being. So I think, yes, if you look at the entry criteria and look at the lower bounds of FEV1 and some of the other things that are allowed, one might conclude that that might be a fairly moderate to severe group. But, in fact, those are not typical of what's enrolled in these trials, and the FEV1 is much more in the upper range rather than the lower range, typically. I think that was true for these as well.

DR. SESSLER: Dr. Gross?

DR. GROSS: I'd certainly agree. I think these are indications of the patient deteriorating quite

significantly. So from a clinical point of view, I'm not sure I would accept these criteria, or criteria as severe as these for discontinuation. But from the scientific point of view, we're comparing four separate treatments. Is that right? We're looking at four separate treatments. So if you're using the same yardstick for each of those

four, then it really doesn't matter.

DR. VOLLMER: No, my point is not -- the between-group comparisons is perfectly valid, but in terms of inferring from these studies whether you can make the recommendation that a patient on salmeterol who is poorly controlled is a good candidate for this depends in part on whether we think we've studied patients on salmeterol who are poorly controlled. If we haven't studied such patients, then we haven't got the evidence to make that inference. So that's why I'm trying to better understand the patient population, and I guess what I didn't see well was a good characterization.

I would welcome it if you have some data on this, of the actual people who got into the study, as opposed to those who met the initial criteria for run-in and what they looked like, and the number of symptoms, and their FEV.

DR. SESSLER: Dr. Boushey would like to make a comment, and then Dr. Ford and Dr. Joad.

DR. BOUSHEY: Thank you. Just on the issue of whether patients uncontrolled on beta agonist therapy alone

qualify for combined therapy, the guidelines are explicit that they do. In a patient who presents, as many patients do, with very poorly controlled asthma and all they've been taking is beta agonists alone, you need not first give just a low dose of inhaled steroid and prove them responsive before advancing them to the next stage.

The guidelines are written for the severity of disease, which does not require that they be on a lower level of therapy before they are candidates for a higher level of therapy. So a person doing poorly on beta agonists alone is appropriately treated with a combination of therapy according to the current guidelines.

DR. NIEDERMAN: That may be, but there's no data we saw that that's been tested with this product.

DR. BOUSHEY: May I ask Dr. Shah to speak to that, because he would know that. I don't.

The second point I want to comment on is Dr. Kelly's, and that is what we mean by asthma control. People have struggled with trying to come up with a single score for asthma control, and various people have proposed them. Liz Juniper has proposed one that's been validated and published. The elements included in her score are FEV1, symptoms over the previous days, and beta agonist use

over the previous days. She comes up with a composite score based on a two-week recall of symptoms and beta agonist use and the FEV1 on presentation. So that's one single score. There are various attempts to reduce this.

But the elements of all these controller scores are FEV1, peak flow, beta agonist use, symptoms, and some use nocturnal wakings. Since all those endpoints improve with this combination therapy, I think it's likely, almost certain, that these composite scores, where they calculate it, would improve as well.

DR. VOLLMER: Before you get to the other point, a clarification, if I might. I know the guidelines lay out severity criteria based on symptoms and lung function, a variety of factors. My recollection would be that not everyone poorly controlled on beta agonist alone would immediately jump into the moderate or severe category. Just for some people the guidelines say it's appropriate, but not all people.

DR. BOUSHEY: It depends on the severity. But my point is just that if they're quite poorly controlled on beta agonist alone, the guidelines permit, in fact instruct, that you go right to the treatment for moderate severe asthma. You don't have to first give the treatment for mild persistent asthma and then step up. If a person presents with severe asthma and all they've been taking is

a beta agonist, the guidelines say you can give them prednisone, inhaled steroids at high doses, long-acting beta agonists. You don't have to go up step-wise. In fact, we would discourage that. We think you should go right to the proper level.

DR. VOLLMER: I think that point is well taken. The point that I would hope we all keep coming back to is when we get to the labeling and how it's written in there, that we be careful about blanket statements. If it's phrased the way you've stated it, I have no problems with that. If it simply states that the patient is not well controlled on beta agonists, or is a candidate for this, then I might take issue with that statement.

DR. BOUSHEY: Well, I'm not part of Glaxo, but I understand their proposed labeling to be for patients in whom combination therapy is appropriate, and that is, by implication, I think a reference to the guidelines.

DR. SESSLER: Dr. Shah, did you have anything that you wanted to add briefly? And then Dr. Ford, and Dr. Joad.

DR. SHAH: Yes. We realize that the question

about clinical evidence, that the patients who are on short-acting beta agonists alone, is there benefit of using these two drugs together compared to the individual agents? There is a study published that we had conducted with these

two drugs separately, given in patients who were only on short-acting beta agonists but who clearly had the criteria for moderate to severe asthma as defined by the NIH guidelines.

In those patients -- it was a study published in the Annals of Allergy and Immunology by Dr. David Pearlman as a first author -- we showed very clearly that treatment with the two drugs together provided much greater improvements in lung function in patients who were receiving the two drugs together than the individual drugs alone.

Additionally, again, we're not able to present these because we're not connected to the presentation equipment, but we also had subsequently done a study -- we have an HFA MDI formulation of Advair in development currently. We have specifically designed a study to look at those patients who are on short-acting beta agonist but

have moderate to severe disease. These are data that the FDA has not yet had a chance to review in detail because they're all preliminary, but we had agreement from them that if this issue came up, that there would be an opportunity for us to present those.

Again, we can do it maybe later on if we have time, but the data again confirm that giving these two drugs together in these patients does improve asthma

control better than the use of these individual drugs.

DR. SESSLER: Are the Pearlman data in the materials?

DR. SHAH: There is a reference, but it's not presented as the full data. It was provided as part of the FDA package that we submitted on the product.

DR. SESSLER: I think it's an important question, and I don't know if you'd be able to provide that for the beginning of the afternoon session or not.

DR. SHAH: Certainly.

DR. SESSLER: I think it would be of interest for the committee to have that.

DR. SHAH: I'd be happy to do that.

DR. NIEDERMAN: But just to clarify, you are requesting in your labeling that asthma, without specifically referring to severity, that is "uncontrolled" on inhaled beta agonist be a candidate for this medication? The labeling you're requesting is not confining this to moderate to severe, as in the patients in this study? You would include mild asthma as candidates for this medication in the way that you've requested in the labeling?

DR. SHAH: Well, I think the label that we provided actually would exclude mild patients, because what we're saying is that this product is appropriate for patients in whom combination therapy is appropriate.

DR. NIEDERMAN: But for a family practitioner, that's a fairly vague statement.

DR. SHAH: Well, I think the point would be that if a physician believes that a patient can be managed with a single medication, they are unlikely to use a combination product. This is something that they're clearly doing now, and as Dr. Fuller presented data from Europe, where the indication is actually very similar to

what we're proposing, the use of the product has been primarily in the more moderate to severe patients, which is what we're all discussing, and we believe that this is the appropriate patient population.

DR. NIEDERMAN: Would you want to add that to your label, or would you want to leave it more vague, as you've proposed it?

DR. SHAH: I think the only concern we have is that clearly none of the products currently have any reference to the guidelines and how the product should be used. That's a different question on whether that is or is not needed. But on the other hand, I think the point that we also know is that if you look at the diagnosis of asthma in terms of severity, what's occurring is that patients are underreporting their symptoms and underreporting their severity, and the risk is that by restricting it to strictly moderate to severe patients, many patients who

could really benefit from a product like this will potentially not be considered candidates.

All we're asking is what's occurring now in the

appropriate use of this product, that for patients who do have moderate to severe asthma, if they're being undertreated, that it would be medically appropriate for these patients to receive this product.

DR. NIEDERMAN: I don't think anybody is saying they couldn't get the product. The question is should they get a shot at monotherapy with an inhaled corticosteroid, and if that doesn't work, then go to combination therapy?

DR. SESSLER: Maybe a point of clarification, and, Dr. Meyer, you can help me if I misstate this. But there's a dynamic process that involves the sponsor and FDA primarily, with input from the committee, as to the labeling, so our concerns would be heard in that regard. Is that right, Dr. Meyer?

DR. MEYER: We'll certainly consider the input that the committee provides. I think it's also important to point out that the indication in the labeling has to be based on the data that's available to us in the NDA.

DR. SESSLER: Thank you.

Dr. Ford, you've been waiting patiently. No? Okay.

Dr. Apter?

DR. APTER: Two points. One is, with all the questions about how to titrate up and how to titrate down, and if physicians will titrate down, those would be the basis, it would seem to me, of postmarketing studies. It would be very interesting to know how clinicians use the medications and the outcomes of what they do.

The other point is that Flovent Diskus is about to be available in the same denominations as Advair for the fluticasone part, correct? Fifty, 100, and 500. Fluticasone MDI is available at 44, 110, and 220. I don't know if the company and the FDA would consider some form of tracking those doses, because I do think it will be confusing for both patients and clinicians alike who aren't familiar, if polka dots to track across the moderate range, something to track across those three medications.

DR. MEYER: First of all, I want to clarify that I used a fairly vague term about the availability of the Flovent Diskus. But I think I'll turn to the sponsor if they want to comment on the dosage strength of the product. But it's somewhat different from what you just said.

DR. SHAH: Right. For Flovent Diskus, the strengths that have currently been submitted to the FDA are 50, 100, and 250. We don't have a 500 Diskus currently submitted to the FDA for Flovent Diskus alone. That is

something that potentially we're thinking about doing in the future.

DR. SESSLER: Thank you.

Dr. Joad?

DR. JOAD: In general, I would really like the package insert to reflect the nomenclature that we're now using with the guidelines, and as part of that, I really think moderate to severe persistent asthma needs to go into the indications because of exactly what's been said. There are some people who are going to come in on short-acting bronchodilators who fit into the moderate to severe persistent asthma who should go on it, and there are those who don't who should not go on it, and that's pretty much agreed upon, and it fits the data that the company provided, as far as I can tell. It seems to me that should be part of the labeling.

DR. SESSLER: Dr. Vollmer, did you have anything that you wanted to add?

Dr. Fink?

DR. FINK: I think for the mild asthmatic, the mild persistent asthmatic, I'm less concerned about the use of this product. I think those patients tend to be under-classified and undertreated, and if the data supports what

was shown, which is that the addition of salmeterol may let you get by with a lower dose of steroid, I'm not sure there

is any reason to be concerned about using Advair 100 in a mild persistent asthmatic rather than using a potentially higher dose of fluticasone alone. So I really don't have a concern about the labeling for the mild asthmatic.

DR. NIEDERMAN: Although in the study, if I understood it right, the doses for the mild patients with the fluticasone was the same whether it was with or without the salmeterol in that 3002 trial.

DR. SUSAN JOHNSON: That's correct.

DR. FINK: In that particular trial. But the other data looking at fluticasone with the addition of salmeterol showed that you had a "steroid sparing effect," if you want to call it that.

DR. SESSLER: I have a quick question that may help, I suppose, with this issue for the sponsor. That is, were patients categorized either in advance or post-hoc into mild persistent, moderate persistent, and severe persistent asthmatics by any of the data that were

collected at enrollment time?

DR. SHAH: Actually, the inclusion criteria, if you go by the guideline classification of asthma severity, which includes lung function and symptoms and rescue therapy used, all of these are or's, meaning that if you have one or the other, you're classified into that severity category. Because of our inclusion criteria of FEV1 being

less than 80 percent of predicted, indeed everybody would be fitting into a more moderate persistent asthma. We haven't yet specifically studied mild persistent asthma with Advair in the context of this program.

