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PULMONARY-ALLERGY DRUG PRODUCTS

ADVISORY COMMITTEE

Friday, September 5, 2003

8:00 a.m.

Holiday Inn Gaithersburg
Gaithersburg, Maryland

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P R O C E E D I N G S

Introductions

DR. PARSONS: I am Polly Parsons. I am at the University of Vermont and Chief of Pulmonary and Critical Care Medicine and Chief of Critical Care Services there.

DR. KENNEDY: I am Dr. Bill Kennedy. I am a regulatory consultant and I am the non-voting industry representative on this panel.

DR. KERCSMAR: Dr. Carolyn Kercsmar, pediatric pulmonologist at Case Western Reserve University, in Cleveland.

DR. JOAD: Jesse Joad, pediatric pulmonologist at the University of California at Davis.

DR. NEWMAN: Lee Newman. I am a pulmonologist at the National Jewish Medical and Research Center in Denver, and Professor of Pulmonary Medicine at the University of Colorado.

DR. APTER: I am Andrea Apter, Associate Professor of Medicine at the University of Pennsylvania. I am and adult allergist, immunologist, epidemiologist.

MS. TOPPER: Kimberly Topper. I am the executive secretary for the committee.

DR. CHINCHILLI: I am Vernon Chinchilli. I am a biostatistician at the Penn State Hershey Medical Center.

MS. SCHELL: My name is Karen Schell and consumer representative. I am a respiratory therapist in Emporia, Kansas.

DR. CROSS: I am Carroll Cross. I am an adult pulmonary-critical care specialist at University of California in Davis, Sacramento.

DR. MORRIS: I am Pete Morris. I am in the Division of Pulmonary and Critical Care Medicine at Wake Forest University.

DR. ANTHRACITE: My name is Ray Anthracite. I am a lung specialist at the FDA.

DR. CHOWDHURY: I am Badrul Chowdhury, at the FDA.

DR. MEYER: Bob Meyer. I am the Director of the Office of Drug Evaluation II at FDA.

DR. PARSONS: We are going to move on to the conflict of interest statement from Kimberly Topper.

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the

record to preclude even the appearance of such at the meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants 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 U.S.C. 208(b)(3) and 21 U.S.C. 355 (n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in one of Ariflo's competitors valued between $25,001 to $50,000.

Dr. Carroll Cross has been granted waivers under 18 U.S.C. 208(b)(30 and 21 U.S.C. 355 (n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in two firms that make competing products to Ariflo and in the sponsor of Ariflo. Each stock is valued between $5,001 and $25,000.

Dr. Carolyn Kercsmar has been granted a waiver under 18 U.S.C. 208(b)(3) for membership on

a competitor's Speaker's Bureau. She receives from $5,001 to $10,000 annually.

Dr. Kercsmar has also been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock in the sponsor of a competing product to Ariflo. The stock is valued at less than $5,001. Because this stock interest falls below the de minimis exemption allowed under 5 CFR 2640.202(a)(2), a waiver under 18 U.S. 208 is not required.

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.

In addition, we would like to disclose that Dr. William Kennedy is participating in this meeting as an acting industry representative, on behalf of regulated industry. Dr. Kennedy reports that he owns a nominal amount of stock valued at less than $5,000.

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. PARSONS: We are now going to ask Dr. Chowdhury to start the discussion.

Topic Introduction

DR. CHOWDHURY: Good morning, Madam Chairperson and members of the Pulmonary-Allergy Advisory Committee. I welcome you to this meeting and thank you for your participation.

This meeting is to discuss the new drug application for cilomilast tablets by GlaxoSmithKline. GlaxoSmithKline is seeking approval of cilomilast tablets for the maintenance of lung function in patients with chronic obstructive pulmonary disease who are poorly responsive to albuterol.

Please keep in mind that the indication of maintenance of lung function is unique amongst all drugs that are currently approved in the U.S. for

chronic obstructive pulmonary disease. All clinical issues related to cilomilast are open for discussion.

As you can see from the agenda, GlaxoSmithKline will present first and give an overview of the clinical data, followed by the agency's presentation. As you listen to the presentation, I request you to keep in mind the questions that are in the FDA briefing book and also attached to the agenda since you will discuss and deliberate on these questions later in the day.

We look forward to an interesting meeting and, again, thank you for your time, effort and commitment in this important public health service. Thank you.

DR. PARSONS: We will now move to the presentation by GlaxoSmithKline.

GlaxoSmithKline Presentation

Introduction

DR. WHEADON: Thank you, Dr. Parsons. Good morning.

[Slide]

I am David Wheadon, Senior Vice President of U.S. Regulatory Affairs at GlaxoSmithKline. On behalf of GSK, I would like to thank the committee

and the agency for the opportunity to share information on Ariflo, the first PDE4 inhibitor to be considered for approval for the treatment of COPD. This morning I will start GSK's presentation by sharing with you the background information about the serious nature of COPD, as well as treatment options currently available to this group of patients.

[Slide]

Chronic obstructive pulmonary disease is a debilitating, progressive illness. As many of you will recall based on these elegant illustrations by Dr. Frank Netter, patients may present with emphysema or chronic bronchitis but most patients have elements of both. Typically, after many years of smoking patients who develop COPD will begin exhibiting progressive symptoms such as chronic cough, increase in mucus production and worsening lung function.

However, patients usually do not seek medical attention until they experience significant breathlessness. They often modify their life styles to compensate for both the breathlessness and activity limitation associated with reduced expiratory airflow. As the disease progresses, the

systemic manifestations such as weight loss, muscle wasting and cyanosis become increasingly evident, as we can see from these illustrations.

[Slide]

The societal burden of COPD is enormous and the disease currently affects an estimated 24 million Americans. During the past year direct and indirect costs associated with COPD were estimated to be over 32 billion dollars in the U.S. alone and it is likely that these costs will continue to increase. COPD is currently the fourth leading cause of death in the U.S. and by the year 2020 it is expected to become the third leading cause of death worldwide.

[Slide]

COPD continues to be a significant global public health challenge. In the U.S. it remains a major cause of morbidity and mortality and, sadly, as we can se from this graphic, in contrast to such other debilitating illnesses as HIV infection and coronary-artery disease, the mortality rate for COPD continues to increase.

Airflow obstruction is one of the clinical hallmarks of COPD. As you know, we all lose lung function after the age of 25 but patients with COPD

lose lung function at two to three times the normal rate. This is important since lung function, as measured by FEV1, has been shown to correlate with clinical outcome.

[Slide]

This study by Anthonisen et al. shows that patients with the highest mortality are those with the lowest percent predicted FEV1. These data imply that preventing or delaying progressive decline in lung function should result in improved diagnostic outcome. This is particularly important to keep in mind as you review the data we will present today.

[Slide]

There are limited treatment options for patients with COPD. Due to the irreversible nature of the lung damage that occurs in this disease, treatment has been directed at improving symptoms and is largely palliative. The only medications approved for COPD are bronchodilators. These do not address the complex nature of COPD and often do not adequately control the disease. The only therapeutic modality that has been shown to slow the rate of decline of FEV1 is smoking cessation. However, even in patients who stop smoking there

may be continued inflammation in the lungs and a persistence of symptoms that require treatment.

[Slide]

As I have previously stated, COPD is a progressive and complex disease which involves inflammation, bronchoconstriction and structural changes within the lung. These pathological processes lead to airflow limitation and hyperinflation which are responsible for the clinical sequelae of the disease. Because of the complex nature of the disease bronchodilators may not meet many of the needs of patients and new treatment options are, indeed, needed.

[Slide]

Ariflo is a second generation PDE4 inhibitor, which was designed to retain the therapeutic activity of the first generation compounds with an improved safety profile. It has 100 percent oral bioavailablity, low plasma variability and a low potential for drug interactions. These attributes are important because they are associated with consistent and reliable drug delivery and obviate the need to monitor blood levels during treatment. Ariflo, an orally administered PDE4 inhibitor taken twice

daily, broadens the approach to the treatment of COPD by targeting inflammatory mediators as well as airway smooth muscle activity. Thus, it provides an important new option for the treatment of COPD.

[Slide]

Since theophylline has been used widely in respiratory disease for decades, it is natural to want to compare theophylline, a non-selective PDE inhibitor, to Ariflo, a highly selective PDE4 inhibitor. However, it is important to note that these drugs belong to two distinct classes of medications. Theophylline, a xanthine structurally related to caffeine, exhibits adverse effects that may be related to broader, non-selective PDE inhibition. In addition, theophylline has other pharmacologic properties including antagonistic effects on adenosine receptors but the exact mechanism of therapeutic activity has not been fully elucidated.

Also unlike Ariflo, the pharmacokinetic profile of theophylline is unpredictable due to drug and food interactions. Additionally, wide blood level variability can lead to the requirement for dosage adjustments in many patients, including elderly patients and smokers, thereby requiring

blood level monitoring.

[Slide]

Ariflo has been extensively studied in patients with COPD. The initial clinical development program for Ariflo was global in scope and consisted of one pivotal study in North American and two in Europe. Due to the variability in some of the results between North American and European trials, GSK conducted, following consultation with the FDA, an additional pivotal study of similar design in North America. As is always the case in drug development, additional studies were conducted to evaluate the mechanism of action and to evaluate long-term safety.

The eight placebo-controlled clinical trials evaluated over 3,400 patients with greater than 2,000 patients receiving Ariflo and over 1,400 patients receiving placebo. The two open-label long-term trials evaluated over 1,000 patients for up to three years. Overall, there were nearly 3,000 patient years of exposure to Ariflo in the clinical development program.

[Slide]

The American Thoracic Society and European Respiratory Society have differing definitions of

COPD. The American Thoracic Society does not base the diagnosis of COPD on reversibility, whereas the European Respiratory Society definition includes only patients who are poorly reversible to bronchodilators.

As this was a global program, GSK chose the more conservative definition and evaluated only patients who were poorly reversible to albuterol in the pivotal studies, as shown by the shaded area in this diagram. It is important to note that this patient population may be more difficult to treat and are known to have a decreased FEV1 response to medication as compared to more reversible patients. This is the population that is reflected in the proposed indication.

[Slide]

The indication for which we are seeking approval is the maintenance of lung function in patients with COPD who are poorly responsive to albuterol. We certainly believe that the data that we will share with you this morning is supportive of the approval of Ariflo for this indication.

[Slide]

Following me this morning will be three other speakers, starting with my colleague, Dr.

Katharine Knobil who will briefly discuss the mechanism of action and the pharmacological rationale for the use of PDE4 inhibitors in the treatment of COPD. Dr. Knobil with follow this with the efficacy data from the Ariflo clinical trial program.

The safety profile of Ariflo will then be reviewed by Dr. Kathy Rickard. Following Dr. Rickard, Dr. Fran Sciurba will provide an insight into the benefit of Ariflo in treating patients with COPD. I will then return with some concluding remarks and the presenters will be available for questions. Dr. Knobil?

Rationale for the Use of Ariflo in COPD

DR. KNOBIL: Thank you, Dr. Wheadon.

[Slide]

At this time I would like to discuss some of the features of inflammation in COPD, the rationale for using PDE4 inhibitors for the treatment of COPD, and then I will discuss some data specific to Ariflo. Cilomilast is the active ingredient in Ariflo and, since some of the studies use different formulations of cilomilast, I will use both Ariflo and cilomilast interchangeably.

