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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY AND ALLERGY DRUGS ADVISORY COMMITTEE

OPEN SESSION

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Charles Lee, M.D.

C O N T E N T S

P R O C E E D I N G S

Welcome

DR. DYKEWICZ: Good morning. Welcome to the meeting of the Pulmonary and Allergy Drugs Advisory Committee. I am Mark Dykewicz, the chair, associate professor of internal medicine in the Division of Allergy and Immunology at Saint Louis University.

First of all, a few ground rules to maintain order. Members of the committee, when you are going to speak, first I would like you to raise your hand so I can recognize you. Then, when you do speak we want you to push down on the button to activate your microphone. Perhaps even more important, when you are done speaking, push the button again to deactivate the microphone so we don't hear all sorts of side bars that will confuse us. So with those sort of ground rules, let's begin with introductions, starting with Bob Meyer.

DR. MEYER: I am Dr. Robert Meyer. I am the director of the Division of Pulmonary and Allergy Drug Products in the Center for Drug Evaluation and Research.

DR. PURUCKER: I am Dr. Mary Purucker, in the Division of Pulmonary Drug Products.

DR. GILBERT-MCCLAIN: I am Dr. Gilbert-McClain, medical reviewer in the Division of Pulmonary and Allergy Drug Products.

DR. LEE: I am Charles Lee, medical reviewer in the Division of Pulmonary and Allergy Drug Products.

MS. SHELL: I am Karen Schell. I am the consumer rep.

DR. JOAD: I am Jesse Joad. I am a pediatric pulmonologist and allergist at UC Davis.

DR. APTER: I am Andrea Apter. I am an allergist and immunologist from the Pulmonary, Allergy and Critical Care Division of the University of Pennsylvania.

DR. ATKINSON: I am Preston Atkinson. I am an allergist/immunologist from Children's Hospital at University of Alabama at Birmingham.

DR. FINK: Bob Fink, pediatric pulmonologist at Children's Hospital in Washington, D.C.

DR. STOLLER: I am James Stoller, I am a lung doctor at the Cleveland Clinic.

DR. BONE: I am Henry Bone. I am an endocrinologist, specializing in bone and internal disorders, in Detroit.

DR. PARSONS: I am Dr. Polly Parsons. I deal in pulmonary and critical care medicine at the University of Vermont.

DR. WISE: Robert Wise, pulmonologist, from Johns Hopkins University, in Baltimore.

DR. MALOZOWSKI: I am Saul Malozowski. I am a pediatric endocrinologist at NIDDK, NIH.

DR. DYKEWICZ: Thank you. Now we will begin with the statement of conflicts of interest.

Conflict of Interest Statement

MS. TOPPER: 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 potential 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 a conflict of interest at this meeting, with the following exceptions:

Dr. Andrea Apter has been granted waivers under 18 USC, Section 208(b)(3) and Section 505(n)(4) of the FDA Modernization Act for her

ownership of stock in two competitors. The first stock is valued at between $50,001 to $100,000, and the second between $5,001 and $25,000. The waivers permit Dr. Apter to participate in the committee's deliberations and vote concerning the new drug applications, NDA 20-833 and 21-077, sponsored by GlaxoSmithKline.

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

We would also like to disclose that because of their reported interests, Dr. Nicholas J. Gross and Dr. Michael S. Niederman, who are committee members, are excluded from participating in all official matters concerning NDA 20-833 and 21-077, sponsored by GlaxoSmithKline.

Further, with respect to FDA's invited guest, Dr. Robert Wise's employer, Johns Hopkins Bayview Medical Center, has the following contracts and/or grants: Research grant negotiations are in progress with the American Lung Association-Asthma Clinical Research Centers, ALA-ACRC, and GlaxoSmithKline and AstraZeneca. Dr. Wise serves as the PI of the ALA-ACRC data coordinating center.

He is PI of the Clinical Center for Lung Health Study, funded by NIH-NHLBI with drug contribution, ipratropium, from Boehringer-Ingelheim.

He is PI of the Clinical Center for Lung Health Study II, funded by NIH-NHLBI with drug contribution (triamcinolone, from Rhone-Poulec Rohrer, now Aventis.

He is PI of a pending research grant for a clinical trial of tiotropium, sponsored by Boehringer Ingelheim.

He is co-sponsor for a Childhood Asthma Management Program, funded by NIH-NHLBI with drug contribution (budesonide) by AstraZeneca, and nedocromil, contributed by Aventis.

He is the PI of Clinical Center for a study of COPD evaluation instruments, sponsored by Merck.

He receives less than $5,000 in consulting fees from Aventis, Boehringer Ingelheim, Novartis, Bristol-Myers Squibb, McNeil and AstraZeneca.

Her receives between $5000 to $10,000 in consulting fees from Johnson & Johnson, He consults on a non-pulmonary drug.

He receives between $10,000 and $15,000 in

consulting fees from Pfizer. He consults on a non-pulmonary drug.

Finally, he receives less than $5000 from GlaxoSmithKline in support of a local thoracic society and pulmonary grand rounds.

In the event that 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. Thank you.

DR. DYKEWICZ: Thank you. We will now begin with the topic introduction by Dr. Bob Meyer, Director of the Division of Pulmonary and Allergy Drugs of the FDA.

Welcome and Topic Introduction

DR. MEYER: Thank you. First off, I should mention that Dr. Sandra Kweder, who is our Office Director, sends her apologies for not being

On behalf of the Center for Drug Evaluation and Research and the Pulmonary and Allergy Division, I would like to welcome the advisory committee members and guests, and to thank you in advance for your participation in what I consider to be an important meeting. We very much appreciate your willingness to lend your expertise to the advice which we hope to take away today.

We are here today to discuss two applications; Advair Diskus for the maintenance treatment of COPD and Flovent Diskus for the maintenance treatment of COPD. While we certainly understand that corticosteroids are commonly used in the treatment of patients with COPD, both in the acute setting where the treatment is mainly systemic, and in the maintenance setting where treatment is commonly either inhaled or systemic. The FDA has not to date approved such use.

We are also very much aware of guidelines, including those published by the National Institutes of health, that make recommendations for the use of inhaled corticosteroids in COPD for a limited subset of such patients, based, by their own evidentiary standards, on less than substantial evidence. So, these two applications we are

discussing today, one for a corticosteroid in combination with a long-acting bronchodilator and one for a corticosteroid alone, represent groundbreaking and important issues for the FDA.

I would like to make clear that GlaxoSmithKline has done a very elegant clinical development program for Advair Diskus for the maintenance treatment of COPD that also has allowed the FDA to separately address the efficacy of the two components of that combination product, both fluticasone and salmeterol for the treatment of COPD as well. Since the salmeterol metered-dose inhaler is already approved for COPD, we do not fee that the application for the Serevent Diskus for COPD warranted advisory committee discussion.

In designing this program that GlaxoSmithKline conducted, including the choice of endpoints, GlaxoSmithKline met and worked with the Pulmonary Division. Therefore, FDA agreed beforehand on the choice of primary endpoints. However, as in any development program but particularly for a novel groundbreaking program, we stated at the time of these discussions, and feel now, that a full assessment of efficacy and safety needs to be considered in assessing the

advisability of approving these drugs for this indication, not just the effect on the primary endpoint.

Further, I would point out that our knowledge of the potential risks and of the potential benefits of inhaled corticosteroids for COPD has evolved since we had these discussions with the sponsor at the inception of the program. I think we need to put the sponsor's specific data which we will hear today into the perspective of what we now know and what we need to know about any such treatment in the year 2002 and beyond.

The Advair and Flovent Diskus products, as you know, are approved for the maintenance treatment of asthma and are available for us in the practice of medicine. In fact, I would suspect a rather large number of COPD patients are already receiving one or the other of these products since both are rather brisk sellers in the marketplace and since we know such treatment of COPD is common. However, FDA neither wants to nor can it restrict the practice of medicine.

What you advise us today will not lead to nor lift any restriction of the practice of medicine. Rather, if your recommendation is for

approval, you are indicating that you believe the sponsor has provided substantial evidence of the efficacy and safety of each of these two products for the maintenance treatment of COPD, including chronic bronchitis and emphysema, and that they should be labeled and promoted as such.

I would like to remind you of the evidentiary standard of the Food, Drug and Cosmetic Act under which the FDA has its authority. The FD&C Act calls for, and I quote, evidence from adequate and well-controlled investigations [are done]...to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by experts that the drug will have the effects it is purported to have.

Further, the sponsor, and again I am quoting, has included all tests reasonably applicable to show the drug is safe under the conditions of use suggested in the proposed labeling thereof, end quote. This is, necessarily, a higher standard than what a practitioner would use to make a judgment that an individual drug is right for an individual patient. What we are talking about today is not such a choice in the practice of medicine but whether the U.S. Food and

Drug Administration should specifically label these drugs for this use as providing a clear and defined benefit, given the safety risks.

Finally, let me again be clear that we are here today to talk about two separate applications for two separate products. Each of these applications must be separately thought about and discussed, and recommendation on one drug should not, in and of itself, force a recommendation on the other. Neither should we be focusing in this meeting about class issues with inhaled corticosteroids, because your recommendation should be focused on the data that you have read and will see presented today, though, admittedly, you must consider these data in the milieu of what we know or don't know about COPD and what we know or don't know about inhaled corticosteroids in the treatment of COPD.

Again, I would like to thank you for your time and effort, and welcome you to what I am sure will be a very interesting and important discussion. Thank you.

DR. DYKEWICZ: Thank you, Bob. We will now begin with the GlaxoSmithKline presentations, beginning with an introduction by Dr. David

Wheadon.

GlaxoSmithKline Presentations

Introduction

DR. WHEADON: Good morning.

[Slide]

I am David Wheadon, Senior Vice President of Regulatory Affairs at GlaxoSmithKline.

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On behalf of GlaxoSmithKline, I would like to thank the agency and the committee for this opportunity to review our applications for Flovent Diskus and the combination product, Advair Diskus, for long-term, twice-daily maintenance treatment of chronic obstructive pulmonary disease, including emphysema and chronic bronchitis.

[Slide]

As you have already heard, one medication already approved for the treatment of bronchospasm associated with COPD is Serevent inhalation aerosol. Serevent Diskus for COPD was studied as part of the development program for Flovent Diskus and Advair Diskus, and a supplemental new drug application for Serevent Diskus is also under review by the FDA. However, as the active ingredient of Serevent Diskus, salmeterol, is

already approved for COPD it is not the subject for today's meeting.