But we do have clinical data -- and I was just told that our slides are now available -- in patients who clearly are on short-acting beta agonists that have mild asthma that the combination of these drugs does indeed result in better improvements in the control of asthma than the individual drugs. If those data would be of any benefit for the panel members, we're more than happy to review those.

DR. SESSLER: I think now would be a pretty good time to go ahead and show those data, if you have

them.

DR. SHAH: This is, as I said, the study that was published in the Annals of Allergy, and it was a study with Dr. Pearlman as a first author where we compared patients who were on short-acting bronchodilator therapy at baseline, and FEV1 criteria for inclusion was 50 to 80 percent of predicted, which, as per the guidelines, would be moderate to severe persistent asthma. We had a comparison of the treatment groups, and in this study of placebo, salmeterol administered alone -- these were all with the MDI. Two doses of fluticasone, the 88 and the

220, and the concurrent use of these two doses of fluticasone.

This was administered for four weeks, and we looked at FEV1 as well as serial FEV1 results in this study, as well as other measures. What the study showed was that -- these are the results of mean change in FEV1 from beginning to end of the study across the treatment groups. What you see is a consistent trend that we have shown previously, that in these patient populations, the

lowest dose of fluticasone is really all that's needed to provide comparable benefit, and higher doses are not beneficial more than the lower dose in these less severe patients.

However, when we gave these two drugs together, irregardless of whether it was with the low dose and salmeterol or the high dose and salmeterol, you had almost double the improvements in lung function in these patients compared to the use of these individually. Despite the small number of patients -- this was really a pilot study done at the time -- we demonstrated these were differences that, because of the magnitude, were statistically significant in the individual drugs.

If you look at the 12-hour serial FEV1 -- so this is results at the fourth week. We administer a dose in the morning and then monitor lung function over the

course of 12 hours at that time in the study, at four weeks.

What we clearly see in this study again is that the two combination treatment groups provided significantly greater improvements in lung function over that 12-hour

duration compared to the individual drugs. Indeed, as I said, the improvements here are substantial. I mean, a 1-liter improvement over even the lowest dose of FP with salmeterol provided that degree of benefit.

DR. SESSLER: Could you -- I'm sorry. If you have another slide, go ahead.

DR. SHAH: Well, as I said, we now have an HFA program where we looked at the same population, and the results are identical. As I said, the FDA did not have a chance to review these data, but we had agreement from them that if this issue came up, that we would be able to share some of these with you. Again, these are preliminary data. What I have is the primary efficacy measures for these studies. The secondary efficacy measures are still being reviewed and validated, so I don't have those at the present time to share with you.

But this was a study where we looked at the 42/88 dose of the Advair HFA and compared that to FP 88 and salmeterol 42 individually, again in patients who were on Ventolin, and inclusion criteria would have placed them in

the moderate to severe category according to guidelines. In these patients, we looked at the primary endpoint of change from baseline in morning FEV1, a pre-dose FEV1, as we've done before, and a serial FEV1 AUC.

Again, we see that this combination product, the HFA product resulted in significant improvements compared with the individual components, and this improvement was about 200 mLs, which I think would represent a clinically meaningful difference for most patients as well.

Again, if you look at area under the curve, we saw the same results over the 12-hour dosing at 12 weeks with the combination, which provided much greater improvements in the lung function over the course of 12 weeks of therapy compared to the individual agents.

So I think clearly there is evidence to substantiate what is currently occurring in clinical practice and is advocated by guidelines, that in patients with moderate to severe asthma, even if they're treated with short-acting beta agonists, the use of these two drugs together does provide much better control than the use of these drugs individually.

DR. SESSLER: Thank you.

DR. NIEDERMAN: Now, Curt, or Dr. Shah, if I understand, those findings aren't in some ways inconsistent

with the 3002 data, because if you look at the FEV1 parameters which you have here on page 54, it looks very similar, but if you look at the clinical parameter of withdrawing due to worsening asthma, that's where the differences don't appear with the fluticasone versus the combination. So I guess they're not really different data from what you've already presented in the 3002 study, but you don't have the worsening asthma endpoint that you've shown us in this trial.

DR. SHAH: Correct. These studies did not have withdrawal criteria to withdraw patients because they were all getting active treatment, and they were all on short-acting beta agonists, and we've previously shown that even salmeterol alone in these patients over a period of three months provides significant improvements over baseline. So we didn't expect patients, and indeed we didn't have many patients who withdrew due to worsening exacerbations.

DR. NIEDERMAN: Whereas in the other populations, you had differences in both lung function and withdrawal. Again, in this 3002 study, you did have the lung function differences that didn't correlate in differences in withdrawal. So the fact that you have this other study in which you've just shown differences in function but no data on withdrawal, I'm not sure if it

changes the data available to us in answering this

question.

DR. SHAH: I think what I would also just want to make a quick point on was that in these studies that we designed to look at the effect of salmeterol, the relevant comparison should have been on the serial FEV1 data because of the known effects of salmeterol in improving lung function. So those were the focus for that comparison. The real comparison for the withdrawal was between the Advair group and the Serevent group, because we expect the fluticasone component of that product to control inflammation, resulting in improved control of asthma in terms of exacerbations, and that's really why the differences between those two groups do not appear to be as marked in that study.

But I think we have to realize that that study was specifically designed, and that endpoint was not the relevant comparison for Advair and FP in that analysis. It was a serial FEV1 comparison which was the relevant comparison. In that comparison we did show, as Dr. Johnson presented, numerically greater improvements in the Advair

versus the FP-alone group, which is what we would expect to see with the long-acting beta agonist.

DR. SESSLER: Thank you.

Are there any last questions for FDA, in particular for Dr. Johnson's presentation?

(No response.)

DR. SESSLER: Let's go ahead and break for lunch. We'll come back at 1:00 for the agenda items for the committee discussion. Thank you.

(Whereupon, at 12:02 p.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:02 p.m.)

DR. SESSLER: Good afternoon. I'd like to welcome everybody back. I think everybody thought I had a really big mouth and a loud voice and didn't need to turn the microphone on, but thanks for turning it on. I'd like to welcome everybody back to the open committee discussion now on Advair Diskus, and I'd like to review the agenda in a little bit of detail here, just so that we all know what the afternoon's discussions will entail.

First, there will be a discussion of background material that will be summarized in comments by Dr. Meyer,

and those of you who have the agenda will see the title here, "Discussion Background for the Committee," and then a few key discussion points. We'll spend a little bit of time with that.

Following that, we will address a series of questions that have been posed to the committee. As you can see, the first question is really a key question and basically asks the question of approvability of the drug, and my comments here are directed largely to the committee. I want to make sure everybody understands fully about that particular point. What we'll be doing is having open discussion about this question, and then I will actually ask for a vote. We'll go around the table with a nay or yea response and any discussion at that time.

This question really addresses the approvability and, in general, addresses whether the drug is approvable for any of the indications that we've discussed today, and you can see that on the second page, these specific areas, specific indications really, are addressed in more detail. So if we have a response that is

a positive response, as you can see, we would go ahead to Questions 2 through 5.

The second question really deals with some of the population questions that we've discussed with previous comments: Patients inadequately controlled on short-acting beta agonists alone, et cetera, et cetera. So there are four different categories there. I will take each of those in order, and we'll have open discussion about those, and then I'll basically poll the committee again for a yea or nay sort of view on these, although this will not be as formal a vote-taking as we will take actually on the first question.

We'll then address numbers 3 and 4. If the Question 1 is responded to in a negative fashion, we'll jump to Question 5 for discussion of that. Then we'll finish today's activities with the question on pediatrics, which is the sixth question.

So that is the basic outline of the agenda, and I wanted again to have it laid out in advance so everybody

has some clear understanding of where we're going to be going with the various questions today.

So I'd like to turn to Dr. Meyer for a discussion of the background material for the committee, and obviously this is material that we've been reviewing all day and have reviewed in advance of the meeting, but also I think to emphasize a few points and offer his comments.

Dr. Meyer?

DR. MEYER: Thank you.

First of all, I did want to make clear, and it is in your background document, what the fixed-dose combination drug policy is for the FDA as contained under 21 CFR 300.50. That states that two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect, and the dosage of each component, the amount and frequency, is such that the combination is safe and effective for a significant patient population requiring concurrent therapy as defined in the labeling.

Again, the sponsor's proposed indication states that Advair Diskus is indicated in the maintenance treatment of asthma as prophylactic therapy in patients where combination therapy is appropriate.

This raises a few key discussion points, some

of which have already been touched upon, but I will go through the ones as we've laid them out here.

Number one, given the variability of asthma and clinical circumstances which arise in the treatment of asthmatics, what are the advantages and limitations of a fixed-dose combination in the practice setting?

Secondly, is the inability to titrate within a single strength of Advair -- that is, to increase the number of puffs temporarily for increased symptoms without changing the device, is that an important limitation that will be acceptable in actual use and understood by patients and caregivers?

Another key discussion point is how will caregivers and patients best assess the optimal corticosteroid dose in the face of an effective long-acting bronchodilator to assure that the fluticasone component is neither overdosed nor underdosed?

So those are some of the key discussion points or things that we thought might be worthy of the committee discussion. Again, some of those have been touched upon, but that might be nice background discussion to the formal questions.

I do want to make one other comment with regard to some of the discussion about the FDA perhaps labeling this product specifically in reference to the NAEPP

guidelines. I think it's important to understand from our perspective that perhaps we would not want the labeling to be inconsistent with accepted practice and guidelines, but as was stated at the recent meeting of the NAEPP, those guidelines are seen as a living document; i.e., they're subject to change. Therefore, I think there are some concerns about putting something into the label that refers to a version of the guidelines that may change in the future.

The other thing is that I think that having a label adhere too closely to the guidelines would perhaps put us in a situation where there's either a tacit endorsement of the agency in terms of where this drug best fits into the practice of medicine, or a tacit restriction, and I don't think we see that as our role, to be either tacitly endorsing or restricting the practice of medicine.

DR. SESSLER: Thank you.

What I'd invite now are comments that center, to a certain extent, around the key discussion points that Dr. Meyer has outlined, and relate in general to the first question. So it's a bit open-ended, but I'd like to invite

committee comments as it relates to these areas.

Everybody is shy this afternoon, falling asleep, big meal.

DR. FORD: I think it's after lunch.

DR. SESSLER: Please.

DR. FORD: I think our charge was to think of advantages and limitations. In terms of advantages, clearly, at least it's an opinion here, having both drugs combined into one product will likely improve adherence, although we do not have the data where that has been specifically tested as a hypothesis.

In addition to that, it is clear from the data we've seen today that there are some benefits to having the two drugs together in terms of the rapidity of onset of action. The device with which the drug or the combination is delivered is relatively easy to use, although we have a big job ahead of us in terms of really training providers to not be more confused than they currently are in terms of the variety of delivery devices that are available to them.

On the other hand, there are some limitations. I think there's been a lot of discussion about the

titration issues, and I think that the labeling should reflect that and perhaps provide some suggestions in terms of alternatives that are available in that regard. One minor issue might be -- well, the safety profile is such that I don't think one would be concerned about situations where one would be trying to define what is the primary agent causing a toxicity. I don't think this is really relevant at this point.

So overall, I think that there are many advantages to this drug, and the major disadvantage is flexibility in regard to titration.

DR. SESSLER: Thank you.

DR. NIEDERMAN: Curt?

DR. SESSLER: Michael.

DR. NIEDERMAN: I would echo those comments, and I do think that this is a product that has potential for great value, and potential as well for abuse. I think that in thinking about the titration issues and the practicality to either go up or down, it seems very unlikely that this will easily be done. What it's going to

mean if it's an off-hour time and a patient has only Advair at home and they have an exacerbation, they need more inhaled corticosteroid, they're either going to have to be storing an extra fluticasone inhaler at home or try to get access to it, and I think that's going to, at least in certain situations, create the potential to use the combination medicine excessively.