[Slide]

As you know, smoking accounts for at least 80-90 percent of cases of COPD. Smoking causes inflammation in the airways and the destruction of lung parenchyma that is associated with emphysema, as well as increased mucus production that is associated with chronic bronchitis. Bronchoconstriction results as a direct result of cigarette smoking or as a result of uncontrolled inflammation. Bronchoconstriction, inflammation and structural changes all contribute to the airflow limitation that is characteristic of COPD.

One of the clinical manifestations of airflow obstruction and loss of elastic recoil is hyperinflation. This is important because, when hyperinflated, a patient is forced to breathe at a higher lung volume, increasing the work of breathing and amplifying the feeling of breathlessness. Hyperinflation may be exaggerated during activity when expiratory time is shortened, resulting in further shortness of breath. The pathophysiologic changes in the lung are progressive and lead to chronic symptoms such as breathlessness, coughing, wheezing, sputum production and can lead to exacerbations. Together, these can have a significant impact on a

patient's health status and lead to severe disability and premature death.

[Slide]

In contrast to the inflammatory response seen in patients with asthma, the predominant inflammatory cells in the lungs in patients with COPD are CD8-positive T-cell lymphocytes, macrophages and neutrophils. This study, by Retamales and colleagues, shows that these inflammatory cells are increased in the peripheral airways of ex-smokers with COPD and the increase in these inflammatory cells correlated with COPD severity. In this study COPD severity was determined by the degree of emphysema that was established on quantitative CT scanning. The study on the next slide confirms this result.

[Slide]

This study, by Saetta and colleagues, evaluated the peripheral airways from surgical specimens from smokers with normal lung function and from patients with COPD. This study confirms the results on the previous slide that there is a correlation between COPD severity and the numbers of CD8-positive T-cell lymphocytes. In this case severity was measured by FEV1 percent of predicted.

The significant correlation observed between increased CD8-positive T-cell lymphocytes and increased airway obstruction suggests a possible role for these cells in the pathogenesis of smoking-related airflow obstruction.

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There are at least 11 phosphodiesterase isoenzymes which are expressed in many different cell types in the body. Each has a different function, depending on the predominant isoenzyme, as expressed in each cell type. For example, PDE5, which is expressed predominantly in vascular smooth muscular cells, has become quite popular lately for its effect on erectile dysfunction. PDE4 is the predominant isoenzyme expressed in many other cell types that are important in the pathophysiology of COPD, including the inflammatory cells that I have just discussed, as well as mucus secreting cells and fibroblasts. Cilomilast was chosen for clinical development because it had early evidence of activity in many of these cell types and has the potential to provide important clinical benefits in patients with COPD.

[Slide]

Phosphodiesterase inhibitors act by

increasing intracellular cyclic AMP. Intracellular cyclic AMP can be elevated by one of two distinct pathways. It can be elevated by activation of adenyl cyclase which converts ATP to cyclic AMP, or elevated by preventing the breakdown of cyclic AMP by phosphodiesterase. Ariflo selectively inhibits phosphodiesterase-4 which results in an increase in cyclic AMP in the cells that express this isoenzyme. In the smooth muscle of the airways the elevation of cyclic AMP leads to bronchodilation. This is a well recognized effect of increasing cyclic AMP so I will not discuss this one further.

In other cells, such as epithelial cells and fibroblasts, the inhibitory effects of cyclic AMP may lead to a reduction in fibrosis and remodeling, and in inflammatory cells, such as neutrophils and CD8-positive T-cells and macrophages, elevation of cyclic AMP produces an inhibitory effect on the release of mediators and cytokines and may also increase the numbers of these inflammatory cells in the lung.

[Slide]

Structural changes in the lung that occur in COPD are mediated by proteolytic enzymes or MMPs, proteolytic enzymes that are known to play a

role in tissue destruction that leads to emphysema in patients with COPD, as shown in this photomicrograph, here.

In vitro cilomilast significantly inhibited MMP-1 and MMP-9 release from fibroblasts and inhibited the conversion to their active forms. It also inhibited the degradation of collagen gels, which is a model of extracellular matrix, by fibroblasts. These effects were not seen with the PDE3 inhibitor amrinone, nor with the PDE5 inhibitor zaprinast, thus suggesting that these effects are specific to PDE4. These in vitro data suggest Ariflo may have a clinically important effect on tissue remodeling in vivo.

[Slide]

The data on this slide show that cilomilast attenuates release of chemoattractants for human neutrophils. The Y axis shows the neutrophils for high power field, and a reduction in the number of neutrophils is a measure of reduced neutrophil chemotaxis, bronchial epithelial cells, shown on the left, and sputum cells, shown on the right, which were obtained from patients with COPD were cultured in the presence or the absence of cilomilast. The cell culture media from

both the bronchial epithelial cells and the sputum cells incubated standard cilomilast had significantly less chemoattractant activity for neutrophils than culture media from the cells that were untreated with cilomilast. Thus, cilomilast may play a role in reducing the numbers of neutrophils that migrate to the airways or to the lung parenchyma in patients with COPD.

[Slide]

The preclinical observations with Ariflo suggested a potential to modulate the inflammatory response in patients with COPD. Two studies were done to assess this result. Study 110 showed a trend in the reduction of sputum neutrophils in favor of Ariflo and study 076 showed a trend toward a decrease in subepithelial neutrophils in bronchial biopsies in patients with COPD.

Even more importantly, as shown here, study 076 also showed a significant reduction in the number of airway macrophages after 12 weeks of treatment with Ariflo, and these airway macrophages were obtained from the bronchial biopsies.

[Slide]

In addition to a decrease in the number of subepithelial macrophages relative to placebo,

treatment with Ariflo also resulted in a decrease in the number of subepithelial CD8-positive T-cell lymphocytes, with an approximate 40 percent decrease from baseline. Given the correlation of CD8-positive T-lymphocytes in relation to COPD severity and the importance of inflammation in COPD, these results provide the rationale for the use of Ariflo in patients with COPD.

[Slide]

This slide is similar to the one I showed earlier but now shows the cells that express PDE4 and the processes that potentially could be mitigated by the PDE4 inhibitor Ariflo. In the interest of time I have only shown a small portion of the data, but there are also data to support the actions of Ariflo in each of these cell types. The processes underlying the pathophysiology of COPD provide targets for therapeutic intervention and PDE4 inhibitors represent a promising class of molecules for the treatment of COPD.

Ariflo Clinical Development Program

[Slide]

Now I would like to switch gears and discuss the Ariflo clinical development program. I will discuss the efficacy data and Dr. Rickard will

discuss the safety results from the clinical studies.

[Slide]

The Ariflo Phase III development program included over 3,400 patients with COPD. The 15 mg dose evaluated in the Phase III development program was selected on the basis of the results of the Phase II studies. There were four 24-week pivotal studies, two conducted in North America and two conducted in Europe. Since patient care and diagnosis of COPD are different in North America and Europe this global program allowed the evaluation of Ariflo in these different patient groups.

[Slide]

Six supporting studies were also conducted. Studies 110 and 076 have already been discussed. Study 168 was primarily a cardiovascular safety study and efficacy data are presented in your briefing document. Studies 041 and 040 were also primarily safety studies that followed patients from the pivotal trials in an open-label fashion for up to three years. The FEV1 data from these studies will be briefly discussed as it supports the indication for which we are

seeking approval. Study 111 evaluated static lung volumes and provides complementary information to the pivotal trials.

[Slide]

The core design of all the pivotal trials was similar. The studies included a four-week run-in period during which time patients discontinued all COPD medications with the exception of scheduled albuterol, and all patients were given albuterol for use as needed. Eligible patients were then randomized to either Ariflo 15 mg twice daily or placebo for 24 weeks of treatment. Patients were evaluated at 11 regularly scheduled visits during the course of the study.

[Slide]

The key inclusion criteria were a COPD diagnosis. Patients were to be 40-80 years of age and patients were required to have greater than or equal to a 10-pack year history of smoking. Patients were also required to be symptomatic prior to randomization, including symptoms of cough, sputum production and breathlessness. However, patients were not required to be symptomatic for entry into study 156.

[Slide]

Lung function requirements included a post bronchodilator FEV1 between 30 and 70 percent of predicted, and an FEV1/FVC ratio of less than or equal to 70 percent of predicted. Patients also had to be poorly reversible to bronchodilators as defined by an increase in FEV1 of less than or equal to 15 percent, or less than or equal to 200 ml in response to albuterol. For reversibility testing patients were given 400 mcg of albuterol in the European studies, whereas patients were given 200 mcg of albuterol in the North American studies. These inclusion criteria led to the evaluation of a COPD population that has not been traditionally studied in large COPD development programs.

[Slide]

This slide puts the population studied in the Ariflo clinical development program into perspective with the other COPD clinical development programs. In contrast to the Ariflo program, other COPD programs did not exclude patients on the basis of reversibility to albuterol. To orient you to this graph, the Y axis is reversibility to albuterol in milliliters and the X axis shows the individual clinical development programs. In these studies the FEV1

response to albuterol ranged from 240 ml at screening in the Advair studies to 330 ml on day one in the Combivent studies. By comparison, the population in the Ariflo studies demonstrated a mean FEV1 response to Ariflo of only 80 ml. Poor reversibility has been associated with an increased rate of decline in FEV1 and, as Dr. Wheadon has already mentioned. Lower FEV1 is associated with higher mortality. Since it is well accepted that reversibility is associated with response to many medications used to treat COPD, the efficacy data that will be presented today needs to be interpreted in the context of the population that was evaluated in the Ariflo clinical program.

[Slide]

Patients were excluded if they had a diagnosis of asthma, and patients were not randomized if FEV1 was not reproducible within 20 percent during the run-in period or if an exacerbation of COPD requiring oral steroids occurred in the run-in period.

[Slide]

In all pivotal trials there were two co-primary endpoints. The first was the change from baseline in FEV1 at trough levels of Ariflo.

This was measured in the morning at the end of the dosing interval when serum concentrations were at their lowest. The second was change from baseline in the total score of the St. George's Respiratory Questionnaire, or SGRQ. Co-primary endpoints are required in European clinical programs so these were also included in the North American program for consistency with the European studies.

[Slide]

Secondary measures of efficacy included in the pivotal trials were FVC, COPD exacerbations, post exercise breathlessness as measured by the Borg scale, summary symptom scores and exercise tolerance as measured by the six-minute walk. Summary symptom scores were not collected in study 156 as patients were not required to be symptomatic on entry into this study.

[Slide]

On this slide are the baseline characteristics for all four pivotal trials. Age, race and smoking history were similar across the four studies. There was a higher proportion of women in the North American studies and this is consistent with the demography of COPD in the United States.

Average FEV1 post albuterol was approximately 50 percent of predicted with an FEV1 reversibility to albuterol of approximately 6.5 percent across the clinical trials.

Mean DLCO as a percentage of predicted was lower in North American studies, which is indicative of significant emphysema in this population.

Fewer patients in the North American studies reported a history of chronic bronchitis, and this was particularly true for study 156. This may be due to the fact that patients were not required to be symptomatic upon entry into this study.

Overall, the patients represented in the clinical program had moderate to severe COPD and, importantly, were poorly reversible to albuterol. Additionally, the data on this slide suggest that the COPD populations in North American and Europe were different, as shown by differences in gender, degree of emphysema, degree of chronic bronchitis and, to a smaller extent, reversibility to albuterol.

[Slide]

This graph represents the change in trough

FEV1 over 24 weeks for Ariflo compared to placebo in North American study 039. The Y axis shows the change from baseline in FEV1 in liters and the X axis shows the study week. The primary analysis for FEV1 was the average change over 24 weeks. Ariflo, illustrated here in yellow, maintained FEV1 over the 24-week study period whereas the placebo group showed a decline in the same period of time. The decline in the placebo group was seen throughout the study period and this resulted in an average change of 40 ml between the treatment groups.