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Flovent contains fluticasone propionate, a synthetic glucocorticoid with high topical anti-inflammatory activity and negligible oral bioavailability. Flovent is indicated for the maintenance treatment of asthma, and is approved in the U.S. as a metered-dose inhaler and in two powder formulations.

No inhaled corticosteroid, including Flovent, is currently approved for the treatment of COPD in the U.S. To date, Flovent has been approved for the treatment of COPD in 67 countries outside the U.S. Worldwide, as of August 31, 2001, the exposure to Flovent was estimated to be 14.4 million patient years for the treatment of asthma and COPD. For the treatment of COPD, marketing approval is sought for doses of 250 mcg and 500 mcg administered twice daily.

[Slide]

Advair, the combination of fluticasone propionate and salmeterol in a single inhaler, is indicated for the maintenance treatment of asthma, and is available in the U.S. as a powder

formulation via Diskus. Advair is not currently approved for the treatment of COPD in any country, and the U.S. application was the first submission globally. Worldwide, as of April 30, 2001, the exposure to Advair was estimated to be 1.4 million patient years for both asthma and COPD. Marketing approval is sought for both the 250/50 mcg and the 500/50 mcg strengths of Advair Diskus administered twice daily for the treatment of COPD.

[Slide]

COPD continues to be a significant public health challenge. It remains a major cause of morbidity and mortality in the U.S. and worldwide and, sadly, the rates are increasing, in contrast to many other diseases. COPD affects an estimated 21.7 million Americans and is currently the fourth leading cause of death in the U.S., with expectations for it to become the third leading cause by 2020. The burden of this disease on society is enormous. In 1997, direct and indirect costs associated with COPD were estimated to be over 30 billion dollars in the U.S. alone, and it is likely these costs will continue to increase.

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Despite the enormous burden of COPD, this

disorder often fails to receive adequate attention from the medical community. Recognition of this oversight led to the Global Initiative for Chronic Obstructive Lung Disease, or GOLD. An output of this initiative was the development of evidence-based guidelines for the management of COPD. These guidelines were developed through collaboration with the National Heart, Lung and Blood Institute and the World Health Organization.

[Slide]

In GOLD, the recommendation for the use of inhaled corticosteroids in the management of COPD was based on a considerable body of evidence, which you can see on this slide. These studies demonstrated the beneficial effects of inhaled corticosteroids on a number of clinical parameters. Dr. Malcolm Johnson, who will follow me, will present further details on these studies.

[Slide]

This growing body of evidence has also led to the use of inhaled corticosteroids as common practice for the treatment of COPD in the U.S. As shown here, prescription data from the NDC health patient database of U.S. patients diagnosed with COPD, show that 40 percent of patients are already

using inhaled corticosteroids. Furthermore, this data indicates that 46 percent of patients were prescribed two more COPD maintenance medications. Of these patients, 72 percent were prescribed inhaled corticosteroids as part of their treatment regimen. Additionally, more than half, 57 percent were being treated with an inhaled corticosteroid in combination with an inhaled maintenance bronchodilator.

Thus, we can see inhaled corticosteroids are already being used extensively by physicians for the management of this chronic debilitating disease. In order to ensure that they are used appropriately, we need to provide guidance to physicians on how best to use these agents for the treatment of COPD.

[Slide]

In summary, COPD is a serious public health issue for the U.S. with considerable unmet needs. Approval of new medicines is important for the appropriate treatment of this debilitating disease. The data we will share with you this morning will show that Flovent and Advair provide valuable treatment options for physicians in the management of their patients with COPD.

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To outline the order of the presentations today, Dr. Malcolm Johnson will review the scientific and clinical rationale for the use of Flovent Diskus and Advair Diskus for the maintenance treatment of COPD. Following that, Dr. James Donohue, of the University of North Carolina, will present a clinician's perspective on the diagnosis and management of this difficult condition. Dr. Tushar Shah will then review the efficacy and safety data from our clinical development programs for Flovent and Advair. Finally, I will return to present concluding statements and presenters will then be available to respond to questions from the committee. I would now like to introduce Dr. Malcolm Johnson.

Scientific and Clinical Rationale

DR. JOHNSON: Thank you, David.

[Slide]

Good morning, ladies and gentlemen. I am Malcolm Johnson. I am the global director of Respiratory Science for GlaxoSmithKline.

[Slide]

COPD is a disease characterized by a multi-component pathology -- inflammation,

structural changes in the airways and airway obstruction.

[Slide]

The underlying pathophysiologic processes involved in this disease are shown in this slide. With airway inflammation we see increased numbers of inflammatory cells in airway tissue, cells such as neutrophils, macrophages and the CD8 positive subgroup of T-lymphocytes. There is evidence of increased pro-inflammatory mediators, such as interleukin-8 and tumor necrosis factor alpha. In addition, there is an imbalance between protease and anti-protease enzymes.

The structural changes involve alveolar destruction and an increase in alveolar air space. There is deposition of collagen, hypertrophy of glandular tissue and, in some cases, airway fibrosis has been detected.

With airway obstruction, this is a result of smooth muscle contraction and bronchoconstriction, increased cholinergic tone and loss of elastic recoil due to a destruction in parenchymal tethering. It is this complex underlying pathophysiology that leads to the clinical characteristics of the disease symptoms,

fall in lung function and exacerbations. It is against this pathophysiological construct and the clinical characteristics involved that we need to assess the effectiveness of drug intervention.

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So, beginning first with the inhaled steroids, the first question we need to address is, is there evidence that inhaled corticosteroids have an anti-inflammatory effect in the disease COPD?

[Slide]

Well, ten studies have been reported that have addressed this issue. Seven of these studies have concluded that there is evidence of an anti-inflammatory effect of inhaled corticosteroids in COPD. These studies range from six weeks in duration to 24 weeks in duration and, importantly, four of the studies involved fluticasone propionate.

These studies concluded that there was a reduction in neutrophils not only in the bronchoalveolar lavage fluid but in the sputum of these patients. There was a reduction in some of the key inflammatory mediators involved in this pathophysiology and, importantly, two of the studies detected an important anti-inflammatory

effect of inhaled steroids at the level of airway tissue, in particular, a reduction in this important CD8 positive subgroup of T-lymphocytes and in one case a change in the ratio between the CD8 and CD4 positive cells.

Three studies failed to find an anti-inflammatory effect of inhaled steroids. In the main, they tended to be of shorter duration and involved a smaller number of patients.

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What I would like to do is to focus in a little bit more detail on one of the studies taken from this table. This is a study involving fluticasone propionate at a dose of 1500 mcg a day for a treatment period of 8 weeks. During the course of this treatment the numbers of inflammatory cells in the sputum of these patients was the endpoint assessed.

There was, indeed, a significant reduction in the total number of inflammatory cells in these patients receiving fluticasone, and this was largely accounted for by reduction in the numbers of neutrophils in the sputum. Evidence that this is, indeed, a treatment effect is afforded by a washout phase during this study. As you can see,

the numbers of inflammatory cells then increased back to pre-baseline values.

[Slide]

So, I think we can conclude, based on the ten published studies, that there is overwhelming evidence of an anti-inflammatory effect in this disease, a reduction in some of the key inflammatory cells and inflammatory mediators. In addition, there is at least experimental evidence that inhaled steroids, like fluticasone propionate, may have a beneficial effect on some of the structural changes associated with COPD, in particular, to reduce the degree of hypertrophy of glandular tissue.

[Slide]

The next important question then is to assess the evidence for inhaled corticosteroids having a clinical effect in this disease.

[Slide]

Here, we have 19 studies from which to draw the evidence. Thirteen of these studies -- and you saw this table in Dr. Wheadon's presentation, concluded that there was a clinical efficacy effect of inhaled corticosteroids in COPD. These studies ranged from four weeks duration up to

three years of treatment with the inhaled steroid. They involved a total of four different types of inhales steroids administered on a daily basis, with the doses shown in this column of the table.

The clinical outcomes assessed here were to show an increase in either pre- or post-bronchodilator FEV1. Six of the studies showed a reduction in symptoms in COPD and four of the studies showed a reduction in exacerbations. The longer-term studies, although not showing an impact on decline in lung function over time, did, indeed, show a clinical effect on other outcomes and I will come back to this later in the presentation.

Six studies concluded there was no clinical benefit for inhaled steroids in this disease. Two of these studies were also those that failed to find an anti-inflammatory effect of inhales steroids. In a further three studies, the patients involved in these studies had lung function equal to or greater than 80 percent predicted.

[Slide]

As before, what I would like to do is to take a number of these studies now and look in a

little bit more detail. I would like to begin with this study, which is a large Canadian epidemiology study that was conducted in Ontario between the years of 1992 and 1997. It involves more than 22,000 patients that had been hospitalized as a result of an exacerbation of COPD.

The study focused on the outcome of the 12 months after discharge and looked at all-cause mortality in these patients or the risk of repeat hospitalization. The analysis showed, in fact, that those patients that were previously taking inhaled corticosteroids had a 26 percent lower relative risk of either all-cause mortality or repeat hospitalization as a result of an exacerbation of their disease.

[Slide]

What I would like to do now is to go on to look at two studies that have specifically looked at fluticasone propionate. The first study is the Paggiaro study. Patients included in this study, more than 280 in number, were classified as non-reversible in that they did not achieve more than a 15 percent increase in FEV1 following bronchodilator.

The study involved fluticasone propionate

at a dose of 500 mcg twice daily, and the study was conducted over a 24-week period. Those patients receiving the inhaled steroid showed a progressive increase in pre-dose FEV1, whereas those on placebo showed a progressive decline in pre-dose FEV1. At 24 weeks there was a 160 ml difference between the steroid treated arm and the placebo treated arm.

[Slide]

The key significant factor about the Paggiaro study was that this was the first study that was designed to look at exacerbations of this disease. The patients included in this study -- as I said, there were more than 280 -- had a history of exacerbations. They had at least one per year for the previous three years.

For the purposes of this study, exacerbations were defined as worsening of COPD symptoms requiring changes to normal treatment. Severity of exacerbations were further defined if they were mild, if they were self-managed by the patient at home; if they were moderate they were treated by a physician; and if there were severe exacerbations, they required the patient to be hospitalized. The last point is that multiple exacerbations requiring oral corticosteroids were

allowed to be included in the analysis of this data.