I think certainly to answer whether that's a reality or not, there's going to have to be some very careful attention after marketing to look for the potential for overusing this, particularly in emergency situations. I think there will probably be some reluctance to change doses downward, and I don't know if it will be possible to

monitor. But I think that the advantages are clear.

The disadvantages are that patients are going to stay focused on whatever they're taking and try to use more or less of it, rather than titrating the different medications, which seems very cumbersome and very unlikely to be done in the real world. So I think if there's some sort of way to monitor that after this drug is released, both in terms of patients being overdosed or underdosed, I

think it's important that we watch that.

DR. SESSLER: Dr. Gross?

DR. GROSS: I think basically what it comes down to in the end is a tradeoff. Is it worth accepting the small risks involved to get the benefit of the imperative use of corticosteroids? There is some flexibility within the three dosage choice that we have right now, hopefully four doses soon. We've discussed the disadvantages of the slight lack in flexibility, but I think at the end of the day, one has to decide on the basis of the tradeoff. Is it worth it? And I would say probably yes.

In other words, I'd be prepared to accept the present situation and assume that we're not going to have exactly the right dose of steroid used on some occasions, but I personally don't think it's a big problem.

It's already been stated that dose-response to

steroids is pretty flat anyway, and at least this way patients will be getting some steroid whenever they use their beta agonist.

DR. SESSLER: Dr. Fink?

DR. FORD: I think the combination is of obvious benefit in terms of adherence. The titration is the thing that I think is most bothersome, and particularly in regards to point three, how will caregivers and patients best assess optimal corticosteroid control in the presence of a long-acting beta agent. I think that is a problematic issue in that if someone is well controlled on Advair 250 or Advair 500, how will you provide guidance to the average patient or physician that it's time to step down?

That really, I think, ideally should be addressed in the package labeling with some kind of recommendation that if a patient has been well controlled for three months or for some period of time, that an attempt to step down dosage should be made. I think to leave it too vague is to ensure that patients are never stepped down, and with the presence of a long-acting beta agent, I really think there should be some time constraint. I would suggest maybe two or three months of good control, then titrating down should be recommended.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I'm not sure how obvious the

advantage of putting them in one inhaler is. I think it's intuitively for clinicians an obvious thing, but I'm not sure that there's any data to support it.

Having said that, I think it's a good deal that they are in one inhaler, because I sort of believe that concept too, although I don't have any data to support it either.

I had a couple of comments about titration because I was involved a little bit with the guidelines, and particularly with developing the different dosing for the inhaled corticosteroids and this whole aspect of titration of inhaled corticosteroids. The guidelines do recommend what Dr. Fink just said, that after three months of good control, that you step down therapy. I think we're all concerned with the use of too much, particularly those who practice in pediatrics, the use of too much steroid when you don't need it, and if you produce a barrier to down titration, no matter how small that barrier might be, that might increase the risk of using more inhaled steroid than you need.

On the other hand, in terms of the flexibility of titration, I think that this particular combination of dosages provides, based upon literature, all the flexibility that you need. That is, you cannot find literature anywhere that supports reducing the dose or

increasing the dose that shows a difference in effect, if you don't at least double the dose of half the dose. When we do that -- and clinicians do less than that. They do these minor titrations. But in terms of the dose-response curve, we tend to use sort of downstream events from the inflammatory process, which are peak flow and FEV1. You can't see differences that are probably clinically significant if you don't at least double your dose or at least half your dose.

I think the ACRN study in which they took moderately severe asthmatics, added salmeterol and were able to reduce the dose in half of the inhaled corticosteroid without producing any adverse effects confirms that. It also confirms the fact that we probably overdose inhaled steroids to a significant amount in a lot of patients.

So I think the titration flexibility is there. The barrier to the titration is the fact that you have to buy another inhaler to do it. That's the barrier. But in terms of actual dose titration of patients going up and down, I think a lot of times what we see is we may reach a certain threshold dose in a certain type of patient, and once we reach that threshold, that's what they need. So

you can get into trouble by back-titrating too far in that patient because you go below their threshold. But again,

that's anecdotal data as well.

Having said all that rambling whatever it was, I'm actually in favor of this combination. I think it's shown to be as effective as concurrent therapy. It's not more effective than concurrent therapy. I think it continues to be a hypothetical advantage in terms of having it in one inhaler device, but if having it in one inhaler device simplifies anything to do with asthmatics and the delivery of inhaled corticosteroids in more asthmatics, I'm for it. So I'm for this.

DR. SESSLER: Dr. Joad?

DR. JOAD: I also am in favor of this product and see that the advantages outweigh the disadvantages. I'll have some comments about the product labeling, but I think overall it's a good idea.

DR. SESSLER: Dr. Apter?

DR. APTER: I, too, think the advantages outweigh the disadvantages, but I'll also be very

interested in being able to follow, perhaps as postmarketing, how clinicians use it, titrating up, titrating down.

I think when you talk about titrating down, the data I would be most interested in is what happens when patients go from 500 to 250, and with a large group, to make sure there are no systemic effects of steroid

withdrawal.

DR. SESSLER: Dr. Vollmer, anything to add?

DR. VOLLMER: No, I don't have anything to add to that. I would also favor approving the use of this, although I have concerns about labeling and postmarketing also.

DR. SESSLER: Dr. Dykewicz?

DR. DYKEWICZ: Well, we've kind of segued, actually, in terms of titration questions into this other point, how will caregivers and patients best assess the optimal corticosteroid dose if we're doing all this titration business. Of course, I think, as with all assessments of asthma, this should be done through a combination of looking at patients' symptoms, which by

themselves are not adequate to make a full assessment about the patient's status, in combination with peak flows and spirometry, and there should be some sort of a statement that might reflect that.

As I stated earlier this morning, I feel that the two-fold to two-and-a-half-fold dosage increments that this product would provide are the appropriate magnitude to use for seeing that there be a significant change in the patient's status, as Dr. Kelly has pointed out. So I don't believe that some of the inconvenience in terms of the ability to titrate is a major factor in that regard.

Obviously, we are talking about, again, in acute exacerbations, having to treat the patient acutely with some other device, some other medication product, but I think that's something that's doable. And again, looking at the advantages of this product for chronic treatment as opposed to the disadvantages of the product when you get into acute flares, I think the advantages do outweigh the disadvantages of it.

DR. SESSLER: Ms. Conner?

MS. CONNER: I agree and am in support of the combination with, once again, my focus on education, particularly technique with this device. Since there's no availability of a spacer oropharyngeal deposition of the inhaled corticosteroid, it's going to be probably more intense than it might have been with the spacer. So we need to make sure there's emphasis on rinsing, and also on the need for the availability of a short-acting beta agonist as rescue. Just so those points are emphasized.

DR. SESSLER: My opinion is that the safety and efficacy data are compelling from the clinical trials that were performed. I'm also encouraged by the safety experience with a higher dose of salmeterol from the experience, as well as some of the published reports. I think that's good in terms of misuse by the patient.

I think the titration issue is certainly

important, and personally I think that presents an opportunity to the sponsor to figure the optimal way to allow more precise titration of the steroid component with probably a second inhaler. Certainly this should not be an impediment to its proper use, and I think it will involve

another product to be used concomitantly in terms of adjustments up and down. But I think with something like that, and that doesn't seem to be excessively complicated, it should be effective in terms of allowing titration upwards and downwards.

I think the labeling obviously is key, and I differ a little bit from Dr. Meyer's opinion in the sense that I think we have embraced to a certain extent the terminology of mild, moderate, and severe persistent asthma, and mild intermittent asthma, and I think we do need to include that in some meaningful fashion, because I think that language has become part of our culture in terms of caregivers for asthma, as well as asthmatic patients. In fact, that may be one of the fine separating points in terms of some specific subcategory, such as the patient who is inadequately controlled by a short-acting beta agonist. I think the data presented are important to demonstrate that while it may not be of value for that individual who has fairly mild asthma, in fact it may be appropriate for somebody who has moderately severe asthma.

So I think I would encourage, I guess, revisiting the labeling issue as it relates to the terminology, given some of the limitations that were mentioned in terms of this perhaps being a moving target. Nevertheless, I think that those terms are pretty well entrenched right now.

What I'd like to do is see if there are any last minute comments. I think everyone has had a chance to express their comments, and what I'd like to do at this point is go ahead and go around and address the first question in a formal voting fashion. I'll read the question.

Given the efficacy data presented for the combination compared to the components alone and the hypothesized benefit of increased convenience and compliance, do the benefits of Advair as a fixed-dose combination outweigh its risks?

I'll ask for a yea or nay sort of vote, and I'll put Dr. Vollmer on the spot and have him start, and we'll go around the table, if you will. The voting members will be members and consultants, and that will be starting with Dr. Vollmer.

DR. VOLLMER: I vote aye.

DR. APTER: Aye.

DR. FINK: Yes.

DR. GROSS: Yes.

DR. JOAD: Yes.

DR. KELLY: Yes.

DR. DYKEWICZ: Yes.

DR. NIEDERMAN: Yes.

MS. CONNER: Yes.

DR. SESSLER: Okay, very good. Thank you.

So we can now, I think, ignore Question 5, having heard no no's.

Let's go ahead. I think there's a lot of material to tackle here, especially in Question 2, but also in Questions 3 and 4.

Question 2 is: For what populations of asthmatics should this product be indicated?

I was going to go down in a fashion where we would go from the top to the bottom, but it may be that the bottom two are fairly easy to tackle. Let's start with those. Let's start with patients already well controlled on an inhaled corticosteroid and salmeterol and actually work our way up.

What I'm looking for here is some discussion among the group, and then we will have a less formal show of hands just in terms of whether we feel that this is or is not indicated, and obviously there's going to be some

opportunity for hair-splitting here as far as subsets

within these four categories. But let's start with that, and I'll open it for comments from the committee.

DR. GROSS: Can I say something? It's a little bit hard to ask the question directly because it's this product. Does this regard as one product or three products? I mean, obviously the answer will vary depending upon which product you're asked about, or which form of the product.

DR. MEYER: They are technically three different products, but they will share a labeling.

DR. GROSS: There won't be differences in labeling?

DR. MEYER: The labeling may refer to the products within it specifically about dosage strength for a specific indication, but it will be a unified labeling.

DR. GROSS: There will be exactly the same hard label on each one of the separate products?

DR. MEYER: Yes.

DR. SESSLER: Any comments? Michael?

DR. NIEDERMAN: I'd like to go back to the

question we were talking about earlier, and that is if we look at the data in that 3002 trial, I guess I'm not convinced that, as presented in that trial, there's a compelling need for the combination therapy over fluticasone alone for the population that was studied. I

think that may need to be -- it's hard to define exactly who was studied and whether, for example, that lack of difference would have applied if a higher dose of Advair was used, so comparison of 100 to 100.

But I guess that I am unsure whether, guidelines notwithstanding, we want to be in a position where effectively we're saying that any asthmatic who shows up at a family practitioner's door saying that their asthma is uncontrolled on anything they've been using is an appropriate candidate for combination therapy. I think this is a very effective regimen certainly for the moderate to severe asthmatic.