As you can see, the difference between Ariflo and placebo continued to widen over time, and this suggests that endpoint analysis, or last on-treatment observation, may be a more appropriate way to evaluate the FEV1 response. At endpoint there was an 80 ml difference between Ariflo and placebo and this difference was also statistically significant.

[Slide]

Now I will show all four pivotal trials. I have already shown you study 039 where Ariflo showed a maintenance of FEV1 over the 24 weeks whereas the placebo group showed a steady decline.

North American study 156 was conducted after the other three pivotal trials and confirmed the results of study 039. Ariflo was associated with a maintenance of FEV1 over time, over the six-month treatment period, whereas there was a decline in the placebo group.

Like studies 039 and 156, European study 091 showed a similar result, with a maintenance of FEV1 with Ariflo and a steady decline in the placebo group.

European study 042--in this study the placebo group did not show a similar decline in FEV1 as the other three studies and it is unclear why the results were different in this study.

All four studies showed a consistent treatment difference between Ariflo and placebo. However, the results of the European studies were not statistically significant. The p value is here. While it is less than 0.05, when adjustment was made for multiple comparisons this was not statistically significant. Therefore, all four trials showed maintenance or improvement in FEV1 during treatment with Ariflo, shown here in yellow, while three of the four studies showed a decline in the placebo group, shown here in blue. In this

poorly reversible population the decline in FEV1 observed in these trials is not surprising and has been seen in other large studies of patients with COPD.

[Slide]

As I mentioned, the consistent decline in the placebo arms of the pivotal trials has also been seen in other large studies of patients with COPD. In these four studies, the Lung Health Study, the ISOLDE Study, EUROSCOP and the Copenhagen City Study, evaluated poorly reversible patients. In patients receiving placebo or active treatment it can be seen that they all had declined in FEV1 over time, and this is a well recognized clinical manifestation of COPD.

[Slide]

Due to the incurable and progressive nature of COPD care for patients mainly focuses on the reducing symptoms and improving quality of life. The St. George's Respiratory Questionnaire, SGRQ, has been widely used to assess quality of life in patients with respiratory disease. It is self-administered and divided into three domains, symptoms, activity and impact on daily life. A total score ranging from 0-100 is calculated from

the questionnaire, with higher numbers indicating more impaired quality of life. A decrease in score indicates an improvement in quality of life, with a change of minus four units considered to be a clinically meaningful improvement. It is important to note that no pharmacologic intervention for COPD has consistently shown an improvement of four units over placebo.

[Slide]

Shown here are the results of the mean change from baseline in SGRQ over 24 weeks in North American studies 039 and 156. The SGRQ was assessed at baseline, week 12 and week 24 or early withdrawal. The Y axis, on the left, shows the mean change from baseline in total SGRQ. As I have mentioned, a decrease in score reflects in improvement in quality of life.

In study 039, shown here, the patients in the Ariflo group experienced an improvement in quality of life from baseline of 3.7 points while patients in the placebo group had a decline of 0.4 points. When compared to patients in the placebo group, patients in the Ariflo group experienced a clinically meaningful improvement of 4.1 points.

Similarly, in study 156, shown on this

side of the slide, patients in the Ariflo group experienced an improvement in quality of life of 3.2 points. Unlike study 039, patients in the placebo group also experienced an improvement in quality of life of 1.3 points. The difference between Ariflo and placebo was statistically significant but did not reach the predefined clinically meaningful difference of four points. However, overall in the North American studies the Ariflo-treated patients demonstrated a consistent improvement from baseline in quality of life.

[Slide]

On this slide the North American studies I have just shown you are shown here and the European studies are shown on this side of the slide. In the European studies the change from baseline in SGRQ for patients treated with Ariflo was similar to the North American studies but the placebo groups also improved, resulting in no significant differences between the groups. The reasons for the differences between the placebo response between the North American and European studies are not clear but may be related to some of the differences in baseline characteristics.

[Slide]

The secondary endpoints, as I have already mentioned, included FVC, six-minute walk, symptom scores, post-exercise breathlessness and COPD exacerbations. A check mark indicates that Ariflo was significantly improved over placebo whereas a T indicates a trend in favor of Ariflo. FVC at endpoint was significantly improved by 110 ml and 60 ml in North American studies 039 and 156 respectively.

Changes in FVC were not significant in the European trials but trended in favor of Ariflo. The results were not consistent for the six-minute walk or summary symptom scores but there was a trend in favor of Ariflo for post-exercise breathlessness across the pivotal trials. Time to first moderate or severe COPD exacerbation was significantly improved for patients receiving Ariflo in study 039.

While study 091 did not achieve either primary endpoint, this study also showed a significant improvement in time to first COPD exacerbation. Because of the high morbidity and mortality that is associated with COPD exacerbations, reducing exacerbations is one of the most important goals of the treatment of COPD.

Although these studies were not specifically designed to evaluate COPD exacerbations, they are included as secondary endpoints and these results are shown in more detail on the next slide.

[Slide]

This slide shows the exacerbation-free survival for all four pivotal trials. As you can see and as I have already mentioned, study 039 and study 091 showed a statistical significant improvement between the treatment groups in favor of Ariflo. These studies also showed a decrease in oral steroid use associated with exacerbations in these two studies.

Study 156, shown in this corner, may not have shown a difference in exacerbations since patients were not required to be symptomatic upon entry into the study as was required for all the other pivotal trials. As a result, this may have led to a lower rate of exacerbations and, in fact, the placebo group in this study had an exacerbation rate that was nearly 20 percent lower than any of the placebo groups in the other three studies.

In European study 042 the relative risk of experiencing a COPD exacerbation was comparable between Ariflo and placebo-treated patients. These

data suggest that Ariflo may have positive effect on COPD exacerbations, however, a study specifically designed to evaluate exacerbations needs to be conducted to confirm this result.

As I have discussed, the pivotal trials achieved statistical significance in both primary endpoints in the North American studies, and the supporting data from the secondary endpoints provides support for the approval of Ariflo.

[Slide]

I will now discuss the remaining supporting studies. The long-term extension studies were conducted primarily to evaluate the long-term safety and tolerability of Ariflo. They also further evaluated FEV1 over time. Subjects from North American study 039 were eligible to enter long-term study 041, and subjects from European studies 042 and 091 were eligible to enter study 040. While these were not controlled studies and patients could be on other medications to treat COPD, they provide important long-term data.

[Slide]

Shown here is the long-term extension study 041. The first part of the graph, right here, shows the double-blind, pivotal trial 039.

For this part of the study Ariflo is shown in yellow and the placebo group is shown in blue. At 24 weeks all patients received open-label Ariflo. Patients previously receiving Ariflo through open-label extension remained, in yellow, while patients previously receiving placebo who then received Ariflo are shown here in orange.

During the open-label period the use of concomitant COPD medications was similar between the treatment groups. For the former Ariflo group FEV1 was maintained out to 84 weeks at a value similar to the baseline value on entry into study 039.

[Slide]

This slide shows the results from European study 040. The results are similar to those seen in 041, with the maintenance of FEV1 for as long as 60 weeks and a value similar to baseline in the patients that were previously treated with Ariflo. Even with the caveats of uncontrolled studies, these data indicate that Ariflo may maintain FEV1 at a value similar to baseline substantially beyond 24 weeks.

[Slide]

Traditionally clinical development

programs for COPD have evaluated FEV1 as the primary efficacy measure. However, there are other physiologic measures that provide clinically relevant information for patients with COPD. Pictured here is a chest x-ray that shows normal lung parenchyma and a chest x-ray from a patient with severe COPD. As you can see, the lungs of the patient with COPD are severely hyperinflated, with a flattened diaphragm and evidence of emphysema. There is evidence to indicate that FEV1 alone may have some limitations as a clinical outcome measure for the evaluation of efficacy in COPD. For this reason we have used the measurement of lung volumes as another complementary method to evaluate the effects of Ariflo in this patient population.

[Slide]

This diagram shows the relationship between the different lung volumes. Total lung capacity, shown here, is the total volume of gas in the chest after full inspiration. Functional residual capacity is the volume at the end of a tidal exhalation and residual volume is the amount of gas in the chest after a full expiration.

With progressive disease, as shown here on the right, the loss of elastic reflow leads to

hyperinflation with an increase in total lung capacity, functional residual capacity and residual volume. These changes cause the patient to breathe at a higher lung volume and FRC and RV increase the work of breathing and reduce the respiratory reserve that is needed for normal ambulatory function. Reduction of hyperinflation is important because it reduces the work of breathing and is associated with improved exercise capacity. Lung volume reduction surgery is very effective in this regard but is quite invasive. So, an effective pharmacologic intervention to achieve a reduction of hyperinflation would be preferable.

[Slide]

Study 111 was designed to evaluate the trough effect of Ariflo on static lung volumes over 12 weeks. The entry criteria into this study were similar to the pivotal trials, with the exception that patients had to be hyperinflated with a residual volume of greater than or equal to 120 percent of predicted at baseline. Demographics and pulmonary function characteristics were similar between the Ariflo- and placebo-treated patients and similar to the pivotal trials. It is important to note that these patients were also poorly

reversible to albuterol.

[Slide]

The primary efficacy variable was volume of trapped gas at trough as measured by the difference between TLC measured by plethysmography and total lung capacity, or TLC, measured by single breath helium dilution. Ariflo reduced the mean volume of trapped gas by 140 ml. However, this difference was not quite statistically significant.

Since plethysmography is generally better than single breath helium dilution to measure lung volumes in patients with COPD, the results of these measurements are shown on the next few slides.

[Slide]

Using plethysmography, Ariflo demonstrated a significant improvement in residual volume at trough that continued to improve over time. Again, here is the placebo group and the patients treated with Ariflo. The difference between Ariflo and placebo was nearly 300 ml at endpoint.

[Slide]

Again, with plethysmography Ariflo demonstrated a significant improvement in functional residual capacity, with a difference from placebo of nearly 300 ml at endpoint. Again,

the difference in FRC continued to widen over the 12 weeks of treatment. This substantial decrease in air trapping was not associated with a significant improvement in trough FEV1 and again highlights the utility of evaluating lung volumes in addition to FEV1 in patients with COPD. Later Dr. Sciurba will speak to you about these results and the important clinical benefits that they provide to patients.

[Slide]

Given the clinical experience with theophylline and the fact that there are some similarities in their mechanisms of action, it is inevitable that a comparison will be made between Ariflo and theophylline. However, a direct comparison with data currently available is really difficult to make, and this is for several reasons.

First, there are no studies of similar design that can be compared directly. For example, most of the studies in the recent Cochrane meta-analysis were very small, ranging from 8-60 patients, of short duration, one day to eight weeks, and have varying entry criteria for reversibility, and were primarily designed to show a bronchodilator effect of theophylline.

Theophylline is a non-selective phosphodiesterase inhibitor and the bronchodilator response is thought to be predominantly due to the activity or the inhibition of phosphodiesterase-3, while Ariflo selectively inhibits phosphodiesterase-4. Phosphodiesterase-3 is thought to have more activity in smooth muscle whereas phosphodiesterase-4 is more prominent in inflammatory cells. In fact, theophylline at therapeutic levels has very little activity on PDE4.

It has also been proposed that theophylline has some anti-inflammatory properties, however this has not been well characterized in patients with COPD. It is not thought to be due to phosphodiesterase inhibition. One of the largest studies with theophylline is shown on the next slide.