[Slide]

There were about 140 patients in the placebo and 140 patients in the fluticasone propionate treated arm of the study. There was a numerical reduction in the total number of exacerbations in the steroid arm but this did not reach statistical significance. When the number of patients that experienced one or more exacerbations were further analyzed, again there was no change in the total number but there was a significant decrease in the numbers of patients experiencing either a moderate or a severe exacerbation and, interestingly, a significant increase in the number of patients experiencing a mild exacerbation, suggesting that the steroid treatment was changing the spectrum of exacerbations from moderate to severe towards the mild end of the spectrum.

[Slide]

The next study that has involved fluticasone that I would like to discuss is the ISOLDE study. This was the largest and longest study conducted with fluticasone propionate in COPD. It involved more than 750 patients who,

again, were non-reversible, showing a less than 10 percent change in predicted values, and the mean FEV1 was 50 percent at baseline.

The study involved first of all a two-month period where corticosteroids were withdrawn, this run-in period. Interestingly, a subanalysis carried out by Gerard and colleagues, and published in Respiratory Medicine in 1999, showed that in the patients that were withdrawn from steroids there was a six-fold higher incidence of exacerbations compared to those patients not previously treated with this class of drug.

After the run-in period the patients were randomized to either receive fluticasone propionate at a dose of 500 mcg a day from a metered-dose inhaler or a corresponding placebo for a period of three years.

[Slide]

In this slide I am looking at the post-bronchodilator FEV1 data taken from the ISOLDE study. On the vertical axis is the post-bronchodilator FEV1; on the horizontal axis, the time points up to three years of treatment. Those patients receiving the inhaled steroid in the first three months of treatment showed a

significant increase in the post-bronchodilator FEV1 volume. This value then remained statistically higher than those patients in the placebo arm of the study, and there was no evidence that these two lines were converging over the three years of treatment.

[Slide]

The second important data from the ISOLDE study was that the effect of the steroid on exacerbation rate was assessed, and for the purposes of this study exacerbations were defined as requiring oral corticosteroid and/or antibiotic intervention. The patients receiving fluticasone propionate showed an approximately 25 percent reduction in exacerbation rate in this study, exacerbations per patient per year.

[Slide]

The final element of the ISOLDE study I would like to review is the impact of the steroid on quality of life or health status. This was assessed in this study using the St. George's Respiratory Questionnaire. Using this questionnaire, the data is expressed that an increase in score from this questionnaire reflects a decline in quality of life. The data from the

ISOLDE study showed that fluticasone propionate treatment reduced the decline in quality of life in these patients. That decline was reduced to an extent where there was approximately a two-fold increase in the time required before the decline in quality of life passed through a level of clinical significance.

[Slide]

So, I think we can conclude that the weight of evidence is in favor of a clinical effect of inhaled corticosteroids in COPD. That effect is to reduce symptoms, to increase both pre- and post-bronchodilator FEV1 and to reduce exacerbations.

[Slide]

Turning now to salmeterol, and as we heard from Dr. Wheadon, this is a drug already approved for the use of COPD here, in the United States.

[Slide]

Salmeterol is quite clearly a long-acting bronchodilator in this disease condition. This is change in FEV1 on day one, shown in green, and after 12 weeks of treatment shown in yellow.

Quite clearly the drug is effective in increasing FEV1 and, importantly, this effect show

no effect of tolerance during this prolonged period of treatment. In addition, an important increase in baseline lung function was detected in these patients as a result of exposure to the long-acting beta-agonist.

[Slide]

So, I think we can conclude that the major impact of a long-acting beta-agonist is to address the component of airway obstruction and to reduce the element of broncho-constriction associated with this disease.

[Slide]

Now, if we consider salmeterol and fluticasone in combination, what we have here are two drugs that influence different aspects of the underlying pathophysiological process, salmeterol, as I have just said, largely addressing airway obstruction and fluticasone propionate addressing some of the key elements of the underlying inflammatory process in this disease. When salmeterol and fluticasone are brought together in the context of Advair as a combination therapy, there is an opportunity then to capitalize on the fact that these drugs do influence different elements of the underlying disease process and

therefore, there is an opportunity to have an additive nature to the combined treatment. The additive nature would increase, then, the reduction in symptoms, the increase in bronchodilator activity and a reduction in exacerbations.

[Slide]

However, finally, there is increasing evidence that there is a positive molecular interaction between corticosteroids and long-acting beta-agonists. The first example of that is shown on this slide. It comes from a study from Dr. Braniuk and his colleagues at Georgetown University. The study showed that the administration of clinical doses of corticosteroids -- here beclomethasone dipropionate was administered intranasally for a period of three days, and this led to an increase in the density of beta-2 receptors in the respiratory mucosa of the recipients.

This effect is the result of activation of the gene and coding for the beta-2 receptor. It is a classic effect shown by all corticosteroids. And, a result of this increased density of beta-2 receptors will be to promote the activity of salmeterol.

[Slide]

In turn, there is increasing evidence that long-acting beta-agonists like salmeterol will potentiate the inhibitory effect of corticosteroids, like fluticasone propionate, on the release of the inflammatory mediators from key cells. In this study, which was conducted in human airway smooth muscle cells, human necrosis factor alpha was used to induce the release of the neutrophil chemoattractant interleukin-8 and TNF-alpha and IL8 are two key mediators in the pathophysiology of COPD. The corticosteroid alone has an inhibitory effect on IL8 release and, as you can see from the slide, this effect is further increased by the addition of the long-acting beta-agonist salmeterol. This effect is due to salmeterol priming the glucocorticoid receptor, the target receptor for corticosteroids, and rendering then that receptor more sensitive to steroid-dependent activation. The outcome of this then would be to promote the anti-inflammatory effects of fluticasone propionate.

[Slide]

So, I can conclude then for the scientific and clinical rationale for combining fluticasone

and salmeterol in the treatment of COPD in the following way: fluticasone propionate is an effective inhaled anti-inflammatory corticosteroid and the evidence is overwhelmingly in support of a clinical benefit in COPD. Salmeterol is a long-acting beta-2 agonist with, again, demonstrated efficacy in this disease. Each molecule is, indeed, influenced by a different aspect of the underlying pathophysiology of COPD and, when brought together, they provide a broader cover than either drug alone.

Finally, there is increasing evidence of a positive interaction between these two classes of drugs, which may be important in improving their overall efficacy when used in combination in COPD.

I will now hand over to Dr. James Donohue, who will give you a clinician's perspective on the treatment of COPD. Jim?

Clinical's Perspective

DR. DONOHUE: Thank you, Malcolm.

[Slide]

Good morning. My name is Jim Donohue. I am presently chief of the Division of Pulmonary and Critical Care Medicine at the University of North Carolina, in Chapel Hill. I am happy to be here

today to speak to the advisory committee on behalf of GlaxoSmithKline. I will speak to you as a clinician with many years experience in the management of patients with COPD and the use of COPD therapies. I will also speak to you as a clinical investigator who has conducted numerous clinical trials on COPD in the course of my career for many different companies, including GlaxoSmithKline. Therefore, I hope I can be of some help and provide some insight into therapeutic management of COPD.

[Slide]

Today I would like to focus on COPD from a clinician's perspective, including how we diagnose this condition and how treatment is evaluated. I would like to also mention the Global Initiative for Obstructive Lung Disease, or GOLD, guidelines which are useful for COPD. Finally, I will discuss how I use the available medications in my own clinical practice.

[Slide]

COPD is a clinical diagnosis. It is based on a patient's medical history, especially their smoking history; their age; their symptoms; and persistent airflow obstruction on spirometry. A

post-bronchodilator FEV1 of less than 80 percent of predicted, in conjunction with an FEV1/FVC ratio of less than 70 percent confirms the presence of airflow limitation. The key words -- it is not fully reversible. This is the definition of COPD from the GOLD guidelines.

[Slide]

While the airway response to short-acting bronchodilators, as expressed in the percent increase or change from baseline FEV1, is very important in the diagnosis of asthma. Reversibility to albuterol does not exclude the diagnosis of COPD and, in fact, is more the rule than the exception. Recent treatment guidelines for COPD do not include reversibility testing as a criterion for the diagnosis of COPD, and we will review some of the data to support this in the next few slides.

[Slide]

One of the pivotal studies in North American, known as the Intermittent Positive Pressure Breathing Trial, the IPPB Trial, for COPD was conducted in the late '70s and early '80s, and published by Nick Anthonisen, in Winnipeg, and colleagues. The study was supported by a grant

from the National Institutes of Health and involved multiple sites.

The investigators evaluated the response to isoproterenol, the short-acting bronchodilator. It was a huge study, 985 patients, the largest study at its time. It was conducted over a three-year period. Pre- and post-bronchodilator spirometry was evaluated at screening and subsequently every three months over the duration of the study. The entry criteria for COPD included an FEV1 of less than 60 percent of predicted and an FEV1/FVC ratio of less than 60 percent -- so very reasonable criteria.

Looking at the demographic data, they are very typical of the patients that we see in a modern pulmonary practice and also in our clinical trials program. The patients have a mean age of 61; at this stage predominantly male, although that will change; the smoking status, 54 pack years; 40 percent were current smokers; and the lung function as reflected in the FEV1 was 36 percent of predicted.

[Slide]

One of the most interesting things about this most important study was the point that

reversibility is common in patients with COPD, particularly in clinical trials. Using a 12 percent increase in FEV1 over baseline as a threshold for defining reversibility, fully half of these patients were reversible at baseline or at screening. Furthermore, for those patients who were non-reversible at the screening visit, 30 percent of those would be reversible on a subsequent clinic visit. Overall, nearly 68 percent of these subjects had a 15 percent increase in post-bronchodilator spirometry at least once over the seven visits during the trial.

These data clearly demonstrate that bronchodilator response at a single visit does not necessarily correlate at subsequent evaluations, and based on this study, reversibility really is typical of COPD and doesn't have a whole lot of relevance to the diagnosis. For this reason, reversibility has not been included as a diagnostic criterion in either the ATS guidelines nor the recent GOLD guidelines.

[Slide]

To follow-up on this, data from several large clinical trials conducted in COPD are consistent with the IPPB trial. Shown on this

slide are the key demographic data from these trials. The patients included are similar, of course, to the IPPB. The mean age of the patients is in their 60s; male predominant, heavy pack smoking; FEV1 40 percent, 36 percent and 45.