I'm not sure that opening the door to anybody with asthma -- and I think the wording right now is very vague. "Anybody who is appropriate for combination therapy

or uncontrolled on any other medication" basically I think refers to all of asthma, and I don't know that we've seen enough data to convince that there's a benefit for all of asthma rather than some more well-defined populations.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I would like to agree with him in terms of the mild persistent asthmatics who have not been on inhaled steroids before, that there wasn't any compelling evidence. But again, I think it's a problem in those studies in how they -- there's a difference in

patients who come in uncontrolled on as-needed bronchodilator, and I think that's what we're all struggling with. Just saying you're uncontrolled on short-acting bronchodilator is way too non-specific because it can mean a lot of different things. I don't know exactly how to deal with that.

One of the ways, unfortunately, is going to the guidelines and saying that patients with moderate to severe persistent asthma and using that as a guideline, but they didn't use that as criteria to come into the studies. So that's a very difficult problem as well.

I agree, but I don't know how to deal with it.

DR. SESSLER: Let me take a stab at that. It seems that although patients were not specifically labeled as having mild, moderate, or severe persistent asthma as such, the entry criteria for the three studies that we reviewed in detail, as well as the short-acting beta agonist study that was presented later on -- correct me if I'm wrong, but I think all those patients met criteria for at least moderate persistent asthma. I think that's correct. So perhaps what we should do is address these series of hypothetical situations within that context. That would presuppose that the patient had at least moderate severity. In other words, the FEV1 was reduced by 80 percent or so.

It may be that that's easier to do, because I think the populations that were studied specifically do fall into those categories, and then maybe address these four within that context, and then come back and look at the more mild patients who obviously were not studied as of yet.

DR. NIEDERMAN: So your position is that you're saying that you would characterize the studies as not having studied mild asthma.

DR. SESSLER: That's right.

DR. NIEDERMAN: So you would specifically restrict this to moderate to severe asthma.

DR. SESSLER: Dr. Meyer?

DR. MEYER: Not to muddle the discussion too much, but the patients who were undergoing the FEV1 assessments for entry into these trials are washed out of their beta agonist prior to them being studied. I don't believe the guidelines refer to such a washout in terms of assessing the FEV1, so I'm not sure how neatly you can conclude that these patients would meet the FEV1 criteria or criterion for severity. It's not a simple fit.

DR. SESSLER: No, it's not. It's not perfect.

DR. JOAD: I think the guidelines are in the absence of a controller medication. So, if anything, they would be even worse, because in all studies, even the ones

who were on salmeterol, everybody in all those studies was always on a controller. So in the absence of medication,

they would have been even worse, if anything. So that would move them toward the moderate to severe guideline.

DR. MEYER: I'm not speaking to the controller, but my point is about actually having bronchodilator on board or not. These assessments for entry into the clinical trials are specifically done so that the bronchodilators are washed out.

DR. KELLY: And the guidelines are set up so the severity classification is without medication.

DR. FINK: But for these trials, weren't the patients' eligibility actually that you were inadequately controlled prior to washout? And the inadequate control would classify you as moderate persistent prior to washout.

DR. SUSAN JOHNSON: I was hoping that the company might be able to show us the eligibility criteria again so that we can show this information. But my understanding is that, in fact, they were not defined as uncontrolled patients in order to be randomized to this study. They were allowed to have an FEV1 between 40 and 85 percent of predicted normal after washout of their beta agonist, but not necessarily uncontrolled on their current therapy.

DR. FORD: I think that in reference to the

guidelines, the point that Dr. Kelly just made is quite appropriate, that the ascertainment of severity is made prior to therapy. So in that sense, a washout period might in fact provide the opportunity to make that assessment on that basis. But also, that range of FEV1 goes through mild, moderate, and severe. Above 80 in the guidelines is generally considered mild, although the classification which I was involved in developing as part of the committee is based on the clinical property that assigns individuals to the highest severity group.

So a number of measures were used in the studies that we've seen, and it may be that individuals on qualifying the basis of FEV1 being greater than 80 percent, but their symptom profile in fact puts them in the moderate to severe persistent category on that basis. Having said that, I think that the points that are being made are quite appropriate, that the labeling be done in such a way that we would avoid indiscriminate use of this combination therapy, and I think that the statement, as vague as it is, begins to get to the heart of it where it says "where combination therapy is appropriate."

But in all fairness, in real practice, there are documents that are being used to determine the appropriateness of combination therapy, and generally we define these individuals with moderate or severe persistent

asthma. I don't know a better standard for doing this right now, and I think that at a minimum, we should reference the guidelines in order to drive that point across.

DR. SESSLER: Dr. Apter?

DR. APTER: One of the difficult parts of the guidelines, and I think which also precipitates this discussion, is the distinction between severity off medicines, the severity class, and current control. "Out of control" can mean a lot of things. It can mean seeing them in the doctor's office, very much reduced FEV1, up all night, and that sort of out of control patient I wouldn't want to start on Advair that day. I would want to control them with prednisone and then perhaps start that medication.

So I wouldn't want people to think that that very out of control person would benefit from the immediate institution of that medication, which works more slowly.

DR. NIEDERMAN: It certainly seems possible to go back through the data and ask for the first study, the 3002 study, define a subpopulation who had an FEV1 of, say,

70 percent and better, and treated only with an inhaled bronchodilator, and see whether or not that group, when randomized, did any better with one regimen or another, or if that group was really even studied. I think we can

probably get some of the answers we want from a breakdown of who was actually enrolled in the study.

DR. JOAD: Just for some information, wasn't that mean FEV1 about 67 percent or something? Quite low, way below 80 I think for all the studies. It was like 67 to 70 percent or something like that, but it wasn't 80.

DR. DYKEWICZ: But there was a range.

DR. SHAH: That is correct.

DR. SESSLER: I guess from a labeling standpoint, the focus of the questions that have been developed by the FDA personnel really center around alternative therapy, it seems. In other words, if we take the one extreme that we started with, they're already well controlled on combination therapy, but it's with two different products, the question asks, I think, is this a reasonable individual to make the switch?

I think if you look at it in a way that's the

question being posed, this could be given as either an alternative or perhaps even a preferred alternative to some of the other possibilities. The importance, I guess, as I understand it, for labeling is that labeling needs to reflect the population studied. Is that correct? Or the indications, I guess. Maybe I should rephrase that.

DR. MEYER: Well, the labeling certainly has to derive from the data that we've been provided in the NDA.

Correct.

DR. SESSLER: Right. So it appears that all the patients studied met the criteria to have moderate persistent asthma simply by the nature of the fact that they had less than 80 percent predicted for their FEV1 at the time of enrollment. That was the rationale for me to try to steer this into a direction where we would address these same questions, but I can see how we would come up with many exceptions, especially to the first two categories.

For example, initially I thought there was no way that a patient who is inadequately controlled on short-

acting beta agonist alone should be given the combination therapy. The data that's presented showed considerably better air flow on the combination therapy, and yet those patients met criteria for moderate severity. So I would feel uncomfortable proposing the combination drug for mild persistent patients, but I would not feel uncomfortable with it for moderate persistent.

So I can see how we may get into that with each of these questions, where we're really subdividing it out.

DR. NIEDERMAN: Curt, I think the second and fourth categories are pretty clear. I think the studies show for the second and the fourth groups, as the studies were designed, there was a clear benefit. I think where

the questions come are for the first and third, and maybe that's where we ought to focus.

I don't know how the rest of the committee feels. I feel comfortable with the second and the fourth.

DR. SESSLER: Well, let me do this. I think that's why I started with the fourth one, as it seems like it's one of those that's less controversial certainly than the first, and maybe than the middle two as well.

Let me offer an opportunity for some more comments specifically on that question, and then I'm going to ask just for a show of hands and any qualifying comments that people might make, just as a way to kind of get that rolling.

Dr. Ford?

DR. FORD: I would like to comment on the third question here, patients inadequately controlled on short- and long-acting beta agonists. There was discussion --

DR. SESSLER: Let me come back to that, if you don't mind.

DR. FORD: I'm sorry?

DR. SESSLER: What I was trying to do, I guess, was just really focus on the fourth question, and then let's go ahead and finish the fourth one, and then we can head backwards to the third and address that in more detail.

So any other discussion really on the fourth? And this is patients already well controlled on inhaled corticosteroid and salmeterol.

So just a show of hands. Those who feel that this would be a reasonable indication, please do so.

(Show of hands.)

DR. SESSLER: And any who don't?

(No response.)

DR. SESSLER: Okay.

DR. KELLY: Assuming that the cost is reasonable.

DR. NIEDERMAN: Take number 2.

DR. SESSLER: If you don't mind, we'll take number 2, do the easy ones first, and then we'll get to your tougher one. Patients inadequately controlled on inhaled corticosteroids alone. Any discussion on that? So they're inadequately controlled.

DR. FORD: I don't have much to add. I think the data we see are compelling in favor of Advair here.

DR. SESSLER: Okay. A show of hands, please, those who would consider this a reasonable indication?

(Show of hands.)

DR. SESSLER: Any not?

(No response.)

DR. SESSLER: Michael?

DR. NIEDERMAN: No, no. My hand has a tremor, up and down.

(Laughter.)

DR. SESSLER: Dr. Fink, do you want to make a comment?

DR. FINK: I was going to say that the only comment I wanted to make there is when we say inadequately controlled, that obviously there should be some commentary there that we have looked at things such as compliance, environmental control, and other elements of asthma control that may contribute to inadequate control.

DR. DYKEWICZ: Let me just interject. I think we have to be practical here. Some of us are speaking from the specialist perspective. The vast majority of the prescriptions that would be given to patients are not going to be coming from specialists, and I think we have to be mindful that we should have a straightforward, simpler statement that could be easily interpreted by prescribing health care providers, and if we start equivocating too much and putting too much detail in here, I think we're not really going to meet the need of the prescribing health care provider.

I don't think we have to define this necessarily on the basis of NHLBI criteria. I mean, if we're asked the question, we were presented data about

patients who are on inhaled corticosteroids, and essentially we were given data that showed that there was significant improvement in the status of these patients. You could make the argument even on that basis that the patients were inadequately controlled prior to the initiation of the treatment with the Advair.

So I personally don't have any difficulty at all stating without equivocation that this is an appropriate treatment for patients inadequately controlled on inhaled corticosteroids alone.

DR. SESSLER: Thank you.

Okay, Dr. Ford, the third bullet, patients inadequately controlled on short- and long-acting beta agonist.

DR. FORD: Finally, you got to me.

DR. SESSLER: Thanks for your patience.

DR. FORD: I think there's been some discussion earlier particularly about the salmeterol subgroup in one of the trials, and I think that one word of caution here is that salmeterol, as far as we know, is not recommended for monotherapy. In that sense, again, I think this group would be treated similarly to the other groups in terms of assessing their severity at baseline and trying to treat

them in the way that is -- so Advair would be appropriate if combination therapy is appropriate. That is the

language we were given to look at, where combination therapy is appropriate.

Unfortunately, salmeterol is being used a lot out there as monotherapy, and if it's not working, I think Advair is a great option, and, of course, the other beta agonists.

DR. SESSLER: Dr. Fink?

DR. FINK: The one problem I have with the approach we're taking here is that we're sort of going to end up with a package label that says that patients are only treated with inhaled corticosteroids or short- or long-acting beta agonists, and what about those patients who are still receiving theophylline, leukotriene modifiers, and a variety of other drugs where this may or may not be an appropriate choice?

DR. NIEDERMAN: We don't have any data to go on to answer that.

DR. GROSS: One way or the other.

DR. NIEDERMAN: The trials weren't designed to answer those questions.

DR. SESSLER: Dr. Meyer, would you care to clarify on that?

DR. MEYER: Well, I do want to clarify that we will use your advice to help construct the label, but the labeling is not going to be written in such a prescriptive

manner that your concern would represent something that won't be real in the label. I understand your concern, but we don't write labels in such a prescriptive manner.