[Slide]

This study, by ZuWallack and colleagues, evaluated serial FEV1 after the first dose of theophylline, on day one, and after 12 weeks of treatment, and there are about 170 patients in this analysis shown here. These data illustrate three major points: Theophylline had bronchodilator

activity with an acute FEV1 response within one hour which did not change significantly from week one to week 12. This study only enrolled patients that could tolerate the theophylline titration period during the run-in so these are really the theophylline tolerators and 44 percent of patients who withdrew during the run-in dropped due to adverse events due to theophylline. An additional 12 percent dropped because they could not achieve appropriate serum theophylline levels.

This slide also shows the importance of the population chosen for inclusion. When all patients were considered without regard to reversibility, as shown here, there is a 100 ml increase in peak FEV1, which is consistent with what was shown by the Cochrane meta-analysis. However, when only the poorly reversible patients were analyzed there was about a 50 ml increase in peak FEV1 and when theophylline was at trough the FEV1 was back to near baseline levels.

As you recall from the data that I have already shown you, Ariflo did not have a bronchodilator effect in a similar population. Therefore, theophylline is predominantly a bronchodilator whereas the predominant effect of

Ariflo in this population is anti-inflammatory.

[Slide]

So, in summary, Ariflo demonstrated statistically significant benefits over placebo for both co-primary endpoints, FEV1 and SGRQ, in the North American studies. While the European studies did not meet statistical significance, the trends in magnitude of effect from baseline were consistent with the North American studies.

[Slide]

Supporting data provided additional evidence for the efficacy of Ariflo in patients with COPD. Ariflo demonstrated significant benefits in relative risk of moderate to severe exacerbations in two of the four pivotal trials. The long-term extension studies confirmed the efficacy seen in the pivotal trials. FEV1 was maintained beyond 24 weeks and as long as 84 weeks in the open-label studies. Finally, Ariflo demonstrated a substantial reduction in lung hyperinflation at trough in a poorly reversible population.

[Slide]

As we have discussed toady, COPD is a complex and progressive disease, and since there

are few medications that treat the underlying pathophysiology of this disease there is a clear unmet and urgent medical need. The population studied in the Ariflo clinical program was poorly reversible to albuterol and these patients are felt to be the most difficult to treat. They also have a faster rate of decline in FEV1 and low FEV1 is associated with worse outcome. Patients with COPD have had to rely on the same drugs developed for asthma and have not had drugs with mechanisms of action specifically targeted to treat the very different inflammation that is seen in COPD. Ariflo is a novel medication that was specifically developed to treat the processes that are important in this disease.

The data from the pivotal trials are supported by the studies that show the long-term maintenance of FEV1, the anti-inflammatory effects and substantial reduction in hyperinflation with Ariflo, and support the proposed indication.

I would like now to introduce Dr. Kathy Rickard who will review the safety analysis from the Ariflo clinical program.

Safety of Ariflo

DR. RICKARD: Good morning.

[Slide]

My name is Kathy Rickard and I am the Vice President of Respiratory Clinical Development and Medical Affairs for GlaxoSmithKline. In the next 20 minutes I will review safety data for Ariflo. The safety database for the Ariflo program is extensive and the level of scrutiny that we have performed in this program is sufficient to support the approval of Ariflo for COPD.

We believe that the safety data that we will present today demonstrates that Ariflo has an acceptable and well defined safety profile for an oral treatment in patients with COPD.

[Slide]

As part of the evaluation of the safety of Ariflo, the Phase II and II clinical program included over 50 studies including clinical pharmacology studies and dose-ranging studies. I will present data from three clinical pharmacology studies that address specific issues raised during the Phase II/III development program. However, my review today will focus on the Phase III clinical program which consisted of extensive safety monitoring in COPD patients. This included adverse events, measurement of specific parameters to

assess effects of both gastrointestinal and cardiovascular and studies that address long-term safety.

[Slide]

The safety database is extensive and Phase III consisted of over 3,400 patients with COPD, over 2,000 of whom were treated with Ariflo. The vast majority were enrolled in four 24-week pivotal trials and our presentation will primarily focus on these patients. For three of the four pivotal trials patients were randomized in a 2:1 ratio of Ariflo to placebo. These safety data were further augmented by the long-term extension studies which evaluated over 1,000 patients treated with Ariflo for up to three years, providing nearly 3,000 patient years of exposure.

[Slide]

This table presents adverse events that occurred in greater than or equal to five percent of patients in either treatment group. As you will see, the total percentage of patients experiencing adverse events was similar between Ariflo- and placebo-treated patients. Symptoms of gastrointestinal intolerance, which included nausea, diarrhea, abdominal pain, dyspepsia and

vomiting, occurred more frequently in Ariflo treated patients. However, it is important to note that the investigators designated the majority of these as mild to moderate in intensity. Symptoms of COPD, upper respiratory tract infection and coughing, tended to be higher in placebo-treated patients.

Of note, there were no clinically significant differences in central nervous system effects, including headache, between Ariflo and placebo. Unlike the known CNS effects associate with theophylline, there was no increased risk of seizure with Ariflo.

[Slide]

This slide includes adverse events that led to withdrawal in greater than or equal to 0.5 percent of patients in either treatment group. Overall, the percentage of patients withdrawn due to adverse events was higher in Ariflo treated patients and this was largely related to withdrawals for GI intolerance. However, symptoms of COPD led to a higher percentage of withdrawals in patients treated with placebo.

To further evaluate GI intolerance, patients were specifically asked to report GI

adverse events. The next slide will discuss the rationale behind the gastrointestinal safety monitoring performed during the clinical trials.

[Slide]

Extensive safety monitoring was performed to assess GI effects. This was done to evaluate both the adverse events associated with symptoms of gastrointestinal intolerance seen in humans, a known class effect of PDE inhibitors including theophylline and caffeine, as well as a finding of medial necrosis of mesenteric arteries in rat nonclinical studies. This finding was specific to rodents and was not seen in primates even at high exposure for up to a year.

Furthermore, there was no mesenteric ischemia and no downstream effects seen in any organ, including the intestine and the liver, in the rodents. It is also reassuring that although medial necrosis has been seen in rats administered theophylline and caffeine, no clinically relevant effects have been seen after years of theophylline use in patients with asthma of COPD.

[Slide]

During the Ariflo Phase III clinical program regularly scheduled safety monitoring was

conducted. These tests included physical exams, laboratory assessments, orthostatic vital signs, fecal occult blood testing and the collection of adverse events at regularly scheduled visits. Along with the routine safety monitoring, comprehensive testing of patient-reported GI adverse events of potential concern was conducted. GI adverse events of concern were a subset of adverse events and were characterized as such because they were of concern to the patient or interfered with their daily activities. Additional fecal occult blood tests, orthostatic vital signs, laboratory testing and physical exams that specifically evaluated the GI system were conducted for any patient reporting a gastrointestinal adverse event of concern.

Relatively late in the program, following completion of studies 039, 042 and 091 and after initiation of studies 156, 041 and 040, these last three studies were amended at the request of the FDA to include a requirement for colonoscopy. Colonoscopies were recommended for patients with a GI adverse event of concern and a positive fecal occult blood or for direct observation of blood in the stool. This was also a requirement for study

168.

[Slide]

An example of the extensive monitoring performed in patients in the Ariflo program is seen here. Patients who completed the study on average had six fecal occult blood tests, ten sets of laboratory evaluations, 13 sets of vital signs and four sets of orthostatic vital signs checked throughout the six-month period of the study. Patients were questioned on each monthly visit about GI effects. We feel sure that with such close monitoring we were unlikely to miss serious GI effects if they occurred.

[Slide]

This slide presents GI adverse events of concern occurring in greater than or equal to 0.5 percent of patients in either treatment group. Although GI adverse events of concern were more frequent in Ariflo treated patients, again, it is important to note that the majority was designated by the investigator as mild to moderate in intensity.

[Slide]

GI adverse events of concern generally occurred early in treatment, within the first three

weeks. On this slide the Y axis shows the cumulative percentage of patients reporting a GI adverse event of concern. The X axis shows the study day. As you can see, after the first 30 days of treatment the lines of this graph are parallel, showing that these events occurred at approximately the same rate in both Ariflo- and placebo-treated patients.

[Slide]

Fecal occult blood tests were performed routinely at baseline and at the end of treatment. Additional fecal occult blood tests were performed in patients who experienced GI adverse events of concern. As shown on this slide, "total" refers to all fecal occult blood tests performed including routine and those done for GI adverse events of concern. In the total population the percentage of patients with positive fecal occult blood tests was similar between Ariflo- and placebo-treated patients. The same was true for fecal occult blood tests that were specifically performed for GI adverse events of concern.

As stated earlier, several studies were amended to include the requirement for colonoscopy for a GI adverse event of concern and positive

fecal occult blood. In those patients who underwent colonoscopy the findings were consistent with conditions expected for the population studied, including diverticular disease, polyps and hemorrhoids and did not identify any safety concerns. Of note, though the data are not presented here, laboratory tests and vital signs were performed every four weeks. There were no differences between treatment groups in any laboratory value or vital sign obtained routinely or for a GI adverse event of concern, including liver function tests, hemoglobin hematocrit, electrolytes, BUN, creatinine, urinalysis, amylase or lipase. Fecal occult blood tests and colonoscopy results suggest that the symptoms reported with GI intolerance were not associated with GI pathology.

[Slide]

As stated previously, because of the nonclinical findings of medial necrosis of the mesenteric arteries in rats, there was an increased interest in serious potential effects of the GI tract. It is important to note that incidence of several GI conditions, including bowel ischemia and perforation, is found to be generally higher in

patients with COPD.

In the Ariflo clinical program including the 24-week pivotal trials and the subsequent long-term extensions there are five cases of ischemic bowel reported, two in study 156 in placebo and three in the Ariflo patients in the long-term extension studies. In the Ariflo patients one was after a vascular procedure; one experienced a COPD exacerbation associated with constipation and a bowel perforation; and one was admitted for exacerbation of rheumatoid arthritis. This last patient was reported to have sequelae of ischemic colitis by abdominal x-ray. However, the patient continued on Ariflo and completed the study. None of the cases was attributed to study medication and all had other contributing factors.

As a reminder, the patients on placebo had only six months of exposure compared to up to three years on Ariflo. As you can see from this data, the incidence rate overall was lower in the Ariflo group compared to the placebo group. As you can see, the clinical findings do not support the occurrence of mesenteric vasculopathy in man that was observed in rats.

[Slide]

Finally, the incidence of serious adverse events reported in the GI body system is shown here. A serious adverse event included any event that was fatal, life-threatening, disabling or resulted in hospitalization. Serious adverse events were lower in Ariflo-treated patients than patients receiving placebo in the pivotal trial. Taken together, extensive GI monitoring demonstrated no increased risk of serious GI pathology with Ariflo treatment.

[Slide]

As shown, the clinical evidence supports that Ariflo is not associated with increased risk of bowel ischemia. As with other PDE inhibitors and caffeine, Ariflo was associated with mesenteric vasculopathy in rodents that was not associated with bowel ischemia. The clinical program included extensive monitoring of GI events and demonstrated no serious GI effects. In fact, the incidence of bowel ischemia was very low and comparable in the patients receiving Ariflo compared to those receiving placebo, thus providing reassurance that there is no association between Ariflo treatment and bowel ischemia.

[Slide]

As a result of the cardiovascular safety concerns with non-selective phosphodiesterase inhibitors and mild cardionecrosis seen in rats given high lethal doses of Ariflo extensive cardiovascular safety monitoring was performed. This included vital signs, ECGs and Holters. Since cardiovascular disease is common in patients with COPD, potential cardiovascular effects of any new drug are of particular interest.