Please draw your attention here to the percent of patients who are considered reversible. Now, the criteria for reversibility testing varies amongst these trials, ranging from 12 to 15 percent, albuterol either two to four puffs, ipratopium or the combination would be used. We see 62 percent, 68-73 percent in the Durinsky article for the Combivent data, and 42 percent for formoterol. So, reversibility is very common in COPD and, of course, it is not fully reversible.

Let's change gears now and see how we assess treatment responses in COPD, both in clinical trials and in our practices. It is important to recognize up front that the magnitude of changes in COPD are much less than asthma.

[Slide]

Spirometry is regarded as the gold standard in evaluating COPD. It provides objective and reproducible results. We use spirometry to establish the diagnosis in our patients; to tell

them how severe their disease is or for prognostic information; and we monitor the response to treatment.

Additional measures that we use to evaluate treatment responses include assessment of the health status or quality of life of our patients, their symptoms and, most importantly, their exacerbations. These other measures are more subjective and usually studies are not optimally powered or designed to detect treatment differences. However, even small differences across groups may translate to very important benefits for our individual patients.

[Slide]

Currently very few drugs are approved for the management of COPD. I would like to review two relevant examples of the types of responses that we typically observe. Here are the results from the first combination product evaluated in subjects with COPD, Combivent. As you can see, there is a nice, brisk response and there is a reasonable difference between the combination of ipratropium and albuterol and the individual components. That change is 70 ml. So, those of us who are used to thinking in terms of asthma, that may not seem like

a great deal. Nonetheless, from my own personal experience, this small change corresponds to large benefits to the patients that we see in our practices, and this is the first-line therapy for the treatment of patients with COPD.

[Slide]

Furthermore, let's review some of the other efficacy measurements that we look at in clinical trials. Despite the improvement noted in the FEV1 with the combination of albuterol and ipratropium over its components, quality of life, physician's global evaluation, COPD symptom scores and the peak expiratory flow rate do not reach a significant difference amongst treatment groups and didn't change over time. Nonetheless from my clinical experience and that of most pulmonologists, this is a very, very valuable agent and is widely used in patients who have symptoms.

[Slide]

Let's switch now to other clinical trials that we have participated in. You have already seen the FEV1 data from Dr. Johnson for the salmeterol clinical trials program in North America. Let's look at the additional efficacy measures evaluated in those trials.

We note consistent improvement in peak flow and Ventolin use when compared to placebo. However, for many other measures the treatment effects favored salmeterol but did not reach statistical significance. This does not mean that this drug is not beneficial in the treatment of COPD, rather, it suggests that small changes between treatment groups may underestimate the benefit to individual patients.

As you can see from these two examples, the types of treatment responses that we can expect in COPD are quite modest. The effects from Combivent and salmeterol, although modest in the clinical trials, have proved to be extremely valuable treatment options for our patients with COPD.

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Let's address just briefly the GOLD guidelines. These recently developed evidence-based, Global Initiative for Chronic Obstructive Lung Disease or GOLD guidelines have evaluated the appropriate use of pharmacotherapeutics in the therapeutic management of COPD. It was my pleasure to serve as a consultant reviewer for these guidelines. These

guidelines are endorsed by the American Thoracic Society and the American College of Chest Physicians. These guidelines clearly recognize the role of bronchodilators in the treatment of COPD. More importantly, the guidelines recognize that bronchodilators alone or in combination are not adequate to treat all the symptoms associated with this disease. Many patients require a therapy with other classes of medications including inhaled corticosteroids.

[Slide]

In the GOLD guidelines four stages of disease severity were established: at risk, mild, moderate and severe. Based on these guidelines almost all the patients that we see in the clinical trials that I have presented would be classified as having moderate to severe disease. For patients with moderate to severe disease, maintenance bronchodilator treatment is recommended. However, for many patients this is not enough.

As discussed by Dr. Johnson, numerous clinical trials have been conducted evaluating the efficacy and safety of inhaled corticosteroids in patients with COPD. The GOLD reviewing committee evaluated all the peer reviewed published clinical

trials assessing the overall benefit-risk of inhales steroids in COPD. Based on the totality of the data, there was a consensus to recommend inhaled steroids for symptomatic patients who demonstrate a response to inhaled corticosteroids or for those patients with an FEV1 of less than 50 percent of predicted who experience repeated exacerbations.

Thus, current evidence-based treatment guidelines acknowledge the value of inhaled corticosteroids in the therapeutic management of moderate and severe COPD. While effective, oral corticosteroids are associated with significant side effects, as every one knows. For this reason, the GOLD guidelines state that chronic maintenance therapy with oral corticosteroids should be avoided regardless of the severity of the disease.

[Slide]

COPD, make no mistake about it, is a devastating disease. First and foremost, we want to prevent worsening of this condition. In my own practice I emphasize smoking cessation, immunization, prevention of further lung injury such as avoiding crowds in an influenza epidemic, avoiding outdoor air pollution when the ozone

levels are high, or what-have-you. We also strongly recommend an exercise program, some type of pulmonary rehabilitation whether or formal or just an exercise program at home.

The choice of pharmacotherapy is based on the severity of our patient's symptoms, defined both by lung function and symptoms. We usually begin with bronchodilators, anticholinergics, long-acting bronchodilators either alone or in combination. However, for many patients, despite optimal use of bronchodilators, control of their disease remains quite poor. For these patients I would institute a trial of inhaled corticosteroids per the GOLD guidelines recommendations. My experience working in a university practice is similar to that of SININ2 of Toronto. I have found that inhaled steroids reduce exacerbations and reduce the exposure of our patients to oral corticosteroids which are part and parcel of the treatment of an exacerbation.

[Slide]

In conclusion, the diagnosis of COPD is based on several clinical parameters. As I have illustrated, a high proportion of the patients with COPD do demonstrate reversibility to

bronchodilators. For this reason, the presence of reversibility does not exclude the diagnosis of COPD. In evaluating treatment response, spirometry still remains the gold standard. We have had considerable success and experience with use of this measure in assessing treatment responses compared to other more subjective measures.

In general, treatment responses in COPD are quite small, very modest and often are quite variable. However, these small changes between treatment groups may underestimate the benefits seen in individual patients. The use of inhaled corticosteroids in COPD is advocated by evidence-based international guidelines. My personal experience and practice are consistent with this view. Even more importantly, I have found that use of inhaled steroids has reduced reliance on oral corticosteroids with their much greater safety concerns.

I would like to thank you for this opportunity to address the committee and to speak on these issues. I would next like to introduce Dr. Tushar Shah who will be presenting the clinical results on the Advair and Flovent Diskus program. Thank you very much.

Clinical Efficacy and Safety

DR. SHAH: Thanks, Dr. Donohue, and good morning everyone.

[Slide]

My name is Tushar Shah, and I am the vice president of Respiratory Clinical Development for GlaxoSmithKline.

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In the next 50 minutes, I am pleased to review results of Flovent and Advair Diskus program which was designed in consultation with the FDA. I will share with you results which will demonstrate that we achieved the primary objectives for this program.

For Flovent, the results will show that we demonstrated greater efficacy on the primary efficacy measure compared to placebo, with no significant safety concerns. For Advair, the results will show that we demonstrated greater efficacy than the primary efficacy measures compared to each component, without additional safety concerns.

We realize that long-term safety information will be an important consideration in assessing the benefit-risk ratio for the use of

inhaled corticosteroids in the treatment of COPD. I will also summarize some of the relevant long-term safety data from the use of fluticasone propionate in asthma and COPD which will support the safety information from our clinical program.

[Slide]

Before I begin, it may help for me to define some of the abbreviations I will be using in my presentation. FSC refers to fluticasone propionate and salmeterol combination product. Whereas the slides will display FSC 500/50 and FSC 250/50, I will refer to Advair 500 and Advair 250 in my text for purposes of clarity and ease of presentation.

[Slide]

We performed three large multicenter, randomized, double-blind, placebo-controlled trials for the develop of Flovent and Advair in COPD. All three studies were conducted in the U.S. and had identical inclusion/exclusion criteria. For Flovent Diskus, FLTA3025 compared two dosages of FP versus placebo, whereas SFCA3006 and SFCA3007 compared a single dose of FP versus placebo. Hence, three independent studies were performed to assess the effects of Flovent in COPD. For Advair

Diskus, SFCA3006 and SFCA3007, compared Advair to each individual component at the corresponding FP dose and to placebo. In all three studies treatments were administered twice daily for 24 weeks duration.

[Slide]

The design of FLTA3025 included a two-week placebo run-in period during which time patients discontinued all COPD medications other than PRN albuterol. The use of concurrent methylxanthines was permitted as long as the dose remained relatively constant during the trial.

The purpose of the run-in period was to assess if patients met enrollment criteria for randomization and to ensure their adherence to study procedures. Eligible patients were then randomized to either FP 500, FP 250 or placebo for 24 weeks of treatment.

Patients were evaluated at regular scheduled visits during the course of the trial and we had slightly over 200 patients in each treatment group in this trial. Pulmonary function tests and symptom and quality of life questionnaires were administered at clinic visits, and patients also completely diary cards for collection of some

efficacy and safety information.

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The study design for SFCA3006 and SFCA3007 were similar to FLTA3025, with the exception of the treatment groups. In SFCA3006 Advair 500 was compared to Flovent Diskus 500, Serevent Diskus and placebo. The number of patients enrolled in this trial ranged from 164 to 185 per treatment group.

[Slide]

In SFCA3007 Advair 250 was compared to Flovent Diskus 250, Serevent Diskus and placebo. The number of patients enrolled in this trial ranged from 177 to 185 per treatment group.

One advantage of this study design is that within each study we actually have two opportunities to assess the effect of the 250 mcg dose of FP. One is comparing FP alone versus placebo. The second is comparing Advair 250 versus albuterol.

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The inclusion/exclusion criteria were identical for the three trials and were comparable to the criteria used in previous clinical trials conducted for COPD. Patients had to be 40 years of age or older and have COPD as defined by ATS in

order to enter these trials. Patients could be current or former smokers, with a 20 pack a year or greater smoking history. They had to have FEV1 less than 65 percent predicted and an FEV1/FVC ratio less than or equal to 70 percent. Additionally, patients had to achieve a score of greater than or equal to 2, which is regarded as moderate dyspnea on the Modified Medical Research Council, or MMRC, dyspnea scale at screening, and also have symptoms of chronic bronchitis, morning cough and sputum at baseline in order to enter these trials.