The way the proposed indication is currently written, it is, in my opinion, fairly vague, and we're trying to get from the committee an idea of how to work with the company to rewrite that to perhaps better define the population for whom the committee feels this drug really is indicated.

DR. SESSLER: It seems that the crux of the question here, I guess, has to do with the subsets from the two clinical trials of patients who were previously receiving salmeterol and not inhaled corticosteroids, and were then enrolled and apparently had a significantly

different response with the combination compared to just fluticasone alone. Is that correct?

DR. MEYER: I think that's a part of it. We can also look at the clinical trials data and draw some conclusions. I think we're also seeking your expert opinions about not just the data but how you feel from a clinical perspective, too. For instance, with patients who are coming in only on Ventolin, we've not reviewed those data, but it seems as if this combination product works. Now, a cannon would kill a squirrel, but do you really need a cannon to kill a squirrel when a bebe gun might work?

So we're looking for both reflections on the data, and again, we value your opinions, but I think we're also looking for your expert opinions as clinicians and researchers.

DR. SESSLER: Yes, I agree.

DR. KELLY: You have to be a better shot with a bebe gun.

(Laughter.)

DR. MEYER: Point taken.

DR. NIEDERMAN: But along those lines, do the data in the first study meet the FDA requirements for combination therapy? Is it convincing that both components are necessary, as opposed to just the fluticasone?

DR. MEYER: It does, because that study -- and we did have input into the design of the development program. That study was not intended to specifically speak to the subgroups. We found them of interest to look at, and we got some indication out of looking at them.

DR. NIEDERMAN: Forgetting the subgroups. In other words, there were minor differences between combination versus monotherapy when monotherapy was with fluticasone. Is that still enough of a difference to meet the requirement of both components being necessary for the approval of a combination?

DR. MEYER: Yes. Part of that is that

different primary endpoints were intended to get at different parts of the therapy. So I think correctly you're focusing on one of the primary endpoints as raising some issues, and it raised issues for us. But it's important to note that the FEV1 AUC was a part of the

initial endpoints.

DR. SESSLER: Dr. Kelly?

DR. KELLY: We're focusing a lot on a subgroup analysis that was not what the study was designed to find out, and if we're sort of looking at how to decide what patient populations this is effective for, we have to sort of look at the patient population that comes into the study and the primary endpoints it's designed to look at. I think we get into trouble looking at subgroups and doing subgroup analyses. I think the reason that you do subgroup analysis is to ask further questions that you need to answer later on with appropriate studies, because the subgroup analysis can never be the answer, particularly when there's not enough power to draw any statistical inferences from that.

So I think we should be careful a little bit in the way we interpret the data, and we should take the data as it was designed to be looked at. I think the other struggle that we're having as we keep going back to the guidelines -- and the guidelines are just that, they're

guidelines. The National Asthma Education and Prevention Program, even though they'd like more people to follow them, also recognize the fact that they're guidelines. What we're trying to decide here is whether or not this is appropriate, safe, and effective therapy in the treatment of asthma.

I've already heard some comments that salmeterol, for instance, even though approved as monotherapy for the prophylaxis of asthma, is not indicated for that. That's for the guidelines to decide and for other groups to decide. I don't think it's for us to decide necessarily specifically. We're not writing guidelines here. We're writing recommendations for therapy based on what the outcomes of the clinical trials are. That's my only comment.

DR. SESSLER: Bob, you asked about the clinician perspective, and I think that's very important. If I were to put my clinician hat on for a minute, I would put another step in there. I'd ask the patient how they felt when they were started on salmeterol without an inhaled steroid. Obviously, I wouldn't have done it, but I would ask them if they felt like that improved their condition, even though they're inadequately controlled yet, and the natural response is to add an inhaled corticosteroid one way or the other. If they felt like

that had not really improved their condition overall, then I probably would switch and change them to an inhaled steroid. If they felt it gave them some benefit, then I would add the steroid to that and could easily substitute combination therapy.

So I think it has a couple of different correct answers, I guess, depending on the clinical scenario.

DR. JOAD: Well, I'm going to argue for the guidelines since I think that really has organized our thinking, or at least for the moment it organizes our thinking. There is a group by our organized thinking, which is the mild persistent asthmatics, that have not been studied yet, and to say that this is safe and effective for that group which has not yet been studied to me is overreaching what's been done.

DR. SESSLER: Dr. Vollmer?

DR. VOLLMER: Maybe there is room for some sort of middle ground. It seems to me that my biggest problem with the indications as they were written is that it's a circular definition. If you substitute the words "combination therapy" for "Advair," it says that use of combination therapy is appropriate for people who need combination therapy. So it doesn't take you very far.

It seems to me that there is a problem. We

recognize two groups for which we're very comfortable

saying these are classes of people that need it. I think that we also acknowledge there will be people who are being undertreated who need more aggressive therapy. It makes for a somewhat longer label, but could you not say something like this is indicated for individuals with moderate to severe asthma, including those currently taking combination therapy, as well as those not well controlled by inhaled corticosteroids, and in addition may include individuals who are being managed by beta agonists?

You'd have to clarify it somehow, but basically get the point across that people who are not being adequately managed, and you could leave it vague as to whether you specifically reference the guidelines or not. But it acknowledges that there is a third group, there is another group that it's hard to define, hard to be exact about, but it doesn't say, yes, it's automatically going to work for everybody who is not controlled. But it may also be relevant for some people in this other category.

DR. NIEDERMAN: I think what we're saying is that we'd like to see data on people defined as mild and

uncontrolled with long-acting beta agonists to see whether or not monotherapy or combination therapy confers a different outcome.

DR. SESSLER: Dr. Fink?

DR. FINK: I was just thinking, and I hate to

draw on the guidelines too much, because I understand the distinction between guidelines and package labeling, but it comes maybe closer to what we're trying to do if we say it should be considered as step-up therapy for patients inadequately controlled on beta agents, because then at least we're introducing the idea of step up, which doesn't say step down, but at least it implies it.

DR. SESSLER: Dr. Gross?

DR. GROSS: By definition, aren't those patients who are inadequately controlled on short- and long-acting beta agonists, these are people who are persistent either mild or moderate, and they certainly qualify for steroid administration, so that's what they're not getting? So you would probably be wanting to add steroid to that if you followed the guidelines anyway. If

you're going to add the steroid, then it seems to me to be logical that you would do it in the form of changing them to Advair.

I would also say that one of the indications for long-acting beta agonists alone is that you've got to give that therapy twice a day, every day, not on a PRN demand basis. So again, by definition, that means they've got persistent asthma. If you have persistent asthma, whether it's mild or more severe than that, they probably need to be on inhaled steroids as well. So I would say

that all of these patients would qualify as being in the group that should have two medications, one controller and one a long-acting beta agonist and an inhaled steroid. So it would seem to me that they would also qualify for Advair by that criteria.

DR. NIEDERMAN: Why do they need the long-acting beta agonist in all cases?

DR. GROSS: Well, it doesn't say why they need it. It just says patients inadequately controlled on short- and long-acting. That means they're already on those.

DR. NIEDERMAN: But are there patients like that that could be controlled on just a corticosteroid alone?

DR. GROSS: It's conceivable, but that would imply that they're inappropriately given a long-acting beta agonist.

DR. SESSLER: I think that's a good point. I know, Michael, that you've mentioned this a number of times about the 100 trial, I guess it was 3002, where there was very little separation in terms of the dropout rate between the combination versus fluticasone alone. I don't know if one can necessarily translate that into the less sick population studied, but I understand exactly what you're saying there, that there's little incremental benefit, at

least in terms of that primary outcome, by using the combination versus the inhaled corticosteroid.

So coming back to the patient that I mentioned, it's either the choice of a switch or an addition to it, and I think you need to individualize the patient's circumstances.

MS. CONNER: One of the things that's adding to the confusion I think is, once again, we're assuming that these patients as described here have been appropriately treated. Who knows that this person who is inadequately controlled on short-acting beta agonist is on the right medication? I mean, we have to assume that, once again, 85 percent of the practitioners out there have not read the guidelines and wouldn't know mild, moderate, and persistent if you put it in the labeling, and may not be using appropriate therapy at all.

So if we say that the therapy they're using is not working, and that qualifies them for this, I don't know, but I think that's a gray area that we can't take as hard and fast, that all therapy that's used is appropriate therapy.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I agree with Dr. Gross' assessment, and that is that patients inadequately controlled on short-acting beta2 agonists, it's a big group, and some of those

patients --

DR. SESSLER: Short, or short and long?

DR. KELLY: Short and long. It doesn't matter, because I feel like long-acting beta agonist as a single entity controller therapy is inappropriate. So it doesn't matter whether you add the long in there or not, but they could qualify. I mean, that's the question we're being asked here. What we're struggling over is the question of the real mild persistent asthmatics, and I can tell you, at least from my experience, that none of us really know what to do with this group of patients. We don't know whether to use leukotriene modifiers. We don't know whether to use low-dose inhaled steroids. We don't know whether to use low-dose inhaled steroids intermittently. We don't know how to take care of these patients.

It's a big unknown because it's a group that we often don't see as specialists. I think one of the things that we should do, which would be my recommendation, is to say yes to these things and then ask the sponsor to do some good controlled trials in some mild persistent asthmatics so we can find the answers.

DR. SESSLER: That would be an excellent point for the fourth bulleted point on Phase IV studies, although I guess it's not really Phase IV because it would be a new indication, but to study that population. I agree with

you.

DR. FINK: I think an important part of the package labeling that I would be in agreement with what you said if we added to that at the 100 microgram dose, because I think in that group of patients it would be inappropriate to talk about starting at the 250 or the 500.

DR. SESSLER: Any more discussion on the third bulleted point, then? Patients inadequately controlled on short- and long-acting beta agonist.

DR. JOAD: I just have a question on Phase IV. If we said it was indicated for all the things listed here, and then we looked at a group in Phase IV that were considered technically mild persistent asthma and it was not of benefit, then would the product label change? Is that what happens?

DR. MEYER: It's a little bit of a tough scenario to address, because I think it would be very dependent on the data and whether, in fact, that Phase IV commitment was really intended to ultimately change the labeling. It potentially could, but I think there's a lot of vagueness to that as far as giving you a straight answer.

DR. SESSLER: I guess I'll call the question and just ask for a show of hands, then, of those who think that this would be appropriate for patients inadequately

controlled on short- and long-acting beta agonist. This is Question 2, the third bullet point.

Just a show of hands, those who think it would be, and then those who think it would be inappropriate. I think we can toss in the caveats that clearly it's going to be very much patient-dependent. Certainly I'll toss that in from my perspective.

DR. NIEDERMAN: You don't want to put in any restrictions? You just want a blanket yes or not for this?

DR. SESSLER: Well, I'm not sure how to handle it. There are a lot of different restrictions that we could put. My personal restriction would be that we label it in terms of moderate persistent.

DR. NIEDERMAN: If you asked me would I agree for inadequately controlled asthma on long short-term beta agonists in patients with moderate to severe asthma, I would agree. I haven't seen enough data to know the answer for mild.

DR. FORD: Can I comment on this? Because I think that we've been jumping in and out of utilizing the guidelines for guidance on this particular question. By

definition, a patient who is failing therapy on a long-acting beta agonist plus PRN, a short-acting beta agonist, it would be hard to say that, assuming they're taking the medication, this is a patient who has mild asthma. So, by

definition, this is a patient who has at least moderate persistent asthma.