[Slide]

During the clinical development program more than 70,000 ECGs were done, greater than 68,000 in patients with COPD and, of these, greater than 6,000 were performed at Cmax. In addition, over 1,000 Holters were performed. Holter monitoring results were integrated from three of the pivotal trials of 24 weeks in duration and study 168 of 12 weeks in duration. The Holters were obtained at baseline, week one and the end of treatment in these studies. All ECGs and Holters were read in a blinded fashion by independent cardiologists.

It is important to remember that many patients with COPD have significant underlying cardiovascular disease. In fact, approximately 50

percent of the patients in the Ariflo Phase III clinical trials reported at least one medical condition that involved the cardiovascular system. Thus, in this population it is important to ensure that any new therapy does not increase cardiovascular risk.

[Slide]

This slide presents the incidence of new onset ECG abnormalities in greater than five percent of patients in either treatment group. There are small differences in some categories of nuance of ECG abnormalities, however, these are unlikely to be of clinical relevance. In general, the percentages of new onset ECG abnormalities are similar between Ariflo and placebo treatment groups. Thus, extensive ECG monitoring revealed no safety issues with Ariflo.

[Slide]

Again, there were no differences in corrected QT interval between Ariflo- and placebo-treated patients. As you can see, both groups had a change from baseline in corrected QT interval of less than 0.5 msec using Bazett's correction. At any time point on therapy a similar percentage of Ariflo- and placebo-treated patients

had a change from baseline in corrected QT interval greater than or equal to 30 msec. The number of patients with greater than a 60 msec change in baseline in corrected QT interval was also similar between treatment groups. Similar results were seen when QT interval was corrected by Fridericia's. Thus, there is no evidence of QT interval prolongation with Ariflo.

[Slide]

As observed with ECGs, there was no difference between Ariflo and placebo treatment groups in percentage of new onset of cardiac abnormalities during 24-hour Holter monitoring. Of note, there was no sustained ventricular tachycardia observed.

[Slide]

Lastly, the incidence of serious adverse events affecting the cardiovascular body system was lower in the Ariflo-treated patients compared to placebo. Taken together, the extensive cardiac monitoring demonstrated no increased risk of cardiac events associated with Ariflo treatment.

[Slide]

Death occurred infrequently, with death reported in five, or 0.5 percent, of

placebo-treated patients and seven, or 0.4 percent, of Ariflo-treated patients. The deaths were all due to cardiovascular or respiratory causes and none was deemed related to study medication or was unexpected for a COPD population who exhibited a significant number of co-morbidities.

[Slide]

As mentioned earlier, patients completing three of the 24-week studies had the option to continue into an open-label long-term extension study. Safety data was obtained for greater than 1,000 patients for up to three years, including extensive monitoring of gastrointestinal and cardiovascular events, laboratory evaluations, fecal occult blood tests and physical exams. The results were similar to the data from the pivotal studies and identified no serious safety issues during the long-term Ariflo administration. These findings further support the safety of Ariflo for patients with COPD.

[Slide]

In addition to the clinical trials I have just reviewed, clinical pharmacology studies were performed to investigate specific findings in animal models and to establish the potential for

specific drug interactions relative to the population studied. Areas investigated included testicular degeneration seen in rats and rabbits, adrenal cortex hypertrophy in rats and changes in the reproductive organs of female mice, consistent with increased exposure to prolactin. As you will see, none of these findings in animals was found to be of clinical relevance in humans.

Finally, studies were conducted to confirm findings from animal studies that Ariflo would have no significant pharmacokinetic and pharmacodynamic interactions with other drugs, particularly those likely to be used in a population of COPD patients.

[Slide]

Nonclinical data show testicular degeneration in rats and rabbits, but this was not observed in other species, including primates. A clinical study was performed to definitively assess the effect in humans. In order to investigate possible effects in a human reproductive system Ariflo or placebo was administered at a dose of 15 mg twice a day to 100 healthy, young male subjects for 12 weeks. The subjects were followed for an additional 12 weeks after the end of dosing. This study did not identify any clinically significant

changes in the total number of sperm per ejaculate or progressive and overall motility and morphology following chronic dosing with Ariflo.

[Slide]

In other nonclinical studies adrenocortical hypertrophy was seen in rats. This is a well recognized response of rats to PDE inhibitors and is due to stimulation of ACTH release in response to increased cyclic AMP concentrations in the hypothalamus and anterior pituitary gland. Additionally, in the mouse carcinogenicity study a weak effect per mammary tumor induction was observed at high doses. These tumors showed microscopic changes that have been seen with elevated prolactin levels. Studies in mice showed no change in prolactin levels, however, evidence of persistent diesterase was observed. Therefore, the mammary tumor induction was likely related to a state of pseudopregnancy, an event that has no analogy in humans.

A clinical pharmacology study was conducted in humans to explore the effects of Ariflo on the HPA axis and prolactin secretion and additional assessments of HPA axis function were made in six other clinical pharmacology studies.

The results of these studies indicated that levels of prolactin, ACTH, serum cortisol and urinary cortisol were similar from repeat dosing with Ariflo or placebo.

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Finally, Ariflo had no significant interactions or tolerability issues with the range of drugs likely to be co-administered in patients with COPD, including albuterol, ipratropium, theophylline, prednisolone, warfarin and digoxin.

There was also no significant effect of smoking on plasma levels of Ariflo. There was no effect on the bioavailability of Ariflo administered with food or with the antacid Maalox. Co-initiation of Ariflo and erythromycin should be avoided due to increased incidence of GI intolerance, and since unbound plasma concentrations were increased in patients with severe hepatic impairment and severe renal impairment, there is a potential to have increased GI intolerance in these patients.

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In conclusion, the safety of Ariflo was extensively evaluated with up to three years of exposure, which translates to nearly 3,000 patient

years of exposure. For patients with GI adverse events. They predominantly occurred in the early weeks of therapy and most were mild to moderate in intensity. While some patients may experience gastrointestinal intolerance upon initiation of Ariflo treatment, there is no evidence to suggest that Ariflo is associated with an increased risk of serious GI sequelae. Extensive cardiac monitoring throughout the clinical development program demonstrated no evidence of an increased risk of cardiovascular events associated with Ariflo therapy. In summary, extensive safety monitoring identified no clinically significant safety concerns in patients with COPD treated with Ariflo for up to three years.

I thank you for your attention today and would like now to turn the podium over to Dr. Frank Sciurba.

Assessment of Outcome in COPD

DR. SCIURBA: Thank you. Good morning.

[Slide]

I have been asked today to present some concepts in the assessment of outcome in patients with COPD, and particularly to place it in the context of the data we have seen today on Ariflo.

As we have heard, COPD still remains a problem in our society and particularly with respect to symptoms and difficulty in treatment of individual patients.

[Slide]

As you can see in these photographs of two of our patients, these drawings to reflect real patients. Unlike asthma, COPD is a disease in which, despite maximal available treatment, patients remain symptomatic and continue to decline over time. The patient on the left panel is in the typical tripod position, and the reason he is in this position is because his lungs are hyperinflated. He uses his accessory muscles. He uses his arms to anchor his accessory muscles of inspiration; to pull in that final teacup of air by pulling up on his first rib and his clavicle.

New drugs are needed to treat these patients. The many new classes of anti-inflammatory drugs, including PDE4 inhibitors and many products that are evolving, are necessary and offer significant hope for these patients.

Unlike asthma, COPD has a great toll on mortality. This study reflects the data, the catastrophic data from the support study showing

the follow-up of patients admitted to the hospital with hypercapnia and exacerbation, while there is an 11 percent in-hospital mortality rate. At 60 days 20 percent of these patients are dead. By two years a full 50 percent of patients have died.

[Slide]

Unfortunately as expressed in this NIH consensus statement in 1994 by Dr. Fishman, no single parameter in patients with COPD is sufficient to be considered the gold standard to assess outcome in this disease.

[Slide]

This concept was reiterated in a very recent NIH consensus committee statement on clinical research and COPD needs and opportunities, and among the questions raised in this statement by the workshop was what measures of disease status are useful indices of therapeutic benefit? What can be done to promote the development in testing of novel agents for the treatment of COPD? And, suggested that efforts to reduce these barriers include the exploration of alternative outcome measures.

I sincerely believe we need to look at alternatives, including expiratory flow limitation,

if we are going to be able to address the positive impacts of these anti-inflammatory agents as they are going to be increasingly presented to the scientific community and the administration.

[Slide]

FEV1 has been an important proven parameter. On average it does reflect lung function and prognosis. It is a reproducible measure and is responsive to various therapies, which is well established.

[Slide]

As we have seen in this earlier slide, in fact on average FEV1, in this Anthonisen's retrospective analysis, does reflect prognosis. Unfortunately, there are, indeed, limitations to using this as a sole parameter. There is marked individual variation in symptoms and disability independently of FEV1. Symptomatic and functional response to therapy may be independent of FEV1 and it may not reflect changes in important disease activity which could lead to long-term functional decline or frequency of exacerbations.

[Slide]

This slide, Dr. Jones' data, shows the relationship between a symptom quality of life

index, the St. George's Respiratory Questionnaire, and the FEV1 as a percent of predicted. While there is, in fact, a significant correlation, the r squared relationship shows that only 10 percent of the variation in symptom scale is related to the baseline FEV1 parameter. If we focus on patients with a value of 40 percent of predicted, we see a range from nearly normal to nearly completely disabled and the full range in between.

[Slide]

So, what other parameters in an individual explain the symptoms and explain the disease? Well, one aspect that we can look at is hyperinflation. Other parameters include the assessment of inflammation both on the lung and the systemic consequences of inflammation.

This slide shows volume time curves in patients with progressive lung disease. In spirometry maneuver, as most of you know, patients are asked to take a deep breath all the way into the top and blow it out as forcefully and as long as they can. Patients with progressive disease take longer and longer to get the air out. Note that as disease gets more severe, in fact patients do not get all the air out. It is not that their

lungs are getting smaller, the lungs are very large but the air remains trapped in the lungs.

[Slide]

The physiologic consequences of that can be measured. In a normal individual residual volume--the air trapped at the end of a forced expiration--and the functional residual capacity--the air left in the lungs at the end of a normal exhalation--are compared to COPD where there are dramatic increases in residual volume and functional residual capacity.

[Slide]

The consequences of that are significant hyperinflation of the chest with flattening of the diaphragm and shortening of the inspiratory muscles on inspiration. One of my patients put this in their terms. A patient who is a poet told me, "if you want to experience what I feel take a deep breath all the way to the top, let out a teacup of air; don't go down to your level of relaxation but a teacup of air. Now breathe in again from that point and try and stay up there." What you feel is the discomfort of dyspnea from operating your muscles of inspiration in suboptimal positions.

[Slide]

The reason why we have this sensation is that in fact the entire mechanics of the chest wall and muscles are in suboptimal configuration. As opposed to a normal individual where at the end of an inspiration, the chest wall is recoiling outward to balance the inward recoil of the lungs, patients with COPD remain with inward recoil of the chest wall. So, when we start our next inspiration we have to overcome that inward recoil and only then can the increased inspiratory muscle activity result in movement of air in the thorax. We already discussed the impact of flattened diaphragm, decreased air movement for a given amount of muscle contraction and effort.

[Slide]

The clinical consequences are real in patients who have x-rays such as this with hyperinflation. These patients often will describe, "I have difficulty with inspiration." They may have trouble performing the FEV1 maneuver once a year on their birthday but they have to inspire 16-20 times a minute.