[Slide]

Patients were excluded from the trials if they had a current diagnosis of asthma. Patients were also excluded if they needed to use systemic corticosteroids or high dose inhaled corticosteroids, defined as a dose of greater than 1000 mcg a day of fluticasone propionate or an equivalent or other inhaled corticosteroids during the six weeks prior outcome the screening visit. Patients were also excluded if they needed long-term oxygen therapy or experienced COPD exacerbation during the run-in period.

[Slide]

As reviewed by Dr. Donohue, FEV1 was selected as the primary efficacy measure since it is clinically relevant, objective and, most importantly, has been useful in discriminating treatment effects in COPD. These studies were optimized to evaluate this measure. Since salmeterol and FP exert their pharmacological action by different mechanisms, two measures of lung function were prespecified as the primary efficacy measure for assessing treatment effects.

Pre-dose FEV1 was used to compare FP versus placebo and to evaluate the contribution of FP and Advair when compared to salmeterol. Two-hour post-dose FEV1 was used to evaluate the contribution of salmeterol and Advair when compared to FP. The two-hour post-dose FEV1 was selected because it corresponded to the peak bronchodilation period for salmeterol and correlated well with the post-dose 12-hour FEV1 AUC results. This approach for selection of primary efficacy measures was reviewed and agree with the FDA prior to initiating our trials.

[Slide]

The secondary efficacy measures we discussed and agreed with the FDA for inclusion in

this program included the transition dyspnea index, or TDI, for assessment of dyspnea; the chronic respiratory disease questionnaire, or CRDQ, for assessment of quality of life, and the chronic bronchitis symptoms questionnaire, or CBSQ, for assessment of symptoms of cough and sputum production. These three measures were prespecified as key secondary efficacy measures. The TDI and CRDQ are validated instruments and have defined a change from baseline which is regarded as clinically significant. The CBSQ was a new instrument which had not been previously validated or had been evaluated in a clinical trial. Additional secondary efficacy measures included daily diary card information, such as morning peak flow, Ventolin use and nighttime awakenings.

It is important to note that Ventolin use in this program was PRN. Hence, the use of this product during the course of the trial represents a marker of symptoms. This is also true for nighttime awakenings since only information on awakenings requiring Ventolin were collected. Exacerbations based on physician discretion were also recorded, and were defined by the need for treatment with antibiotics and/or oral

corticosteroids. This is similar to the definition that has been used in other COPD trials.

[Slide]

Since these trials were of six months duration and placebo-controlled, withdrawals from double-blind treatment were anticipated. In order to allow for a potential bias caused by patient withdrawal in the analysis of the results, endpoint defined a priori was used. The endpoint represented the last baseline observation. This allowed us to include nearly all patients who received study drug in our efficacy analysis.

[Slide]

Patient demography and baseline characteristics integrated for all three studies are presented on this slide. Results for the individual studies were similar to these and are included in your briefing document. Patient demography and baseline characteristics were similar across treatment groups for the integrated data, as well as for the individual studies. Patients enrolled in these trials had a mean age of approximately 63 years. About 65 percent were male. About 94 percent were Caucasian. Half were current smokers and had a greater than 60 pack year

smoking history.

In this program, slightly more than 25 percent used inhaled corticosteroids previously. This is lower than the level of inhaled corticosteroid use in current practice. They had moderate to severe alveolar obstruction of approximately 41 percent predicted, and slightly more than half were reversible to albuterol, defined as greater than 12 percent, and 200 ml increase in FEV1 following four puffs of albuterol. As reviewed by Dr. Donohue, this is consistent with the level of reversibility seen in previous clinical trials conducted in COPD. Approximately 73 percent of these patients were reported as having emphysema. There can be no question that these patients are representative of the types of patients who are likely to be diagnosed and managed as having COPD in the U.S.

[Slide]

I will now share the efficacy results from these trials. Due to time constraints, I will focus my presentation on the primary measures of efficacy and briefly summarize the findings of the secondary efficacy measures. I will first review the results for Flovent, followed by Advair.

[Slide]

As previously mentioned, the primary measure of efficacy for assessing the treatment effects of FP was morning pre-dose FEV1.

[Slide]

The results of pre-dose FEV1 from FLTA3025 are displayed on this slide. Before reviewing these results, let me quickly orient you to the information on this slide. The Y axis represents the change in FEV1 in milliliters and the X axis is the study week. Additionally, on the right side of the slide are presented the endpoint results for the treatment groups. We have also provided the percent change from baseline in FEV1 at endpoint, and results of statistical analysis will only be presented for endpoint. I will be using this format during the next few slides which will be reviewing the FEV1 results.

On this slide the FP 500 treatment group is depicted in orange, on the top; the FP 250 treatment group in yellow, in the middle; and the placebo in blue, on the bottom. Results from this trial indicate that treatment with FP was associated with dose-related improvements in FEV1. However, we were surprised by the smaller

improvement seen in this trial compared to previous results reviewed by Dr. Johnson.

As the figure indicates, the greatest separation from placebo occurred near the end of the treatment period. At endpoint the improvements in FEV1 were significantly greater for the FP 500 compared to placebo, with a model estimated treatment difference of 57 ml. In this trial no significant differences between FP 250 and placebo were observed for FEV1, the model estimated treatment difference being 32 ml. As you will see in the next two trials, we had more robust treatment effects with both doses of FP in COPD.

[Slide]

Results for pre-dose FEV1 for the FP 500 treatment group from SFCA3006 are shown on this slide. The other treatment groups have been omitted for purpose of clarity and will be presented later.

The FP 500 treatment group is depicted in orange and the placebo group in blue. Results from this trial indicate that treatment with FP 500 was associated with more robust and significantly greater improvements in pre-dose FEV1 compared to placebo. Once again, the greatest separation from

placebo occurs near the end of the trial, indicating we may have not reached a plateau for treatment response. At endpoint the improvements in FEV1 were significantly greater for FP 500 compared to placebo, with a model estimated treatment difference of 105 ml.

[Slide]

Results for pre-dose FEV1 for the FP 250 treatment group from SFCA3007 are shown on this slide. In contrast to what we saw on FLTA3025, results from this trial indicate that treatment with FP 250 was associated with a more robust and significantly greater improvement in pre-dose FEV1 compared to placebo. Even in this trial we do not appear to have reached a plateau in the treatment response. At endpoint the improvements in FEV1 were significantly greater for FP 250 compared to placebo, with a model estimated treatment difference of 112 ml.

[Slide]

On this slide we have provided results for all four treatment groups from SFCA3007. In addition to the comparisons with the FP 250 and placebo group which I just reviewed, we have provided the results with Advair and salmeterol

treatment groups in purple and green, respectively.

This study provides us a second independent opportunity to assess the treatment effects of the FP 250 mcg dose comparing Advair to salmeterol. Greater improvements in FEV1 were seen with Advair versus salmeterol, with a model estimated treatment difference of 69 ml at endpoint, which was statistically significant.

Hence, we have three opportunities to assess if the FP 250 mcg twice daily dose provides clinical benefits in COPD. In two of the three instances we demonstrated robust treatment effects with this dose of FP.

[Slide]

This slide summarizes the pre-dose FEV1 results for patients who were defined as reversible or non-reversible at baseline for the FP treatment groups across the three trials. As expected, a greater magnitude of response was observed with FP treatment in the reversible patients since, by definition, these patients had greater room for improvement. However, in SFCA3006 and SFCA3007, where we had more robust treatment effects, even in the non-reversible patients fairly large treatment effects were observed in this population. As

reviewed by Dr. Johnson, results from studies conducted in less reversible patients indicate that FP provides benefits beyond improvements in lung function. In these trials, reduction in exacerbations and improvements in health status were also seen with FP treatment.

[Slide]

This table summarizes the results of the statistical analysis for the secondary efficacy measures between FP and placebo across the three trials. A check represents where p values were less than 0.05, and dash where p values were greater than 0.05. It is important to note that in SFCA3006 and SFCA3007 we amended the protocols a priori to adjust for multiple comparisons for the three key secondary efficacy measures, denoted by a star.

Before I review these results, I would like to emphasize that we designed and optimized these studies for the primary, not secondary, endpoints. So, our expectations for secondary measures are that they should be supportive of the findings we see on our primary efficacy measures. This is what we observed in these trials.

For comparisons of FP versus placebo

greater improvements were seen for nearly all secondary efficacy measures with both doses of FP across the three trials, with most differences achieving p values less than 0.05. In FLTA3025 many of the differences from placebo for secondary measures achieved p values less than 0.05 for the FP 250 compared to the placebo comparison, as is shown in the first column. This indicates that even in this trial FP 250 provided clinical benefits in the treatment of COPD. For most measures similar improvements were seen between the two doses of FP with the exception of TDI, which is shown in the first line. For this measure, the FP 500 twice daily dose was consistently and significantly better than placebo, and in SFCA3006 achieved a clinically significant difference of 1 from placebo. This was the only instance where we achieved a predefined, clinically significant difference between placebo and FP for the three key secondary efficacy measures.

In general, the treatment effects were not significant for the CBSQ compared to placebo, suggesting that this new questionnaire may not be sensitive at discerning treatment effects.

Unlike previous trials which demonstrated

inhaled corticosteroid treatment, including FP, was associated with reductions in exacerbations, in this clinical program none of the treatments significantly reduced the time to COPD exacerbations compared to placebo. The most likely reason for this discrepancy is that we did not require patients to have a history of COPD exacerbations for entry into these studies, and we withdrew patients who needed oral corticosteroid bursts for treatment of an exacerbation.

We did this because we wanted to ensure that the use of concomitant oral corticosteroids did not hinder our ability to assess treatment effects on the primary efficacy measure, which is FEV1. If our primary endpoint would have been to examine exacerbations, we would have designed a clinical trial very differently than what we have and more like what Dr. Johnson reviewed where significant improvements with FP treatments on exacerbations were seen. These results do support the efficacy of FP in treatment of COPD.