So in that sense, if we're referencing the guidelines, we have an indication for some kind of anti-inflammatory therapy already, and the way to go at it would be either an inhaled corticosteroid alone at this medium dose, or the combination of that with a long-acting bronchodilator, and that's what Advair is.

DR. SESSLER: Additional comments? Dr. Joad?

DR. JOAD: I'd like to know if it's appropriate for our committee to vote on that particular suggestion, that it's indicated for moderate and severe persistent asthma, rather than either 1 or 3. So we don't have to just say yes or no, that we know there's a vote that we can make that might be more acceptable to some of us.

DR. SESSLER: Right. Just to clarify, of course, this is not a binding vote of any sort. This is

really a show of hands to help Dr. Meyer and colleagues.

So your proposal would be to propose this in what subgroups?

DR. JOAD: In the groups that have been previously controlled on beta agonists, period. In that group, Advair would be recommended for those who have moderate to severe asthma. I don't know that we have to even reference the guidelines, but just a general concept

that it's moderate to severe.

DR. NIEDERMAN: Moderate to severe, uncontrolled on current medication.

DR. SESSLER: Okay, we'll do that. We'll do it a couple of different ways.

DR. GROSS: Would that be instead of Question 3?

DR. SESSLER: No, we'll do it in addition to.

DR. FORD: I think we're going to have to decide to either live with the guidelines or set them aside in this particular discussion, because otherwise we are opening the door to subjective interpretation of who is

moderate, who is severe, and if we are going to, in fact, pick options based on moderate versus severe, I would recommend the guidelines, because that's the best evidence-based thing that we have. But if we're not going to use the guidelines, I would recommend we stay away from that nomenclature of moderate or severe.

DR. SESSLER: Here's what I would propose, then, that we do, is that we register -- and I'm sure this has already been received -- that there's a substantial number of the committee members who feel that there is some role for guidelines to play in selecting what patient populations might be best suited for the product. Having said that, what we can do I think is attack this particular

point in two ways so that they have the information that they can use either way, either including our thoughts about the guideline component or not.

So let's take it just as a show of hands, with the caveat that these patients who are inadequately controlled on short- and long-acting beta agonists also have mild persistent asthma or worse, based on what we all as clinicians extract from the guidelines. Okay? And then

we'll revisit it again without that component.

Is that going to be helpful for you, Dr. Meyer, to have the two different parts there? I don't want to get too hung up on this.

DR. VOLLMER: When you say mild persistent, do you mean moderate?

DR. SESSLER: Moderate. Did I say mild? I meant moderate, yes.

So, let me say it again. Inadequately controlled on short- and long-acting beta agonists, and satisfy us that the patient has moderate or worse persistent asthma. Those who think that it would be a reasonable choice in this circumstance?

(Show of hands.)

DR. SESSLER: Any who would not?

(No response.)

DR. SESSLER: Now let's take the next subset of

that.

DR. FORD: I couldn't vote on this, but I'll say that is redundant.

DR. NIEDERMAN: But I think it still makes a point, that this isn't necessarily a drug for everybody with asthma. I think that's the only point that's really being made here.

DR. SESSLER: And I think your point is right on target, too.

So, then, as the question is stated, let's just take it as stated. You can put your hand up halfway.

(Laughter.)

DR. SESSLER: If you put your hand up again, that would be that you think it would be a reasonable place for the product to be positioned as far as labeling, and that is patients inadequately controlled on long- and short-acting beta agonists, period.

Those who would?

(Show of hands.)

DR. SESSLER: Okay. Nays?

(Show of hands.)

DR. SESSLER: Okay, good. So that's some information.

The top bulleted item is patients inadequately controlled on short-acting beta agonists alone.

Discussion?

DR. DYKEWICZ: Well, the question I see here is that we're actually still looking at a broad range of patients, and it depends how you define what inadequately controlled means. But, for instance, you could say patients that were getting daily short-acting beta agonists, which, if you went back to NHLBI criteria, would be moderate persistent. You could also have patients maybe having a less frequent requirement for PRN short-acting beta agonists and still you would consider on the basis of, let's say, spirometry, that they really were not well controlled.

So I think what we're really trying to address is reservations that if a statement is made that it's indicated for treatment of patients who are inadequately controlled with short-acting beta agonists, it's going to include a very broad range of patients, some who may not need this drug.

The problem that I get back to again, though, is that we have to try to keep our statements -- and I'm sure the FDA would be more of this mind -- we have to keep our statements fairly simple. We can't equivocate in terms of in this subset of patients, in that subset of patients. Also, I think we get into problems again referencing the guidelines. These are moving target guidelines. They're

evolving. I think that these are not the other set of guidelines. There are other guidelines out there, and just to refer specifically to NHLBI is probably not appropriate.

My own feeling is that this is a dilemma, and I'm not sure quite how to deal with it, other than what I had brought up earlier this morning in my exchange with Dr. Shah, and that was that perhaps initially somebody might step up to Advair treatment in this subgroup, but then there'd be something in the product labeling which in real practical terms would say then you consider stepping down. If the patient is doing quite well, you might step down to remove the salmeterol, for instance.

So I think our dilemma, if you will, is dealing with this issue that although some patients who are inadequately controlled on short-acting beta agonists would be appropriate for treatment with Advair, not all patients would, and we're trying to find some sort of a means to indicate that in very short, pithy statements in labeling, and again being considerate of the fact that even if we wanted to satisfy our specialist intent to specify with the appropriate subset of patients on the basis of guidelines, this in practice is probably not going to help most practitioners who are prescribing this drug, and I

therefore steer away from using very strict NHLBI statements about the severity of asthma and what subsets of

patients would be appropriate for being treated by this drug.

DR. SESSLER: Dr. Fink?

DR. FINK: I think for patients inadequately controlled on short-acting beta agonists alone, I would have to, I think, fairly strongly disagree with that as an indication, in that I think it is far too broad, and it brings in as many patients who were not studied as those who were. Many people would interpret that as potentially exercise-induced bronchospasm that is not adequately controlled, and there is no data presented today that Advair is at all superior in that situation than salmeterol alone. So I would have to say I would be against this as an indication because I think it errs on the side of broadness to the point that the risks outweigh the benefits.

DR. NIEDERMAN: That would include people who didn't respond to Primatene.

DR. FINK: Right.

DR. SESSLER: Dr. Ford?

DR. FORD: It may not be a bad drug for people who don't respond to Primatene, provided that their disease is sufficiently severe to warrant it. I share the concern that the way that this is stated is so broad that it would just apply to every single patient. Well, not quite every

single patient. But in that sense, I would favor some method for discriminating between the groups whom we think are more severe and those whom we think are less severe. Whether or not we decide to do it with the guidelines, I think this is something that this group, and ultimately the FDA, will have to deal with.

But I think that's what it boils down to, that this is really too broad.

DR. NIEDERMAN: There is also another vagueness in the wording here, and that is that it doesn't specify a time period. So I could interpret this I guess to mean that my patient took one shot of Ventolin, it didn't help him, he's still symptomatic, it's time to try something else. I think this is just way too open-ended, and it

doesn't reflect the data we've seen. I think that in line with the labeling question that was asked earlier, I think if Phase IV studies document that this could be used in an even broader population than the data we've seen, then I think it should be added to the label, rather than added to the label now and subtracted later if the studies don't support that.

DR. SESSLER: I think this was a very easy question prior to the meeting, and it becomes a little bit trickier now with some of the data that were presented, and that's a pilot project. The data looked promising as far

as the patients who were uncontrolled on inhaled short-term beta agonist and seemed to have a higher FEV1 response than even fluticasone alone, and certainly than salmeterol alone. So I guess this is provocative. Is that one of those terms that would fit here?

But certainly this is a huge population that it would be a mistake for the average clinician to over-interpret and say, well, the patient is not doing well with an inhaler, so I'll go ahead and put them on this new drug.

So I think it's perhaps early.

Dr. Gross, you had something else to add?

DR. GROSS: Well, I'm sort of persuaded towards the direction that one should recommend Advair for these patients as well. You're not told anything more about the patients, so we really have to make a decision based upon just this one line here without being able to ask whether they maybe have EIV or whether they've not responded to a single shot of Primatene or something like that.

But if you go with the guidelines, patients with mild intermittent, they're treated with beta agonist PRN, and if they're not well controlled, that probably puts them into the category of mild persistent, and mild persistent patients should have some controller as well as a reliever. So as far as I'm concerned, the next best thing for this patient would probably be to put them on the

lowest strength of Advair.

Now, I know that that as a blanket recommendation, that might seem too broad. But then bear in mind that a lot of patients are lucky to have their asthma therapy adjusted even once after the initial therapy

has been instituted. So how many times are you going to reevaluate and readjust this patient's therapy? You've got to try to hit the middle of the target with your very next shot. I would say my next shot would be to add a combination, and this, to me, would be one of the big advantages of combination therapy, that you do get both aspects of the essential treatment of persistent asthma, and even if you never make any further adjustments, you've probably got two-thirds of the way towards where you should be.

So I would say just given this information, and faced with a real live practice situation, I would probably be looking for something like Advair as my next step.

DR. NIEDERMAN: But, Nick, what you've argued for is a controller, and the question I guess that's being asked is if a controller alone would work, is it worth leaving them on a controller and a reliever, particularly a reliever that has a long half-life where there is a potential for side effects? If it's not necessary, is it responsible for us to say give it to everybody without

trying it without it first? I think that's the question.

I think for a sicker population, it's a very different question.

DR. DYKEWICZ: Strictly speaking, we're talking about two controllers here.

DR. SESSLER: And I think the philosophy, which I think a lot of us embrace, of hitting it hard and then trying to back off is supported by an approach like this, as you point out, rather than stepping up; to start with a fairly hard push to control it and then to back off, and I think this would certainly be one option to do that.

What I'd like to do is to take the prerogative of going back to the approach we used for the third bulleted point, which is to take a couple of votes and let Dr. Meyer sort out the results.

So first, just a show of hands, as it's worded, that does not have anything to do with "severity of illness" or the guidelines whatsoever. That is, would we suggest, just broadly now, that for patients inadequately controlled on short-acting beta agonists alone, is this a population that we want to suggest that Advair will be recommended for? Then I will come back and rephrase it with some language pointing out the focus on moderate to severe asthma as a second point.

So the first one will be a show of hands,

please, for those who think patients inadequately controlled on short-acting beta agonists alone, that this would be a good place for the drug, broadly.

(Show of hands.)

DR. SESSLER: Any nays?

(Show of hands.)

DR. SESSLER: And abstentions, I guess, for those who didn't raise their hands?

(No response.)

DR. APTER: Can you use the word "option" instead of "indicated"?

DR. SESSLER: What do you think, Bob?

DR. MEYER: That's a practice of medicine question.

DR. KELLY: I was for it because I thought Nick was for it, too.

(Laughter.)

DR. KELLY: But the second statement is preferable. It's like preferred therapy would be in the moderate to severe asthmatics. I think taking an exclusionary step at this point, particularly after looking at the safety and efficacy of this product, is a bit much.

DR. SESSLER: Here's bulleted point 1, Part B. How does that sound? This is with a caveat. The same

wording, patients inadequately controlled on short-acting

beta agonist alone, but that the sense is that the patient has moderate to severe asthma, persistent asthma.

Ayes?

(Show of hands.)

DR. SESSLER: And no's.

(No response.)

DR. SESSLER: Is that useful, Dr. Meyer?

DR. MEYER: I'm trying to debate how we're going to accurately translate that. But, no, it is.

DR. SESSLER: Okay. Any other comments on this Question 2? If not, then I'd like to move forward to Question 3.

Do you recommend any additions or changes to the sponsor's proposed labeling on how this product might best be used in practice?