[Slide]

That is really the disability in these patients. During exercise things only get worse.

These are the resting tidal volumes from expiration and expiratory lung volume to inspiration in a normal individual. As we discussed, patients with COPD are markedly hyperinflated. As exercise progresses they have less time to exhale. A normal individual will exhale more completely and breathe deeper and have significant reserve. They can increase their rate. They can increase their flow. Patients with COPD are limited in this air trapping. It gets more extensive and the end expiratory lung volume gets closer and closer to the maximal lung capacity and ceiling and their symptoms get worse.

[Slide]

This study by Dr. O'Donnell shows the disconnect in therapeutic response to albuterol between FEV1 and lung volume response. Dr. O'Donnell investigated a group of patients with irreversible COPD and found that 83 percent of them did have significant reductions in lung volume despite limited improvements in FEV1. Recall, this is a post bronchodilator maximum therapeutic effect of this drug in this study.

[Slide]

Another aspect that FEV1 does not directly

track is the degree of inflammation. This study, which we collaborated on with Dr. Hogg's group at the University of British Columbia, shows the fact that in severe COPD patients who had undergone lung volume reduction surgery, when the tissue is analyzed in patients who had discontinued smoking, there is ongoing, continued inflammation with the important increases in neutrophils, macrophages and the killer CD8 lymphocytes both in the air space and in the tissue.

[Slide]

An editorial by Dr. Shapiro really summarizes this: "The cigarette burns out but the inflammation rages on."

[Slide]

It occurs to me that, in fact, an anti-inflammatory study has been published. The American Lung Health Study shows the impact of the anti-inflammatory effects of smoking cessation, resulting in stabilization of FEV1 relative to the ongoing relentless decline in FEV1 that occurs in the continued smoking group.

[Slide]

So, if we interpret these concepts in the context of the data that we have seen today, in

fact the Ariflo group, cilomilast group, relative to placebo shows a result that could be very similar to that. In fact, this may be the effect we see from these classes of anti-inflammatory drugs--stabilization relative to decline that would normally occur.

[Slide]

This study again shows the data on improvement in residual volume, decreasing residual volume over time relative to the placebo group. At end of study greater than 500 cc difference, 500 cc difference in the Ariflo group relative to the placebo group. Recall, this is a trough. These values were obtained at trough pharmaceutical concentrations. In addition, you see this occurring over time. It is not an abrupt response. This may be what we might expect to see with the control of inflammation in the peripheral airways.

[Slide]

These surrogate markers of inflammation are present in the cilomilast last, decreases in the CD8 and the macrophage concentrations relative to the placebo group.

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In conclusion, clinically relevant

outcomes of novel anti-inflammatory agents for COPD may need to include stabilization of FEV1, reduction in lung hyperinflation and surrogates indicating changes in airway inflammation. These may be most important when measured at trough levels of therapeutic concentrations.

FEV1, while it is indeed a useful measure of severity and outcome in COPD, may not reflect other clinically important measures of lung hyperinflation and inflammatory activity.

I appreciate your attention. Thank you.

Summary Remarks

DR. WHEADON: For those of you suffering the caffeine effects, diuretic not mesenteric, I promise you, we are in the home stretch.

Ariflo is a novel medication that was specifically developed to treat the processes that are important in COPD. Until now patients with COPD have had to rely on the same drugs developed to treat asthma. We believe that the data we have reviewed this morning supports the approval of Ariflo for the treatment of COPD.

[Slide]

Based on the increasing mortality of this disease, it is clear that COPD has been neglected

for far too long. It is only beginning to receive the attention that it deserves. New pharmacological therapy based on the pathophysiology of this disease may change the way physicians approach the management of this progressive and debilitating disorder.

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As you have seen, Ariflo effects are a wide variety of processes that are important in the complex pathophysiology of COPD. There is an urgent need for treatments that address the underlying processes of this disease. Unlike bronchodilators, the novel mechanism of action of Ariflo addresses multiple components of COPD. Therefore, Ariflo represents a promising step forward in the treatment of COPD.

[Slide]

In conclusion, Ariflo offers an important advancement in the treatment of COPD. The objectives of the Ariflo clinical program were achieved in this population for which we are seeking approval. In this poorly reversible population Ariflo demonstrated greater improvements in the co-primary efficacy endpoints of FEV1 and quality of life assessments.

Some patients experienced GI intolerance. This generally occurred early in treatment and was mild to moderate in intensity. There were no clinically significant safety concerns noted with the long-term use of Ariflo in patients with COPD.

In this population that has many co-morbidities and commonly receives multiple medications, Ariflo's lack of interactions with frequently prescribed drugs is important. In addition, since Ariflo is an oral treatment it may, indeed, improve patient compliance. Therefore, we believe Ariflo would be a valuable treatment option for patients with COPD.

I would also like to introduce four additional experts that we have joining us this morning. Dr. Loren Laine is Professor of Medicine at the University of Southern California Medical School and is Chief of the GI Section, LA County, U.S.C. Medical Center.

Dr. Jeremy Ruskin is Associate Professor of Medicine at the Harvard Medical School and Director of the Cardiac Arrhythmia Service at the Massachusetts General Hospital.

Dr. Christina Wang is a Professor of Medicine at the David Geffen UCLA School of

Medicine and Program Director, General Clinical Research Center, Harbor, UCLA Medical Center.

Dr. Gay Koch is Professor of Biostatistics at the University of North Carolina.

This ends our formal presentation and the presenters, as well as our experts, are available for any questions we may answer for you. Thank you.

Committee Discussion and Clarification

DR. PARSONS: There are two minutes left in the Glaxo presentation. If there are, I would say, very specific questions we could start now but I would save more broad questions for discussion later. Are there specific questions regarding specific details for the company that the committee has right now? Dr. Apter?

DR. APTER: I congratulate you on your presentation and I agree that COPD is a neglected disease. Can you tell me why 95 percent of the subjects in the focused trials were white and minorities and other patient groups weren't included?

DR. WHEADON: Well, I will take the first stab at that and then Dr. Knobil can add. Certainly, it is continually a target and an effort

that we have very much focused upon, that is, to increase the variability or the diversity of the patient populations in all of our clinical trials. Unfortunately, as we have seen over and over again in all sorts of chronic illnesses, it is very hard to widen that diversity. We are focusing on it; we are trying to do it very hard in a very focused fashion. Unfortunately, in this particular circumstance in the North American studies we were not able to get the diversity of patients that we were hoping to get.

DR. APTER: COPD dramatically affects other patient groups, does it not?

DR. WHEADON: Certainly we recognize that. Dr. Knobil?

DR. KNOBIL: Yes, COPD does affect all patient groups but traditionally Caucasians have been sort of the largest population of patients with COPD, and we see this in our clinics as well as our clinical trials. The other patient groups are probably somewhat under-represented in our clinical trials and, as Dr. Wheadon has already said, we are working to change that. But especially in European trials, it is difficult to increase the diversity based just on the patient

populations in those regions.

DR. PARSONS: I have been told we are going to take exactly a 15-minute break and we will resume for the FDA presentation. Thank you very much.

[Brief recess]

DR. PARSONS: The next part of the program will be the FDA presentation. I just want to remind people that the plan for this morning was that there would be 90 minutes for the Glaxo presentation, which we have had. There is an additional 90 minutes for the FDA presentation. If the FDA presentation finishes earlier, the plan will be for discussion open to both sides until approximately twelve o'clock, and which time we will break for lunch. So, that is the current schedule that we are on. I would like to now start with Dr. Anthracite who is going to start the presentation.

FDA Presentation

Introduction

DR. ANTHRACITE: Good morning.

[Slide]

SB 2077499, also called Ariflo, also called cilomilast, is a phosphodiesterase-4

inhibitor, as you have heard. It is a new molecular entity and the first drug in its class, and it is orally dosed twice daily.

The indication will be for the maintenance of lung function, as defined by the FEV1, in patients with chronic obstructive pulmonary disease who are poorly responsive to albuterol. This has, as you have heard, been a multinational development program in Europe, Australia, Japan, New Zealand, North America and South Africa.

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Our presenters this morning are going to be several. Dr. Virgil Whitehurst first will present preclinical pharmacology-toxicology from our perspective; followed by Dr. Sandra Suarez who will discuss dose finding; Dr. James Gebert who will talk about statistics and I will return to discuss safety and efficacy. Dr. Whitehurst?

Preclinical Pharmacology-Toxicology

[Slide]

DR. WHITEHURST: Toxicology studies are a major part of the preclinical safety evaluation. These studies determine the toxicity profile of a drug. The characterization of the toxicological profile attempts to identify target organs of

toxicity; the no-observed adverse effect level in animals, commonly referred to as the NOAEL; determine severity, reversibility and monitorability of toxicity; as well as determine the margin of safety, which is a ratio based on exposure comparison between animals and humans. There are several ways to compare the exposure. In this case we used the plasma area under the curve of the drug in both animals and humans.

[Slide]

The toxic effects of cilomilast in animals was studied in mice, rats, rabbits and monkeys. These studies revealed that cilomilast induces arteritis, testicular degeneration, adrenal cortex hypertrophy, myocardial necrosis and GI disturbances in animals. For the purpose of today's discussion, we will focus on the findings related to arteritis due to the severity of the lesion. We are asking your opinion on how to resolve this issue.

[Slide]

First some brief background information on arteritis. Arteritis is inflammation, hemorrhage and necrosis of the blood vessels. Arteritis appears to be a class effect of PDE inhibitors,

rolipram for one and others. There are about 12-15 at the agency, most of which cause arteritis in animals.

The Division's current conclusion based on our experience with PDE inhibitors is that arteritis is irreversible in animals. The sponsor has submitted preclinical data which they feel show that arteritis may be reversible. However, we feel that these data do not adequately address irreversibility.

In addition, the sponsor suggests that arteritis observed in the rat is likely a consequence of vasal dilation and resulting hemodynamic changes. However, we do not believe that the sponsor has adequately demonstrated this association, whether the lesion may be the result of direct drug-induced toxicity.

We are concerned about arteritis in this application because of its lack of a margin of safety. If a safety margin is based on AUC, as in this case, we generally consider a margin of 1 or greater to be adequate to support the safety. A narrow margin of safety suggests that the drug is more likely to cause similar toxicity in humans at the recommended clinical dose.

We derive the margin of safety from the most relevant animal species. When there is a lack of evidence of human relevancy among the animal species the margin of safety is derived from the most sensitive species. In many cases, including cilomilast, the most sensitive species is the most relevant species. As I will show you later, the cilomilast exposure at the NOAEL in the rat, the most sensitive and relevant species, was only a fraction of that in human at the proposed dose.

[Slide]

This table illustrates my point of the lack of safety margin of the cilomilast application. The table also provides a glance at the dose-response relationship of the drug and arteritis. Species tested are listed in the far left column. The doses at which arteritis occurs or is absent is listed in columns two and four. Columns three and five present plasma drug levels, AUC correspondent to these doses. The far right column represents the safety margin derived from the AUCs.

Human AUC here is 22 mcg/hour/ml. As you can see, arteritis was observed in rats and mice but not in monkeys. Note that the dose response of

arteritis is very steep. Take the rat data as an example. No lesions were seen at 20 mg/kg. Lesions were noted at 30 mg/kg and higher. Death occurred at 40 mg and higher. The safety margin derived from the rat data is 0.2. Furthermore, arteritis in rats occurred at an AUC that was only half of that in humans at the proposed clinical dose.