[Slide]

The efficacy results for Flovent from these trials can, hence, be summarized as follows: In all three studies greater improvements in the

primary efficacy measure, pre-dose FEV1, were seen with FP treatment compared to placebo. In FLTA3025 a dose-related improvement was seen with a response to FP 500 achieving statistical significance. In SFCA3006 and SFCA3007 more robust improvements in FEV1 were observed which were significantly different from placebo. Comparison of the response with Advair versus salmeterol in SFCA3007 provides additional evidence for the benefits of the FP 250 twice daily dose in COPD. As expected, a greater magnitude of response in FEV1 was observed in reversible versus non-reversible patients following FP treatment.

Results for the secondary efficacy measures support the primary analysis. Greater improvements were demonstrated for most secondary efficacy measures with FP compared to placebo, with many differences achieving p values less than 0.05. Overall, both doses of FP provided comparable benefits with some suggestion of a dose effect. In FLTA3025 dose-related improvements in FEV1 were seen and were consistent and greater improvements in dyspnea as measured by the TDI were seen with the FP 500 versus the FP 250 dose.

The magnitude of improvements for most

efficacy measures seen with both doses of FP were similar to that seen with currently available treatments, as reviewed by Dr. Donohue. These treatments that are currently available are regarded as clinically useful in the management of COPD. This indicates that the benefits we see with FP treatment in COPD will also be clinically important for these patients.

[Slide]

I will now share the efficacy results for Advair from these trials. Due to time constraints, once again I will focus my presentation on the primary efficacy measures and briefly summarize the findings of the secondary efficacy measures.

[Slide]

As previously noted, to assess the contribution of FP pre-dose FEV1 was defined as the primary efficacy measure to compare Advair versus salmeterol. This approach had been agreed with the FDA during the design of the program.

[Slide]

Results for pre-dose FEV1 from SFCA3006 are shown on this slide. I would like to draw your attention to the purple line on top which represents Advair 500, and the green line below it

which represents the salmeterol treatment group. As before, the Y axis represents the mean change in FEV1 in milliliters and the X axis is the study week of treatment. On the right side we have included the endpoint results, and have highlighted statistically significant differences only for the comparisons being discussed.

[Slide]

We have now included the FP, depicted in orange, and the placebo group, in blue, for completeness. Results from this trial indicate that treatment with Advair 500 resulted in significantly greater improvements in pre-dose FEV1 compared to salmeterol. Improvements were noted as early as the first week, with maintenance of improvement during the treatment period. At endpoint the improvements in FEV1 were significantly greater for Advair 500 compared to salmeterol, with a model estimated treatment difference of 67 ml. The model estimated treatment difference between Advair and placebo was 159 ml.

[Slide]

Results for the pre-dose FEV1 from SFCA3007 with Advair 250 are shown on this slide. The results indicated that treatment with Advair

250 was associated with significantly greater improvements in pre-dose FEV1 compared to salmeterol. At endpoint the improvements in FEV1 were significantly greater for Advair 250 compared to salmeterol, with a model estimated treatment difference of 69 ml. The model estimated treatment difference between Advair 250 and placebo in this trial was 161 ml. The magnitude of improvements with both doses of Advair on pre-dose FEV1 represent an advance in the treatment of COPD.

[Slide]

As reviewed previously, to assess the contribution of salmeterol two-hour post-dose FEV1 was used to compare Advair versus FP.

[Slide]

Results for the two-hour post-dose FEV1 from SFCA3006 with Advair 500 are shown on this slide. The purple line on top represents Advair 500 and the orange line below it represents FP.

[Slide]

We have now included the remaining treatment groups, salmeterol in green and placebo in blue, for completeness. Results from this trial indicate that treatment with Advair 500 was associated with significantly greater improvements

in the two-hour post-dose FEV1 compared to FP. At endpoint improvements in FEV1 were significantly greater for Advair 500 compared to FP, with a model estimated treatment difference of 129 ml. Compared to placebo, this improvement was also significant, with a model estimated treatment difference of 232 ml.

[Slide]

Results for the two-hour post-dose FEV1 from SFCA3007 with Advair 250 are shown on this slide.

[Slide]

Results from this trial indicate that treatment with Advair 250 was associated with significantly greater improvement in two-hour post-dose FEV1 compared to FP 250. Improvements were noted as early as the first week, with maintenance of improvement over the study interval. There was no evidence that the benefits waned with continued treatment. At endpoint improvements in FEV1 were significantly greater for Advair 250 compared to FP, with a model estimated treatment difference of 124 ml. Compared to placebo, this improvement was also significant with a model estimated treatment difference of 214 ml.

[Slide]

This slide summarizes the pre-dose and post-dose FEV1 results for patients defined as reversible and non-reversible at baseline for the four treatment groups in the two Advair trials. As expected, a greater magnitude of response was observed with all treatments in the reversible patients since, by definition, these patients have greater room for improvement. However, for the pre-dose FEV1 responses in even the non-reversible patients were over 100 ml compared to placebo for both doses of Advair. This indicates robust treatment effects for Advair even in this population.

[Slide]

This table summarizes results of the statistical analysis for the secondary efficacy measures between FP and salmeterol versus placebo for the two Advair trials. A check represents where p values were less than 0.05, and a dash where p values were greater than 0.05. As previously noted, in SFCA3006 and SFCA3007 we amended the protocols a priori to adjust for multiple comparisons for the three key secondary efficacy measures, denoted by a star.

Results for salmeterol and FP on secondary efficacy measures in these two trials were comparable, with several comparisons achieving p values less than 0.05. However, only treatment with FP was associated with significant differences from placebo for any of the key secondary efficacy measures. These data support the efficacy of the individual agents in COPD.

[Slide]

For Advair, we have used the same presentation format for the statistical analysis compared with placebo as shown on the previous slide. Greater improvements were seen for nearly all secondary efficacy measures with both doses of Advair versus placebo. Most of these differences resulted in p values less than 0.05. This is better than what was seen with FP and salmeterol alone, shown in the previous slide, indicating that both components are contributing to the effects we see with Advair.

Additionally, for the TDI and the CRDQ, only treatment with Advair consistently achieved a clinically important change from baseline as specified by the developer or this instrument. However, none of the differences between treatment

groups achieved this magnitude of change with the exception of TDI in SFCA3006. As already reviewed, none of the treatments in this program were associated with reductions in time to COPD exacerbations, most likely due to differences in study design and duration.

For most measures similar improvements were seen between the two doses of Advair with the exception of TDI, shown on the first line. For this measure, Advair 500/50 provided greater magnitude of improvements, which were significantly better compared to placebo and salmeterol, as I will review shortly.

[Slide]

In addition, when numerical trends for greater effect with Advair versus the individual components were seen for most secondary efficacy measures, p values less than 0.05 for these comparisons were demonstrated in some instances only. This is shown by a green check for Advair versus salmeterol and an orange check for Advair versus FP, on this slide. The most likely reason for the lack of significance between Advair and components for some of these secondary measures is that these trials were not optimally designed to

assess treatment effects on the secondary efficacy measures.

I will now share with you results for TDI from SFCA3006 with Advair 500 and morning peak flow from SFCA3007 with Advair 250 to illustrate the types of effects we observed on these secondary measures.

[Slide]

Shown on this slide are the results of the transition dyspnea index, or TDI, for Advair 500. The Y axis represents the TDI result, whereas the X axis represents the study week. On the right side of the slide are the endpoint results for the four treatment groups.

The TDI measures the change in patient's level of dyspnea from baseline. A value of 1 has been defined as a clinically significant treatment effect by the developer of the instrument. These results demonstrate that treatment with Advair 500 was associated with greater improvements in dyspnea as assessed by the TDI score compared to each of the individual agents. Improvements were noted as early as the first week, with further improvements noted during the trial. At endpoint the improvements were significantly different for

Advair compared to placebo, with a model estimated treatment difference of 1.7. It was also significantly greater compared to salmeterol, with an estimated treatment difference of 1.2. Both of these differences represent a clinically important change.

It is important to note that while the results with FP and salmeterol for TDI were similar, only the FP 500 treatment group achieved statistical significance and a clinically meaningful difference from placebo. The magnitude of improvements in TDI seen with Advair 500 represent one of the best treatment effects of any medication which was evaluated with this instrument.

[Slide]

Shown on this slide are the results of the mean change on morning peak flow from SFCA3007, which was the Advair 250 trial. The Y axis represents the change in peak flow in liters per minute, and the X axis represents the day of treatment.

Treatment with Advair 250 was associated with a greater increase in morning peak flow beginning one day after initiating treatment, which

increased further during the course of the trial. The magnitude of improvement in peak flow between Advair versus each component achieved p values less than 0.001. Similar findings were observed with FP and salmeterol versus placebo, with the magnitude of improvement seen with FP and salmeterol being comparable. Results from SFCA3006 with Advair 500 were similar to these results. Hence, these results for the secondary measures do support the primary efficacy measures we see with Advair in the treatment of COPD.

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The efficacy conclusions for the results with Advair can be summarized as follows: Significantly greater improvements with Advair were seen on the primary efficacy measures at each strength. This was shown for Advair versus salmeterol for pre-dose FEV1, and for Advair versus FP for the two-hour post-dose FEV1. Results of the secondary efficacy measures support the primary analysis. Greater improvements with Advair versus placebo were seen for nearly all measures, indicating that both components were contributing to the benefit seen with Advair.

Trends for greater improvements versus the

individual components were also seen for most efficacy measures, with some differences achieving p values less than 0.05. As expected, greater treatment effect was seen in more reversible patients. However, the improvements in FEV1 with Advair relative to placebo at both doses were robust even in the patients regarded as non-reversible. As agreed with the agency, a formal dose response assessment was not performed for Advair. However, comparing the responses to Advair in the two trials, it appears that Advair 250 and Advair 500 provided similar benefits for most efficacy measures, with the exception of dyspnea as assessed by TDI. A significant and clinically meaningful greater improvement in dyspnea was only seen with Advair 500 compared to placebo or salmeterol. The magnitude of improvements seen with Advair represent a real advance in the treatment of COPD.

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I will now share with you some of the safety results from the Flovent and Advair clinical program. I will present results of the integrated data since it includes all patients enrolled in the clinical program and represents the best method for

determining treatment effects. I will focus my presentation on addressing the two main issues which are relevant with regards to assessing the safety of inhaled corticosteroids in the treatment of COPD.

The first is the issue of topical effects, with specific review of the pneumonia cases. The second is the evidence we have regarding systemic safety of administering FP in COPD. I will not be reviewing results of laboratory data, cardiovascular data or assessment of safety in different populations. Overall, we did not see any evidence of a safety concern in these measures and groups. This information is provided in your briefing documents and is available for review during the Q&A if needed.