I don't know, Dr. Meyer, if you want to summarize that. Obviously, that's one of those devil is in the details type of questions.

DR. MEYER: I think we can take a fairly broad view of this, and maybe we don't even have to use anything

in the briefing package. But I think the sponsor has spoken to wanting to do some educational efforts, both as a part of their marketing campaign and as part of their package insert and their patient instructions, as far as the best way to use this, and I think we'd be looking for

committee input about particular caveats that need to be conveyed effectively or particular advice that needs to be conveyed effectively to either the practitioners or the patients in terms of how to safely and optimally use the product.

DR. SESSLER: Dr. Joad?

DR. JOAD: I would at least like to make an argument for using the words that are also used in the guidelines in the product labeling wherever possible. So rather than saying "prophylactic use" or "prophylaxis for asthma symptoms," say "controller." Rather than saying "short-acting beta agonist," say "reliever." Rather than saying "call your doctor for these worries," say "as prescribed by your action plan, you should call your doctor. These may include the following conditions." We

don't have to endorse them or recognize that the guidelines won't change, but you have to pick a word anyway, so why not "controller" instead of "prophylactic use"?

DR. DYKEWICZ: Again, I think we get into problems with change in definitions even from NAEPP 1 and 2 as to the use of those terms. Even with the discourse we've just had, there's evidence that people can have some transient misuse of the terms. I think it's not going to be, for the vast majority of patients, and for a large number of health care providers, that helpful to use in

practice.

I think in terms of asking patients to start distinguishing between different controllers and relievers, I know that's something we're certainly intending to accomplish with the dissemination of the NAEPP guidelines, but I don't think we're practically there yet, for the most part. Also, let's face it, in terms of action plans, the vast majority of patients in this country are not being given action plans.

So I'm still kind of in favor of common sense, simple use of terms that don't depend upon definitions in

the NHLBI guidelines but refer to things such as -- maybe instead of "prophylactic," maybe "preventive." But really kind of use simple terminology which I think would be more easily understood by patients, and perhaps even health care providers.

DR. SESSLER: Dr. Niederman?

DR. NIEDERMAN: Again, I think, if I'm understanding the question right, there have been a number of issues that have been brought up today that I think would be helpful to be added to the label. For example, if the label said that "if this medication is used and symptoms are controlled, then effort should be made to reduce dose," the label should say "in selected patients, an effort should be made to change to monotherapy with an

inhaled steroid." Similarly, the label might say that based on what we've just said, that for certain milder patients, this drug would be appropriate after monotherapy within an inhaled corticosteroid has failed.

Finally, I think it's very important to have in the label a very clear warning and discussion about what to

do about exacerbation. I think it has to be very clear that this is not a drug to be used stepping up in exacerbations, that it requires other additional medications. I think that that has to be part of the education of patients for sure, but I think it has to be part of the education of doctors and a very clear warning in the label.

DR. SESSLER: Let me ask Dr. Meyer for clarification on the level of cautions and warnings and so on that appear in the product labeling, the terms where the black box is, just so everybody is clear on terminology. Is a warning a warning, and what's the words, and so on.

DR. MEYER: I think it's actually a little bit of a moving target right now, because we're actually moving away from the breakdown of warnings and precautions, because that can be a bit arbitrary at times. So the agency is actually considering ways to really move away from that distinction. So I think for the purposes of the committee's advice, you can use precaution, you can use

warning, and we'll interpret it accordingly.

I think the other thing I thought might be a

part of your question is Dr. Niederman's observation about the exacerbation setting. That kind of wording, of course, is very strongly included in the current salmeterol labeling, and I appreciate your input on that.

DR. SESSLER: Dr. Kelly?

DR. KELLY: I agree with Dr. Dykewicz' assessment. You might want to know that the NAEPP expert panel spent a whole day deciding whether or not to call it controller or preventive medicine. So these are definitions that change, and they're dependent on a lot of different phenomena.

I also agree with Dr. Niederman. I think there should be very clear statements in there about stepping down and stepping up. I don't know how you're going to term that, but I think that's what we're all worried about, that people will get put on the highest dose of Advair and you'll never see a decrease in that. So once you're under control, that they step down, and again the precautionary statements that this is not appropriate therapy for acute exacerbations.

Just a statement about even doubling the dose of inhaled corticosteroids in acute exacerbations, although we included it in the guidelines, I can tell you because

Dr. Boushey and I were assigned to find the literature to support that, neither one of us were very successful in finding much. It's common practice to do that, doubling your dose of inhaled steroid. But again, to find data to support that as an effective practice, there's a real paucity of data.

DR. SESSLER: Dr. Fink?

DR. FINK: At high doses, at least, I think there should be some typical caution about abrupt interruption of therapy.

DR. SESSLER: Dr. Meyer, any particular sticking points that you wanted to solicit our thoughts on?

DR. MEYER: Well, I think the other points perhaps we want to know some thoughts on best message or best wording would be what to do when you're already on Advair and there is an exacerbation. Obviously, I think the company has laid out their thoughts on that. We've laid out our thoughts on that. But translating that into instructions is one question. I suppose that would be the big one, particularly the best way to tell people not to double the dose of this product, and perhaps what needs to be done in terms of adding other inhaled or oral corticosteroids, the best message specifically tied into this fixed-dose combination product, or even changing dosage strengths within this product line.

DR. KELLY: Brenda could talk about this, but that's really dependent on the action plan that's developed by the clinician. We use oral prednisone a lot. I think everybody would agree that using your short-acting inhaled beta2 agonist -- I know there's a strong statement in there that you need to keep on your short-acting inhaled beta2 agonist for acute, severe exacerbations. Then the rest of it is really dependent on the severity of the patient and that experience. So some of it would be oral prednisone. In some patients it might be doubling the dose of inhaled corticosteroid, but it's hard to --

DR. MEYER: Right. I guess I'm not really after the science of how to handle an asthma exacerbation. The thing is there are certain things you should do with this product, there are certain things you shouldn't. You shouldn't double the dose even if there are data about 100 micrograms BID of salmeterol. Those are clinical trial data, not in people with preexisting heart disease and so on. So I guess what I'm after is any advice the committee might have in terms of practical language, visual signals, something to help with the proper use of the product.

DR. NIEDERMAN: You might want to specifically make the statement that this is a medication intended for the maintenance of chronic asthma, and that in the setting of an acute exacerbation, additional medications should be

added, but this medication should be continued at its usual dose and other medications added. I think that's certainly the sense that we have, it's going to be safest that way.

I think you could allow, but I wouldn't put it in the label, that if you were on the 100 dose, you would go out and buy a new Diskus and go up to the 500. I think that's not likely to happen and it's likely to be very confusing to patients. So I think that if the message in the label were to say that this is a maintenance medication and at the time of exacerbation it should be continued as ordinarily prescribed but the exacerbation be managed with additional medication, that seems the easiest way to do it.

DR. GROSS: I think it requires some mention that the doctor should be involved in those decisions.

DR. SESSLER: I think there's an obligation really on the sponsor's part to recognize this at the outset, that this is a very real problem that's likely to

occur with a great deal of frequency; that is, that the patient has this Diskus at home and they have an exacerbation. I think there's an obligation on the sponsor's part to help try to solve that problem in advance. I'm not sure exactly how. I'm sure there are a lot of resources to figure out patient education, perhaps the ability in terms of co-packaging, short-acting fluticasone or something of that nature, or something to

allow more than just paying lip service to the idea that you have a problem that's going to come up, but really in a meaningful way provide some support to solving the problem.

DR. FORD: I would echo that. There will be lots of real-life situations that come up in the context of using this drug in diverse populations, and I think that the options that are open to the practitioner and that are likely to be used will vary depending on where one is. But going through the spectrum that Dr. Kelly mentioned with the inhaled corticosteroids or the prednisone, the bottom line is that there are options within the current armamentarium, and it's going to be very hard to be very

specific at this point about what people should do.

What people should not do is to double the dose of the maintenance therapy, and I agree with Dr. Niederman's recommendation in terms of understanding that this is for maintenance therapy and not for treatment of exacerbations.

DR. SESSLER: Dr. Joad?

DR. JOAD: I just read through what they were proposing to say, and short of putting the words "action plan," which I would like, I think it was very clear. They did underline "this is not to be used for acute asthma." They said, "Call your physician under these conditions." I thought they were good conditions. So I thought the safety

was there for that.

DR. SESSLER: Okay. Any further discussion on Question 3?

MS. CONNER: The only thing would be mouth rinsing. I don't know whether that was addressed. I read it so long ago. Rinsing the mouth -- is it mentioned in there? I think that's something, especially with the new device, in the absence of a spacer, that's going to be

imperative.

DR. SESSLER: Dr. Vollmer?

DR. VOLLMER: I just have one item that was touched on earlier. To the extent that you can use somewhat more patient-friendly language in some places, particularly the reference to prophylactic therapy may not be clear to patients and prevention of acute attacks, because it's going to be read not just by physicians but also patients.

DR. SESSLER: Dr. Fink?

DR. FINK: The rinsing the mouth I routinely recommend, but I have been surprised that with the Pulmicort Turbuhaler, I expected to see more problems with thrush in pediatrics, and we have not seen them, and I'm not sure that the dry powder devices don't actually give you less oropharyngeal deposition than a metered-dose inhaler. There is some data to support that statement. So

it's not a bad idea, but I'm not sure it should really be a recommendation.

DR. KELLY: That's a dose-dependent phenomenon,

and about 65 percent of it is deposited in the oral pharynx. It has been shown with higher doses that rinsing the mouth out will make a difference. It's a dose-dependent phenomenon with the metered-dose inhaler, too.

DR. JOAD: Plus it was shown in this set of studies that there was more dysphonia and more throat implications.

DR. SESSLER: Okay, thank you.

Let's move to Question 4. What, if any, Phase IV studies should be required to address the safe and effective use of this product in the general population?

Dr. Niederman?

DR. NIEDERMAN: We talked about postmarketing. I think I'd be particularly interested in seeing the data on frequency of exacerbations in patients on this medication and safety of this medication in patients who have exacerbations, if we see a difference in outcomes and mortality, for example, because in retrospect we see patients who are using this drug in ways outside of the label, I think that's important that we know. So certainly looking for complications specifically in the exacerbation population is important in light of the discussion we've

just had.

I think that if the discussion is going to go towards using this in the milder asthmatic, then I think we should ask that there be a study specifically designed to look at the milder asthmatic.

DR. SESSLER: I suspect Dr. Meyer would like to know, for the first example, if you had a prospective study or more surveillance-related --

DR. NIEDERMAN: No, I'm thinking more of postmarketing surveillance. I guess you could make that a more formal requirement, but I think it's important in some way, since we've all recognized the potential for this medicine to be misused. Particularly in the context of exacerbation, it's important that some data be collected.

I think it would be interesting as well, but probably not in the realm of mandatory, to trend whether or not patients are being truly changed to lower doses when their asthma is controlled. My guess will be that patients will start at a dosage and generally stay there, but I think that would be ancillary data that would be interesting to know.

DR. SESSLER: We all embrace the idea that for the real sick folks who are uncontrolled on a short-acting beta agonist, that we thought the data that was presented kind of after the fact was pretty compelling, and certainly

expanding that to an appropriately powered clinical trial would be, in my view, more worth doing, to look at that de novo asthmatic patient who presents just on a beta agonist, poorly controlled.

Dr. Vollmer?