As was mentioned earlier, arteritis was not found in the monkey. The monkey does not appear to be a sensitive animal model for the detection of arteritis based on the lack of information in the literature and the agency's experience with PDE inhibitors.

You might ask why clinical trials at such a dose were allowed to proceed given the lack of an adequate safety margin. The answer is that the kinetic data was incomplete in the developmental phase and that initially a safety margin for arteritis was present. We recommended that these toxicities be closely monitored during the clinical trials.

[Slide]

To summarize, cilomilast-induced arteritis and death in rats, the severity of the toxicity in

rats increases over a narrow range of exposure. Human exposure at the proposed clinical dose is higher than the toxic dose in the rat.

[Slide]

Therefore, the data provide no margin of safety for arteritis compared to the proposed clinical dose regimen, and arteritis is a significant safety concern. Thank you.

Dose-Finding

DR. SUAREZ-SHARP: Good morning, everyone.

[Slide]

I will focus my presentation on study 032, which was a Phase II dose-response study following multiple administration of oral cilomilast at doses of 5, 10 and 15 mg twice daily given to patients with COPD, for six weeks. I would like to mention that I will be mainly talking about two issues, dose-response for efficacy issue and dose-response for safety issue.

This study, 032, had a parallel design and included around 100 subjects for treatment, and it had a dropout rate which was around 16 percent and was similar across treatments. What I have plotted here, as you can see, is the mean change from baseline in trough FEV1 as a function of visit and

treatment. In this case the blue profile corresponds to placebo. The black profile corresponds to the 10 mg dose, the green to 5 mg, and, in grey, to the 15 mg dose.

It can be observed from this slide that only the 15 mg dose was seen to be different from placebo at all visits, including endpoint. Also, you can observe from this that the 10 mg dose had a lower efficacy than the 5 mg dose. From this study, it was concluded that there was a lack of dose order response for cilomilast at doses of 5, 10 and 15 mg given twice a day, and also that only the 15 mg dose was significantly different from placebo.

[Slide]

What I have plotted here is the relationship between cilomilast trough concentrations as a function of dose just to show you that lack of dose response that I showed in the previous slide has nothing to do with lack of dose proportionality. In other words, as the dose of cilomilast increased the cilomilast trough concentrations increased, as you see here, proportionally.

[Slide]

Further analysis by the FDA showed that the 10 mg dose had a higher baseline FEV1. In fact, both the mean and the median baseline FEV1 was higher for the 10 mg dose. When we would correct for this discrepancy in baseline, we would obtain this plot.

[Slide]

What I have done here is to plot the change from baseline and FEV1 after baseline adjustment as a function of treatment and visit. In this case the green profile corresponds to placebo, white to 5, yellow to 10 and 15 mg is depicted here by blue. It appears that the 10 mg dose may be significantly different from placebo. Also, it might be that we might have a dose order response relationship. However, a lack of existence of dose response or the clinical relevance of this 10 mg dose with respect to placebo cannot be determined because the 10 mg dose was not tested in Phase III clinical trials.

[Slide]

So far I have talked about the relationship between dose and response. Now I am going to show you a correlation between concentration of cilomilast, in this case trough,

with efficacy, in this case FEV1. What I have plotted here is the change from baseline in FEV1 as a function of cilomilast concentrations. It is clear here that it appears that there is not a clear correlation between cilomilast trough concentrations and this clinical endpoint based on FEV1. The reason for that may be that the data was highly variable, as you can see here. Both the trough concentrations and FEV1 were highly variable. You see a high imbalance in the data. Or, it may be because maximum response was achieved at concentrations covered by the 10 mg and 15 mg dose.

[Slide]

Now let's move to the relationship between safety and dose. What I have plotted here is the percentage of adverse events occurring in more than five percent of patients in any treatment group as a function of dose and side effect. You can see here that as the dose increases this percentage of either abdominal pain, diarrhea, nausea and vomiting increased.

[Slide]

How do we know about the relationship between concentrations and safety? Well, what I

have done here is to show you the relationship between cilomilast trough concentrations in patients having gastrointestinal side effects against those having no side effects. It is observed here that I have plotted the cilomilast trough concentrations as a function of visit and dose for abdominal pain, nausea, vomiting and those patients having no adverse events.

It is shown in this slide that these patients having gastrointestinal side effects had cilomilast trough concentrations which ranged from as low as 35 and as high as 1,500 ng/ml, and those patients having no side effects had plasma trough concentrations which were between six and higher than 2,000 ng/ml. This tells us that there is not a clear correlation between cilomilast trough concentrations and side effects. The reasons for that may be various. It may be because of the high variability of the data, or maybe because simply there is no correlation between cilomilast trough concentrations and safety.

However, I want to mention that the sponsor submitted the data from 032. This study was a multiple dose study conducted in healthy volunteers, given doses from 2-20 ml twice a day.

From that study it was shown that the frequency of side effects was correlated to Cmax of cilomilast.

[Slide]

In conclusion, we can say that the dose-response relationship was not fully addressed by the sponsor. I showed you that the 10 mg dose may be significantly different from placebo. However, the clinical relevance of the 10 mg dose cannot be determined because the data from this study was not robust enough and the 10 mg dose, as I mentioned, was not tested in Phase III clinical trials.

We observed that there was a lack of concentration-response relationship and, as I said, that may be due to the large degree of variability in the cilomilast plasma trough concentrations. The coefficient of variation was rather high, higher than 60 percent. The data was highly unbalanced.

A higher incidence of side effects, such as nausea, abdominal pain and diarrhea, was observed with increasing doses of cilomilast.

[Slide]

Finally, as I said, plasma concentrations increased proportionally to dose, however, no clear

correlation between was observed between trough concentrations of cilomilast and some adverse events, and this may be due to the high variability of the data or just because there is no correlation between cilomilast trough concentrations and side effects.

[Slide]

Finally, I would like to acknowledge some people who contributed in the review of this study. Thanks for your attention.

Statistics

DR. GEBERT: Good morning.

[Slide]

I have been asked to give some background material. The results of the individual studies will be given by Dr. Anthracite.

[Slide]

The topics I am going to talk about are the Hochberg procedure which was the procedure the sponsor used to declare significance of the two primary endpoints. I will talk about the repeated measures analysis. I will talk about properties of the endpoint analysis which was the sponsor's supportive analysis. Then, I will talk about sample size and delta of the sponsor's.

[Slide]

The Hochberg procedure is a modified Bonferroni procedure with two endpoints. If both of them are significant at the 0.05 level, they are both significant. If one fails to be significant at the 0.05 level, the other is significant if it is significant at the 0.025 level.

This is statistical significance, not clinical significance. In a regulatory setting this may not be appropriate in some situations because in some situations, because of risk/benefit considerations, you may need both to be significant. It also might cause some troubles about writing a label if you didn't have one study where both of them were significant.

Another kind of subtle thing is that the 95 percent confidence limits on the differences between treatment means are not really appropriate in this situation because sometimes you don't use the 0.05 to judge significance; it is the 0.025 level which you use to judge significance. In some cases 97.5 percent confidence limit might be more appropriate.

[Slide]

The repeated measures analysis compared

treatment over the whole treatment period, in this case 24 weeks. There is no imputation of missing values for the visits. It tends to underweigh dropouts a little bit because they contribute less data to the analysis. It overweighs earlier visits. You have to make some types of assumptions for the analysis about what the correlation structure of the visit date is. This means there are multiple p values. In this case, for the sponsor's results it really didn't matter very much. No matter what assumption was made, they tended to get the same results.

[Slide]

The sponsor used endpoint analysis, which was their supportive analysis which did tend to support the results that they saw for the primary analysis. It gives little or no weighting to the earlier visits. All patients, including dropouts, get equal weight. There is no imputation of missing values in this type of analysis because it uses the last observation for each patient. However, it is equivalent to doing a last visit analysis after you do last observation carried forward for all dropouts. Usually the delta in this particular analysis is larger than the delta

in the repeated measures analysis. However, there is also more variability in this because extreme values are used for those people who dropout because of lack of efficacy, and also because you are using one value from an observation as opposed to the repeated measurement that is using a mean overall visit data.

However, since these are somewhat acting at cross purposes, you don't really know how the p values will compare. Sometimes the p value of the repeated measurement might be smaller than the p value for the endpoint analysis.

[Slide]

The sponsor, in his choosing a sample size, used 90 percent power. Three of the four studies used 2:1 weighting. The alpha level was chosen to be 0.025 for both endpoints. They may have done this to ensure if one failed to be significant the other one could be significant.

Delta is the true differences between the means. It was assumed to be 120 ml for FEV1. It was assumed to be 4 for the St. George's Respiratory Questionnaire total score. Four happens to be the value that is declared to be a minimally important difference by the developers of

the instrument. This may give statistical significance, again, but not clinical significance. A large sample size--it can become significant even if you misjudge what your true delta is. A large sample size also is good for getting the best estimate of what the true delta is in that particular population.

[Slide]

One of the things that I somewhat reflected upon is why did they get significance in this situation when their true delta was smaller than what they had assumed? The two factors that I think influenced it most is the fact that they did choose 90 percent power. They chose high power. Also, they chose an 0.025 significance level. In some cases they only had to get 0.05 to be significant for both.

One of the things that you are going to be asked to reflect on is whether the amount of efficacy observed is adequate for approval. I will turn it over to Ray Anthracite right now.

Efficacy and Safety

DR. ANTHRACITE: Hello again.

[Slide]

The background for this presentation is

that there are four preclinical toxicities of which you heard some. Mesenteric arteritis was our chief concern because it appeared to be the most serious animal toxicity and, in fact, was found in two species. The remaining three will not be addressed because it is only mesenteric arteritis that really reflects on approvability ultimately of this compound.

In terms of dose selection, as you have heard from Dr. Suarez, we do agree that the dose selected at the time it was selected was appropriate for development. In terms of the statistics, we certainly agree with the appropriateness of the analyses chosen.

[Slide]

With that out of the way, this is the outline of what I hope to present to you today. Efficacy will be shown, hopefully, or at least will be demonstrated by four pivotal trials. There will be co-primary endpoints, the trough FEV1 and the SGRQ. Because of the indication, which is maintenance of lung function as defined by the FEV1, although the SGRQ is technically a co-primary, most of the heavy lifting must be done by the trough FEV1, with the SGRQ, the St. George's

Respiratory Questionnaire, filling in as a supportive study for approval. Secondary endpoints were also investigated for support of approval.

The safety analysis which will follow will deal with the usual things one sees with safety analyses, adverse events, serious adverse events, withdrawals due to those adverse events and deaths. We will emphasize gastrointestinal adverse events of concern and the adequacy of the evaluation for the mesenteric arteritis that raised concerns in the preclinical data.

[Slide]

Thanks to the work done by GlaxoSmithKline, I think we can move through many of these slides relatively more quickly than I would have thought. There are four asthma trials with over 1,000 patients in them which will benefit us mostly for safety.

The COPD studies numbered over 5,000 people, most of which we will look at for efficacy will be the well-controlled pivotal trials. The remainder of them are long-term, uncontrolled safety trials which will speak to safety, and there will be some safety data picked up from the mechanism of action and cardiology safety studies.

[Slide]

This has pretty much been gone over by GSK. These are multinational. There is a four-week run-in period with a 24-week double-cling period. This is in COPD patients and they are all current or former smokers.

[Slide]

I think you have also seen that the pre-albuterol FEV1/final capacity ratio of 0.7 was an inclusion criterion, and all of these folks had to have a post-albuterol forced expiratory volume in one second of 30-70 percent of predicted.