[Slide]

The safety database as part of this program was comprised of 2054 patients with COPD, 790 of whom were treated with FP and 347 were treated with Advair. This safety data was supported by safety data from 1298 additional COPD patients from non-U.S. trials evaluating FP and by the extensive safety data in trials conducted in asthma.

[Slide]

Displayed on this slide are the percent of patients with adverse events, withdrawn due to adverse events, and experiencing serious adverse events from the three U.S. trials. Four patients died in the trial in the placebo group. The mean duration of exposure was similar to slightly more in the active treatment groups versus placebo. The percent of patients who experienced adverse events was slightly higher in the FP-containing groups. This was primarily due to a higher incidence of expected topical adverse events associated with the use of inhaled corticosteroids. A slightly higher percentage of patients was withdrawn due to adverse events in the FP 500 group, however, most of these events were not attributed to the drug treatment by the investigators. A similar percent of patients experienced serious adverse events across the treatment groups. There was no evidence that treatment with Advair was associated with a higher incidence of adverse events compared to the individual agents or placebo in this program.

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This slide summarizes the adverse events of special interests when inhaled corticosteroids

are administered. A slightly higher incidence of expected topical adverse events such as candidiasis, throat irritation and hoarseness/dysphonia was seen in the treatment groups containing FP. These were generally considered mild to moderate in severity and rarely led to patient discontinuing treatment.

The incidence of AEs which are attributed to systemic corticosteroids, such as fractures, cataracts or ocular pressure disorder, occurred in a similar rate across the treatment groups.

[Slide]

During the review, the FDA raised the concern that a higher incidence of pneumonia occurred in treatment groups containing FP. In order to better understand these concerns, we have summarized the adverse events and serious adverse event of pneumonia which occurred during the trials. These numbers may be slightly different from those in your briefing document but are the most accurate reflection of the events. These changes have been reviewed with the agency.

The incidence of pneumonia overall was low, with variable distribution across the treatment groups. While there appears to be a

slightly higher incidence of these events in the FP-containing groups, we do not see this in the groups containing Advair, hence, attribution to drug treatment is questionable.

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HPA axis assessments were performed by the measurements of 12-hour cortisol profile in FLTA3025 in 86 patients, and assessment of morning cortisol concentrations and short ACTH stimulation test in SFCA3006 and SFCA3007 in 359 patients.

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As expected, we did see a dose-related decrease in the 12-hour unstimulated plasma cortisol profile at these doses of FP. This was significantly different from placebo with FP 500 but not the FP 250 twice daily dose. Now, we have to remember that this test is regarded as a very sensitive test for assessing the presence of exogenous corticosteroids. From our experience in asthma, at these doses this magnitude of HPA axis effects has not been associated with clinically significant changes in other more clinically relevant measures, as I will review shortly.

The incidence of abnormal morning cortisol and short ACTH stimulation test was low and similar

between the treatment groups. This further supports that the small changes in unstimulated plasma cortisol profiles are unlikely to be associated with clinically significant HPA axis suppression.

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The safety results from our clinical program can be summarized as follows: Treatment of COPD patients with v Diskus was well tolerated. Other than a slightly higher incidence of expected topical adverse events, no new clinically relevant safety concerns were identified compared to placebo.

Treatment of COPD patients with Advair Diskus was also well tolerated. There was no evidence of a greater safety risk compared to the use of the individual agents or placebo.

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I will now review some of the long-term safety data that we have available with FP. I will focus my presentation on the systemic safety data. It is well established that the systemic side effects of inhaled corticosteroids are due to the amount of the drug absorbed into the body. Less systemic absorption of FP in COPD than in asthma

allows us to extrapolate the systemic safety data from asthma to patients with COPD. This approach was agreed with the FDA during the design of this clinical program.

Since we observed similar or less systemic exposure to FP in COPD compared to some of the data in asthma, I will review results from clinical trials in asthma which examined the effects of FP treatment on bone mineral density and ocular effects. In addition to our extensive long-term safety data from asthma, I will review the findings from relevant safety information from a three-year trial conducted in patients with COPD. This was the ISOLDE trial was reviewed previously by Dr. Johnson in his presentation.

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Shown on this slide are the systemic exposures seen with FP in patients with asthma on the left and COPD on the right, as assessed by the area under the curve, or AUC, of the plasma FP concentrations versus time measurements. The Y axis on this slide represents the FP AUC in pgm/hour/ml and the square boxes are the individual patient systemic exposure to FP obtained from the FLTA3001 trial, using the CFC MDI formulation of FP

which is currently on the market. I will be reviewing the results of this trial shortly. Similar results for the Diskus are presented in circles for patients with COPD, on the right, from our FLTA3025 trial. The 440 mcg dose from the MDI corresponds to the 500 mcg dose of the Diskus.

These results indicate that the range of exposure to FP in patients with COPD is similar or less than what has been seen in asthma with the FP CFC MDI. This is consistent with the relationship noted in asthma where the systemic exposure from the FP CFC MDI is approximately double that of the Diskus. These analyses indicate that the results from studies in patients with asthma conducted with CFC MDI specifically can be used to assess the potential for systemic side effects in COPD with the FP Diskus.

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This slide summarizes the clinical trials which examined bone mineral density, or BMD, and/or ophthalmic effects of FP treatment in adult patients with asthma. We acknowledge that a unit change in bone mineral density is of a greater clinical concern in COPD patients since they have lower bone mass compared to patients with asthma.

However, the evidence with oral corticosteroids does not indicate that older, postmenopausal patients are more sensitive to the BMD effects or loss compared to younger patients with corticosteroids. Hence, we believe that these data from patients with asthma still are useful in assessing the risk of bone mineral density effects following FP treatment in patients with COPD. Our data from asthma includes two two-year placebo-controlled trials and five comparative trials where assessments of bone mineral density were performed.

The two placebo-controlled trials were similar in design and patient inclusion and exclusion criteria. One trial, FLTA3001, examined two doses of FP, 88 mcg and 440 mcg twice daily, and the other trial was FLTA3017, which examined a single dose of FP 500 twice daily via the Rotadisk versus placebo.

The comparative trials were all conducted with the CFC MDI as well, and include three trials which compared FP versus beclomethasone dipropionate, or BDP, and two trials which compared FP versus budesonide.

[Slide]

I will now review results for the two-year randomized, placebo-controlled trial conducted with the CFC MDI. Once again, as you recall, the exposure we see with CFC MDI in this study was similar or greater than what we observed with the Diskus in COPD patients, as relevant to this study to this application.

Asthma patients in this study had limited systemic exposure to corticosteroids; were 18 to 50-year olds for males and 18 to 40-year olds for women; and had to have had normal bone mineral density or eye exams at baseline. The percent change in lumbar spine bone mineral density in this trial is displayed on this slide. The Y axis represents the percent change in lumbar spine bone mineral density in grams per centimeter squared at the various times they were performed for the 25, 52, 76 and 104 weeks of treatment.

The placebo group is depicted in blue; the FP 88 mcg BID group in yellow; and the FP 440 mcg BID group in orange. These data show no significant differences in lumbar spine bone mineral density seen during the two years of FP versus placebo treatment. These results are reassuring and suggest that small changes in HPA

axis that we see at these doses are unlikely to be associated with clinically significant systemic effects.

Now, in these studies we also evaluated other regions of the bones, in particular the femoral region and the total body. However, these regions were not prospectively QA and, hence, the conclusions from these other results cannot be made. However, even in those results there were other confounders that affected the interpretation of those data and overall the results are consistent with the lumbar spine, that there is no significant effect as seen with FP treatment at these doses in regards to bone density.

[Slide]

Results of eye examples demonstrated no evidence of posterior subcapsular cataracts or diagnosis of glaucoma during the two-year treatment with FP. The results of the other two-year study with Rotadisk versus placebo were similar, and are summarized in your briefing documents.

[Slide]

The results of bone mineral density from comparative trials with FP provide further reassurance that long-term systemic side effects

with FP treatment are unlikely. These results are summarized on this slide and are provided in your briefing document.

Additionally, in the three randomized, double-blind trials which compared FP to BDP, there was evidence in each trial that FP treatment was significantly better compared to BDP therapy on several bone mineral density measures. These results suggest that not all inhaled corticosteroids may have the same propensity to affect bone mineral density.

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In addition to data from trials conducted in patients with asthma, safety results from the three-year ISOLDE trial in patients with COPD were also reassuring. This trial was conducted with the CFC MDI using a spacer, which we know can further enhance the systemic exposure to FP. This needs to be considered when extrapolating the systemic safety data from this trial to the FP Diskus where lower exposure has been observed.

This slide summarizes the adverse events and serious adverse events of fractures, cataracts and ocular pressure disorders seen in this trial, for the placebo group on the left and the FP group

on the right. In interpreting these data we have to consider that the FP group remained in the study for a longer duration and, hence, had more of a chance for experiencing adverse events. Despite the greater duration of treatment in the FP group, there is no clear evidence that FP was associated with increased risk of these events. These data provide further evidence that long-term systemic side effects in patients with COPD are unlikely at these doses of FP.

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The long-term safety data, hence, can be summarized as follows: The range of systemic exposure with FP Diskus in COPD is similar or less than the CFC MDI in asthma where considerable long-term safety data are available.

Results from two two-year placebo-controlled FP studies were reassuring. No clinically relevant bone mineral density or ocular effects were noted in these studies. These results indicate that small changes in HPA axis observed with FP at these doses are unlikely to be associated with clinical side effects.

Studies comparing FP to BDP provide additional reassurance on the long-term safety of

FP administration. These studies further suggest that not all inhaled corticosteroids may have the same predisposition to affect bone mineral density. Results from a three-year trial in patients with COPD demonstrated no evidence of increased fracture or ophthalmic adverse events with FP treatment.

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The results from this clinical program, hence, support the following dosage and administration recommendations for Flovent and Advair Diskus. For Flovent Diskus, the recommended starting dose is 250 mcg twice daily. For Advair Diskus the recommended starting dose is 250/50 mcg twice daily.