DR. VOLLMER: I'd echo that also. There was a lot of discussion earlier about compliance. I would think that this group or whoever it is that's sitting around this table when the next drug like this comes through again would enormously benefit by having a good understanding of what really happens out in the real world with this product. I can envision a randomized trial, either by individual patient or on a clinic basis, it might be easier to do it that way, where you're getting groups of patients, and I might have it in two different categories, one where you're really looking at the bigger step-up in categories one and three, treat them separately.

But a clear-cut group, those who are currently on both salmeterol and an ICS, and those who are just not being well-managed by their inhaled corticosteroid, and put them either to get combination therapy as would normally be done, or increasing their combination therapy. Actually, the eligibility would be those who are well managed with

combination therapy, and some of those would go on to Advair and some of those would continue where they are, and

you can see what's happening with that group. Then you would get an additional group that needs to step up therapy from ICS, or they're just not being well managed, so they get a little more.

I would take a look at what happens with compliance in those populations, and patient acceptance, and provider acceptance, what do they feel about it. I think just getting some experience on how patients and providers feel about these, whether they find they're really more helpful or not more helpful, looking at long-term utilization patterns, in addition to the health utilization that occurs down the line. But even if that doesn't change much, I think understanding just what's driving utilization and what the factors are that impede or facilitate its use would be very helpful.

Also, I think that it would be important to do trials that particularly focus on issues of step-up and step-down therapy. It may be hard to find enough people in

one organization for this, but the folks who are on beta agonists who aren't being well-controlled who you think should be on this, and some of them get on this thing, and watch what happens as they're stepping up and stepping down, and have an alternative therapy where they're getting combination therapy with separate entities, and just see how that works and get a comparison for the difficulties

involved, because those are the issues we've spent the last several hours struggling over.

DR. SESSLER: Dr. Gross?

DR. GROSS: Those are obviously very interesting and important points, but the question is what, if any, studies should be required? You wouldn't specify those should be required, would you?

DR. VOLLMER: No. Admittedly, these are the things that popped into my mind as things I would love to do. Whether I would require them or not, probably not. But at some point, this is information that you're going to want to have, and I don't know whether you require it here or not. Since this is the first time with this kind of medication in the U.S., maybe you do something a little

different that you might not have to do down the line. But I think it's going to be really important for us down the line to have this experience and knowledge. If you don't require it, you may never get it.

DR. SESSLER: Dr. Ford, and then Dr. Fink.

DR. FORD: I would see it as a priority to develop some database on the off-effect. That is, since a large number of individuals presumably are going to be started on Advair, we need to know about what happens when they come off abruptly, as opposed to coming off in different ways. I think that probably this would be

designed as a clinical trial. I think that's an important direction to inform us about safety of this combination, although I don't think that voices a reservation. But it would be reassuring to have data that support our not having any fears about it here.

The second direction in which I think it would be important to go is to look at various subpopulations. I think that the representation of various subgroups in our population -- I'm talking about ethnic minorities now -- is

woefully inadequate. Five percent African Americans and a few other ethnic minorities, I don't think that is appropriate in the context of an epidemic that is centered primarily in those minority populations. I think that in terms of data collection in Phase IV studies, this is something that one would like to look at.

Also, there's a need for studies of effectiveness now. Considering the socioeconomic barriers that exist in urban, low-income, and minority populations, what is going to be the impact there? I think that in postmarketing surveillance studies, is cost going to be a barrier? And also, if we can learn that adherence is better with this drug compared with others, I think that that will be an incentive for practitioners in those settings to go ahead and utilize Advair, which I believe has a great potential for supporting control of asthma in

these populations.

Finally, education, education, education. The chemical we assess along with the delivery device, and I would say that the medication and its delivery device needs to be assessed in the clinical context in which it's being

utilized, and I think we should look at all of these.

DR. SESSLER: Dr. Fink, then Dr. Apter.

DR. FINK: I would think there are two potential Phase IV studies that I would recommend being required. One would be a growth study in adolescents, which may be required under the class labeling act of steroids already. But if not, I think it should specifically be stated in the prepubescent adolescent, a growth study. I think it would be probably quite valuable to look at a one-year or eighteen-month or two-year study of HPA axis suppression, particularly in those patients on the 500 BID.

DR. SESSLER: Dr. Apter?

DR. APTER: I certainly second what Dr. Ford said and what Dr. Fink said. I think one way to address the issue of compliance, because it can be very difficult looking at compliance and trying to tie it to databases of emergency room visits and hospitalizations, would be to compare to see how many patients go back for their second prescription. It might be easier to get that data because

we've already mentioned today that many people don't refill their inhaled steroid prescriptions more than the first.

DR. SESSLER: Dr. Joad?

DR. JOAD: I would just like to agree with Dr. Fink about the growth study and the HPA axis study in adolescents.

DR. SESSLER: I mentioned earlier about the obligation that I felt the sponsor had in terms of really actively addressing solutions to the step-up/step-down and the risk of the patient just doubling up. I don't know if there's a way of putting that into a formal clinical trial, really testing strategies perhaps rather than individual drugs per se, but it would be well worth some careful thought that might lead, then, to a more consistent approach to helping patients deal with exacerbations and titrating up and down.

DR. KELLY: The long-term growth studies would be very interesting, because if we do enhance compliance, we'll be enhancing compliance of inhaled corticosteroids, which on the one hand is good for the asthma, but depending on the dose, it might be bad in terms of growth or HPA axis suppression. So that's the downside of enhancing compliance, I guess.

But the only study that I would require or would ask to be required would really be the one that we

struggled with all day today, which is a study on the mild persistent asthmatics and taking in a different population. Those populations aren't taken into most clinical trials for efficacy because it's very difficult to show efficacy, because your endpoints tend to be FEV1s and peak flows, so you have to have suppressed FEV1s and peak flows to begin with. So you're going to have to come up with different endpoints, and those endpoints may be exacerbations, and it may require a long-term study of a year or so in order to really determine differences.

But if we really want to know whether or not the mild persistent asthmatics are benefitted by this and not overtreated by it, that's the kind of study we'll have to do.

DR. DYKEWICZ: I would just really second the motion. I think we do need the long-term growth studies and probably some HPA axis studies of longer-term usage.

DR. SESSLER: Thank you.

The sixth and final point relates to pediatrics, and I'll go ahead and read this.

Fluticasone propionate inhalation powder (Flovent Rotadisk) is approved down to age 4 at either 50 micrograms or 100 micrograms twice daily. Salmeterol inhalation powder (Serevent Diskus) is also approved down

to age 4 at a dose of 50 micrograms twice daily. Given the

prior approval of both of these products in the pediatric population down to age 4, and given the data discussed for Advair, what studies would you recommend the sponsor conduct to provide adequate data for Advair's use in the pediatric population?

The specifics they're after include what dosage strength for combination, what control groups, and what age ranges. I'd like to get pediatricians and allergists to weigh in first on this.

DR. JOAD: Well, I can see it could be of quite good benefit to children as well as adults, so I would like to see it studied in children, and I think convenience is as important to them as anyone else. So I'd be in favor of this.

Looking at this, I think the growth and the axis suppression and long-term effect on bone density, all that stuff is particularly important I think to pediatricians because these children are likely to have asthma their whole lives, and we're starting something when they're very young that can affect them when they're older.

So I think good studies of that are really important, in addition to the kind of studies that were done here.

The other thing is I was trying to think of what concentrations I think should be available, and to be honest, I'm not sure I even want one lower, although that's

what you're looking at, just because it seemed like maybe mild persistent asthmatics don't need this. So I was actually thinking a little bit more of an in-between dose, between 100 and 250, rather than a smaller dose. But I don't have strong feelings that way.

DR. FINK: I guess I would say I think studying an Advair 50, so to speak, would be useful in pediatrics, particularly for the younger children. The growth HPA axis suppression studies would be critical, and I think at the young end of the age range, there would actually need to be some studies done about effectiveness of delivery. The Diskus is somewhat different from the Rotadisk, and in particular one problem you have in very young children is getting them to seal their lips on the device and not exhale through it, because with the Diskus, if you exhale

through it, you blow all the drug out all the inhalation ports.

So I think maybe some delivery studies in maybe the 4- to 7-year-old age group would be important in terms of how well does this device fit in that population.

DR. SESSLER: Any comments about control groups? That is a specific question that Dr. Meyer and colleagues raised.

DR. KELLY: Well, you're going to have to do some control groups on using just Flovent by itself at that

low dose, because it's already approved. The issue of whether you do a placebo control has been raised here, and if you're studying moderate to severe childhood asthma, probably you don't want to do a placebo control. On the other hand, if you want to get access to safety data, some sort of control, whether it be a leukotriene modifier or whether it be something else that has no known effect on the HPA axis and growth, would probably be appropriate.

That's a difficult question in this age population. We used the placebo control in the CAMP trial for four years, and we had a lot of patients that needed

therapy as a result of that. So it's difficult to do long-term studies if you have real persistent asthma in children as a placebo control. So you may have to require or look at using one of the other controller medications as your control.

DR. FINK: The other pediatric group I guess you would want to take into account, not as a control group but as a treatment group, is what is the role of this drug in that problematic group of pediatric patients who have something between mild to severe intermittent asthma which does not fit into the NIH guidelines, those children who only wheeze with respiratory viral infections? Is this an appropriate drug to be considered in that group or not? Because there, the risk of daily treatment is actually that

you are overtreating the child between viral infections, even though you may be undertreating them at the time of a viral infection.

DR. MEYER: Can I ask a follow-up on that? How would you see such a study working? Would you use the Advair only during those periods when they're having the

viral symptoms?

DR. FINK: Yes. I mean, clinically there are many mothers who don't start the controller medication until the child has the first sign of a cold, and then they institute whatever therapy is recommended.

DR. MEYER: Right. I guess I'm having a little trouble envisioning how such a trial would be conducted. I guess you'd enroll patients who have that history and come up with treatment with Advair, and then what control groups would you have?

DR. FINK: There you could use a placebo control, because that's what we deal with a lot, looking at the potential for -- I think one of the big questions in pediatrics would be, in that group, does something like Advair offer a therapeutic option compared to oral prednisone? I mean, probably the most standard therapy in that group when they have their viral flares would be oral steroids. So there would be a high level of interest in does an inhaled steroid with less potential systemic

toxicity offer reasonable efficacy.

DR. KELLY: I would agree. There have been

some studies that have tried to look at that with just adding an inhaled steroid, and they've not been very successful. Then there are studies that look at that group with just a bronchodilator. With both of them, there might be an advantage. So it would be an interesting group to study and look at.

DR. JOAD: And although I think that would be interesting, I don't think that's the main focus. I think the main focus should be controller therapy for children with persistent asthma.

Also, I think the design that you used for the adults ought to work with children, where you can drop out with a placebo, there's a way they can easily drop out if they're starting to get worse. People seemed uncomfortable with where you said it may be a little too low for these other studies. They don't have to be as bad to drop out, but it's really nice to have a placebo. I think that really helps, so I think you could use a similar design. PFTs obviously in 4-year-olds is going to be tricky, whether you can get peak flows. Maybe you can, but probably not in all 4-year-olds, so you're going to have to use some other criteria. But they can use the same sort of ones as you used for your secondary criteria in the other

studies.

DR. SESSLER: I'd like to ask Dr. Meyer and Dr. Jenkins if there are any other questions that you would like to pose to the group here.

DR. MEYER: I think we've had a pretty complete discussion, and I certainly thank the group for all their input, and I thank Glaxo Wellcome for their presentation and for the data. As far as I'm concerned, I think we've had a sufficient discussion. I really am appreciative.

DR. SESSLER: Great. I'd like to thank the committee and the FDA and Glaxo Wellcome for all of your thoughtful comments. Thanks.

(Whereupon, at 3:00 p.m., the meeting was adjourned.)