While the responses in most measures were similar between the two strengths, there were suggestions of greater improvements in lung function and dyspnea at the higher dose of FP in FLTA35, and dyspnea with the higher dose of Advair in SFCA3006. Due to these findings, we recommend that patients who do not respond adequately to the starting doses increase their dose to 500 mcg twice daily for Flovent Diskus and to 550 mcg twice daily for Advair Diskus which may provide additional control.

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In summary, I have shared with you results from our clinical program which fulfilled its regulatory objectives. With Flovent we demonstrated greater improvement on the primary efficacy measure compared to placebo, with no new safety issues noted. For Advair we demonstrated superior efficacy compared to the individual components for the primary efficacy measures. These clinical benefits with Advair were not associated with any evidence of a greater safety risk. Results from our long-term safety data provide further reassurance on the use of FP in COPD.

Thank you for your attention. I would like to now reintroduce Dr. David Wheadon, who will provide some concluding remarks.

Conclusions

DR. WHEADON: I will be brief.

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The information we have presented this morning provides compelling evidence for the approval of both Flovent Diskus and Advair Diskus for the treatment of COPD.

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As you have seen and heard, COPD remains a significant public health issue with increasing morbidity and mortality in the U.S. population, in contrast to many other diseases. Despite the increasing burden of this disease, COPD remains both under-diagnosed and under-treated. The only treatment options currently approved in the U.S. are bronchodilators. Despite optimal use of these agents, many patients require additional therapy.

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As was demonstrated by Dr. Malcolm Johnson, inhaled corticosteroids, including fluticasone, reduce inflammation associated with COPD. Furthermore, the majority of clinical studies with inhaled corticosteroids, including fluticasone, illustrated clinically important benefits in the treatment of this disorder. Due to the complex pathophysiology associated with COPD, the combination of salmeterol and FP allows treatment of different aspects of the disease, leading to greater clinical benefits than the individual components alone. The use of inhaled corticosteroids in COPD are further supported by current clinical practice and the new evidence-based international GOLD guidelines.

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The objectives of the clinical program for both Flovent and Advair Diskus were achieved. For Flovent, demonstrably greater improvements in the primary efficacy parameters were seen compared to placebo. Results for the secondary efficacy measures support the primary analyses. The magnitude of improvements observed with Flovent are similar to those seen with currently available treatments which are regarded as clinically meaningful in the management of COPD. No clinically significant safety concerns were noted with the use of Flovent in COPD.

For Advair, demonstrably greater improvements in the primary efficacy parameters were seen compared to the individual agents alone at each strength. Results for the secondary efficacy parameters support the primary analyses. The magnitude of improvements seen with Advair compared to placebo represent a clear advancement in treatment of COPD. This greater improvement in efficacy was not associated with an increased safety risk compared to the individual agents or placebo.

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I would like to conclude by once again thanking the agency and the committee for allowing us this opportunity to present the findings from our pivotal clinical studies. COPD is a treatable disease. Because there are limited approved medications available for the management of this chronic, debilitating condition, new therapeutic options are very much needed. We believe that we have presented compelling evidence that Flovent Diskus and Advair Diskus are such new therapeutic options. The benefits of either medication outweigh the risk of treatment. The approval of these treatments will allow physicians to make informed decisions about the appropriate use of these agents for the management of COPD in their patients.

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In closing, I would also like to introduce two additional experts who have joined us here today. Prof. Romain Pauwels is head of the Department of Respiratory Diseases at the University of Ghent, in Belgium. He is also the Chairman of GOLD, the Global Initiative for Chronic Obstructive Lung Disease, and has been involved in many of the major clinical trials in COPD.

Dr. Jonathon Adachi is professor of medicine at McMaster University, in Hamilton, Ontario. He is a member of the scientific advisory committee for the International Osteoporosis Foundation, and is a past president of the Osteoporosis Society of Canada. His major research interest is steroid-induced osteoporosis.

We, along with our experts, will be happy to address any points of clarification and questions that you may have. Thank you.

DR. DYKEWICZ: Thank you. We will now begin the segment where we have questions posed to the sponsors. I would like to actually begin with one question, perhaps more directed to Dr. Shah, about secondary efficacy measurements. Of course, one of the things that I think may be disappointing about the data presented here is the relative lack of effect on the secondary efficacy endpoints, with the possible exception of dyspnea. This, of course, contrasts with some of the data you presented about studies with other inhaled corticosteroids where some secondary efficacy endpoints were found to be benefited by the trials.

You mentioned that the study design of the trials that were conducted was such that you may

not have been able to capture improvements in secondary efficacy endpoints. You mentioned, for instance, that if you changed the population so that subjects had a history of previous exacerbations of COPD and then were studied you might be able to capture some improvement in terms of time to first onset of an exacerbation.

What other sorts of changes in protocol could you conceive of that would help perhaps better capture changes or impact on the secondary efficacy endpoints? And, does Glaxo have any intention of doing such studies?

DR. SHAH: Those are very valid questions. I think, once again, as Dr. Donohue reviewed, we have to lower our expectations when it comes to the types of effects we can expect in COPD. We don't have as much experience in conducting clinical trials in COPD relative to the amount of experience we have in asthma, where we do show very consistent treatment effects on multiple endpoints, as you are all aware of.

However, I think when you look at the data that we presented, the secondary results we see with our own program are actually very supportive of our primary. We did see evidence of effects on

almost all measures that we looked at for the secondary. Hence, you know, if you compare to how the benefits that have been seen with currently available treatments that are regarding as the gold standard, the results we show in secondary efficacy measures are actually quite robust.

In the context of the exacerbation question, I think we are learning, in terms of looking at exacerbations in COPD, that actually the greatest benefit of inhaled corticosteroid therapy is the reduction in repeat exacerbations. Indeed, if you look at where we see the greatest benefits in studies that have been done in Europe to date, it is the rate of exacerbations, where you have opportunities for multiple exacerbations, where we are seeing the greater treatment effects. In our study, as I indicated, we withdrew patients if they required one burst of oral corticosteroids because we didn't want that to confound our primary efficacy measure analysis and our ability to discriminate on the primary efficacy measure because, obviously, concurrent oral corticosteroids could have an effect on FEV1 which would potentially limit our ability to show treatment effects on that primary endpoint.

So, as I indicated, you know, our secondary efficacy measures are actually some of the best that we have seen in this disease, as has been reviewed by Dr. Donohue. However, we accept that the magnitude of changes we are seeing are lower than our experience that we might be accustomed to in asthma. But I think we also have to understand that this is a different disease and the expectations may need to be lower.

Maybe I can ask one of our experts, Prof. Pauwels, to also comment from his own experience, given his vast wealth of experience in doing clinical trials in COPD.

DR. PAUWELS: Indeed, there is a methodological issue that explains why you don't see an effect on exacerbations. From other studies, I can communicate the following information and the following experience. That is, first of all, it is probably better to select beforehand the people who have repeated exacerbations in order to demonstrate an effect on exacerbations with any treatment intervention in COPD.

Secondly, what is absolutely needed is a duration of at least six months with a large group

or, preferentially, observation of a one-year treatment period.

Of course, the third issue in these studies was that they selected as a secondary outcome measure the time to first exacerbation but, at the same time, actually withdrew their subjects once they had an exacerbation and the majority of the effects that have been seen, and are repeatedly seen with inhaled corticosteroids is on the exacerbation rate, which is the number of exacerbations over a fixed time period. So, the design that was used in these studies didn't allow for study of that.

DR. DYKEWICZ: Thank you. Questions from other members of the committee? Dr. Bone?

DR. BONE: Thank you. I have a couple of questions. I suppose Dr. Donohue would be the one to answer them and I would, obviously, be very interested in the comments of the committee members or from the experts on pulmonary disease. I am just an interloper here for special reasons.

The first question I wanted to ask is what is the life expectancy of the patients that would be candidates for treatment here with moderate to severe disease?

DR. DONOHUE: Of course, that is a very difficult question. We have some data that the life expectancy of a patient with COPD -- again, it depends on what part of the country you are in, but with 39 percent FEV1, 50 percent of those people live five years. That is in the literature. So, the exposure would be, you know, perhaps less. These folks are older. We saw the mortality, 110,000 Americans die each year with COPD; 668,000 hospitalizations. So, we are talking probably about a lot shorter exposure to medications than we would be, of course, in the asthma population.

DR. BONE: Thank you. That was kind of what I was wondering about generally. The second question has to do with the exacerbation issue. I guess I have a different reason for asking about it, but is there a dominant cause for exacerbations, such as infection, or do exacerbations just sort of occur spontaneously?

DR. DONOHUE: Yes, that is also a very important question. Exacerbations are much more frequent in the more severe group. So, when we stratify disease, like in level three of GOLD, we might see as many as two to three exacerbations. At level one it is about 0.8. So, there are issues

there. In general we estimate that one-third of exacerbations are due to bacterial infections, H. influenzae, strep., pneumonia and Moraxella catarrhalis being the leading cause. One-third would be environmental irritants, air pollution or what-have-you, and one-third is everything else. So some are, indeed, seemingly just a loss of control, gradually going down hill. It is very, very hard to identify an offending agent. We can't tell clinically. That is why we just really empirically treat the exacerbations, usually with a short burst of antibiotics and perhaps oral corticosteroids.

DR. DYKEWICZ: Dr. Stoller?

DR. STOLLER: Thank you. My question too regards the COPD exacerbation issue and perhaps Dr. Shah could respond. Recognizing the confounding effect of exacerbations on the primary outcome measure, my question is a descriptive one. In fact, looking at the briefing document and the frequency of dropouts for exacerbations, it is actually rather low across all groups. That is the first observation. I would appreciate a comment about that.

The second is I can't tell how many

patients actually dropped out for an exacerbation during the run-in period. Third, at baseline, what is the baseline frequency historically of exacerbations in the study cohort? In other words, there are data about the baseline frequency and I don't see that represented here.

DR. SHAH: Let me see if I can remember all those questions. In terms of the last question about what was the baseline level of exacerbations, we actually didn't collect the historical information in the study which, in retrospect, I think we would do differently in the future. So, we don't really know the level of exacerbations these patients were experiencing prior to enrolling into the studies.

We actually did have people withdraw for exacerbations during the run-in period. As you know, we did withdraw inhaled corticosteroids. In order to get into the study they had to stop them at the screening visit if they were, you know, on lower doses. It varied across the three trials and it was anywhere from about 15 percent, 30 percent of patients who withdrew for exacerbations during the run-in period in the clinical trials.

I can't remember the last question. Is