Poor responsiveness to albuterol, ultimately called fixed airway obstruction, was defined as post-albuterol forced expiratory volume in one second of less than or equal to a 15 percent increase over baseline, or by a less than or equal to 200 ml increase over baseline.

[Slide]

I will just contrast some of the similarities and differences. Virtually all the four co-primary or primary efficacy endpoints were the same in the four studies, and so was the statistical analysis. The primary efficacy endpoints were a little difficult to appreciate

qualitatively. They were the difference between treatments in mean changes from baseline, so a difference of differences.

Three of the studies had the same randomization strategy, which was 2:1 randomization of cilomilast to placebo. All five of the secondary endpoints were common for studies 039, 042 and 091. Study 156 came later, after the results of the first three were known, and that was changed slightly to provide for 1:1 randomization, plus a couple of other minor changes that wouldn't affect our primary endpoints.

[Slide]

The sponsor has covered this rather nicely too. There has been a slight difference in responsiveness to albuterol by the amount of albuterol given. There was some pharmacokinetic sampling. To point out one thing I believe they did not cover, in study 091 there was a two-week double-blind run-out period, during which placebo patients continued to take placebo and cilomilast patients were re-randomized 1:1 to either receive cilomilast or placebo. We will see the results of that.

[Slide]

These are the demographics and disposition of the Phase III patients. You are going to see some difference in numbers in my presentation and theirs. In some cases I am talking about the Phase III pivotal trials and in some cases later, in safety, I will be talking about all asthma and COPD patients. So it gets a little confusing and I will attempt to define the denominator as I hit it.

These are all the pivotal trials. You can see here, as has been said before, there is male predominance in both groups at randomization. They are mostly Caucasians. They are 65 years of age. They have a mean FEV1 of about 50 percent of predicted, and they have a reversibility of about 6.5 to 6.7 percent. This is the percent reversibility induced by albuterol. I will ask you to remember that number. The smoking history was over 50-pack years. Those who completed the study constituted 75 percent approximately, in round numbers, of the placebo group and 70 percent of the cilomilast group. So, we have 35 or 30 percent dropouts.

[Slide]

Now we will display the data in a somewhat different fashion than you have seen it before.

Prior to this you have seen small differences magnified. This is a little bit complicated. Let me explain it to you. This is the trough FEV1 for one of the pivotal trials, study 039, at each week or visit. On the Y axis is the trough FEV1 in liters and the categories on the X axis are seen in the title to the table. The first two bars are blue and red. Blue is placebo; red is cilomilast. The first two bars are for baseline, followed by week 2, week 4, week 8, 12, 16, 20 and 24. The last column is reserved for the mean change from baseline.

I think you can most expeditiously see the mean change from baseline in the last column of the table, and the mean change is shown to be 30 ml for the placebo group in the negative direction and 10 ml for the cilomilast group. Looking at the 30 ml drop in the placebo group, where in fact does that occur? I think you can see, just by inspection of the placebo row, that most of it occurs in the first two weeks. There is some data variability thereafter but the drop in the placebo group occurs early.

[Slide]

Moving on to the second pivotal trial with

the trough FEV1, this is study 042, we have exactly the same setup and exactly the same size of axes and representations. Again, placebo is in blue; cilomilast is in red. The FEV1 trough is on the Y axis and the visits are given on the X axis. The mean change from baseline again is way over in the right column. The mean change from baseline for placebo is nothing. The mean change from baseline for cilomilast was an improvement of 30 ml, and this seemed to have occurred probably over the first four to eight weeks, if you can trust changes over time in tables like this. Remember the 25-30 percent dropouts? Clearly, any change over time in any of these tables reflects a combination of things, both a change over time and the results of the dropouts.

[Slide]

In study 091, again moving the right column, the placebo group here shows a mean drop of 30 ml and cilomilast shows no change at all. The drop in the placebo group seems to have occurred predominantly over the first four weeks, although there is an additional drop apparently at the end of about 10 cc. In any event, we look at this as the placebo group having most of its drop early on.

[Slide]

This is the same study, 091, for the two-week run-out. The placebo, in blue, at the 24th week continued to get placebo, unknown to them. The brown and orange columns are SB 207499-treated patients at week 24 on the left, and run-out on the right. The ones in brown were randomized to continue taking cilomilast and the ones in orange were randomized to be switched to placebo.

Rather than trying to interpret small differences in the columns, take a look at the cell entries. The placebo-placebo group, which is in blue, shows at week 24 a 1.39 trough FEV1 and a mean trough FEV1 at run-out of 1.38, for a 10 ml drop. The cilomilast group that was continued on cilomilast went from 1.46 to 1.45, a 10 ml drop. The cilomilast group that started taking placebo also showed the same 10 ml drop. So, there seems to be very little difference when cilomilast is replacing the placebo at least over two weeks.

[Slide]

This is the last and final study, the one done with 1:1 randomization. It is again shown in the same graphical setup as the previous ones have

been. If we move to the table in the last column over, you can see that here the mean change from baseline of the placebo group was a negative 20 ml. An improvement was shown in the cilomilast group of 10 ml. If you track back over the placebo visits, I think you can see that most of that drop occurred over the first four weeks.

I will mention too that, again, changes in time are confounded by dropouts. So, it is very difficult to know what this means, at least in terms of maintenance of lung function.

[Slide]

This simply attempts to show all the studies together. BL stands for baseline, as you might imagine. MC stands for mean change. Here you can see that for placebo, just looking across the placebo group for all studies, the mean change was 30 ml down for study 039; no change in study 042; a 30 ml decline in study 091; and a 20 ml decline in study 156. This could equally represent the dropouts or a change over time.

The apparent improvement of cilomilast, which could also represent an effect of dropouts, was 10 ml in study 039; 30 ml in study 042. There was no real change in study 091, and a change of 10

ml in study 156.

Looking at the first yellow column, the difference of differences was 40 ml and this was statistically significant. In study 156, which was a much larger study and also took the heavy advantage of the efficiency of 1:1 randomization, a 20 ml difference of differences was standardly significant.

Recall that I asked you to remember the albuterol reversibility. It turns out that the best difference of differences of 40 ml in study 039 is less than three percent of the baseline.

[Slide]

Moving on to the so-called co-primary endpoint, which in fact was called primary but here serves a secondary role, we have the total St. George's Respiratory Questionnaire. There are only three visits at which this was determined, baseline, week 12 and week 24. The setup for this graphic is very much like the last. It is noted that this is a 100-point scale and we are showing about half of it on the Y axis so this magnifies the differences. The last column in the table again shows the mean change. The placebo shows a 0.4 unit mean change; the cilomilast shows a 3.7

mean change in the negative direction. That mean change in the negative direction is an improvement. As in the Borg scale, you will see that the negative direction is less symptoms, better outcome.

For the purposes of interpreting this, Dr. Jones who developed the instrument has studied it and found that a change of greater than or equal to four units is slightly efficacious. Greater than or equal to eight units is moderately efficacious, and greater than or equal to 12 units is very efficacious. These don't meet either of these criteria.

[Slide]

Here, in study 042, jumping to the right-most column of the table we find the mean difference by the placebo over time is negative 4.9 units which does, in fact, reach the criteria of slightly efficacious. Cilomilast shows an important of minus 4.2 units, which is slightly efficacious but less so than placebo.

[Slide]

In study 091 the St. George's Respiratory Questionnaire, again moving the right-most column in the table, shows an improvement of negative 2.3

units for placebo and negative 2.7 units for cilomilast. So, improvement is shown by both treatments with a slight edge to cilomilast.

[Slide]

Finally study 156, the placebo shows an improvement of 1.3 units; cilomilast of 3.2 units. This has improvement in both treatments with an edge to the cilomilast.

[Slide]

I think overall you can see, just looking at the yellow for example as most of these are not going to be terribly germane, the improvement in cilomilast in study 039 was negative 3.7 units. There was actually a worsening of symptoms on placebo of 0.4 units, to make a difference of differences of 4.1 units. Again, this would be considered slightly efficacious.

In study 156, which is the last two column over, there was improvement in both of the treatments, with a difference of differences of minus 1.9 which did achieve statistical significance. It is, however, not even close to slightly efficacious. So, by our judgment this has provided support in one of four studies.

[Slide]

There was a host of secondary efficacy endpoints and we could have belabored them as well as the tertiaries but, since the indication is maintenance of lung function by FEV1, it seems less needful to delve into things that aren't germane to that particular endpoint.

The trough vital capacity was one. This did tend to track with the forced expiratory volume in one second because they are highly correlated.

The post-exercise six-minute walk for breathlessness by the modified Borg scale, an 11-point scale, we felt unconditionally supported efficacy of some kind in cilomilast. There was a summary diary COPD symptom score; a six-minute walk in meters; and a percent of patients who were COPD exacerbation-free through 24 weeks. Our feeling was, after looking at these qualitatively, that the post-exercise Borg scale did, in fact, support the efficacy of cilomilast.

[Slide]

The Borg scale is an ordinal scale that emphasizes severe dyspnea. Seven of the 11 categories are varying degrees of "severe."

[Slide]

This is a little bit complicated. It is

unlike the last several slides you have seen. This attempts to look at baseline and the mean change for each of the separate studies. Again, the Borg scale has a 10-point scale and about half of that scale is represented on the Y axis, which tends to make the differences magnified. In fact, in every case I think you can see that the orange or beige columns tend, in fact, to be negative, while the blue columns are positive, as a mean change. That represents an improvement, much like the St. George's Respiratory Questionnaire did. Negative changes are very good when you are talking about symptoms. So, 039 showed a mean change that was an improvement or a decrease in symptoms that was superior for cilomilast over placebo, as was 042, as was 091 and 156.

[Slide]

So, in summary of these efficacy trials, the forced expiratory volume at trough in one second was shown over 24-week trials. Now, do recall that the support for maintenance of lung function or the investigation of maintenance of lung function of the four published trials shown were all shown over three to five years. This is over a considerable period of time less than that,

with confounding by 25-30 percent dropouts.

We feel that a placebo decline in three trials occurred over the first few weeks and did not occur at all in the fourth trial. Two of the four pivotal trials statistically supported significance of this endpoint.

In the SGRQ, St. George's Respiratory Questionnaire, a supportive trial for our considerations, one of four pivotal trials was statistically significant and slightly efficacious. We felt that a secondary endpoint, one of five, showed some support for SB 207499.

[Slide]

The question to the committee, that cannot be divorced from showings of efficacy, is has cilomilast shown a magnitude and consistency of efficacy that is sufficient to approve it for the indication of maintenance of lung function?

[Slide]

Having said that, we will go to the integrated safety outline. This will include a variety of different denominators. We choose to look at all of safety together for all patients exposed to a drug. So, in this case we have chosen to look at asthma and COPD. The hope is to find

very infrequent events that might be clinically significant to patients.

Additionally, we look at COPD controlled trials only and COPD uncontrolled long-term safety extensions. Again, as I said before, we look at adverse events, serious adverse events and withdrawals due to adverse events as well as deaths, and we will emphasize gastrointestinal adverse events of concern, as well as the adequacy of evaluation for mesenteric arteritis.

[Slide]

The demographics for all the asthma and COPD patients are not very different from the demographics for safety of COPD patients because the COPD patients mostly drive the numbers. There were only 1,000 asthma patients in all the controlled trials but, if memory serves me, close to 3,000 COPD patients. In any event, it should be no surprise that the male gender predominates, as do Caucasians. The mean age has been dragged down slightly by the presence of the asthma patients, from 64 to 60. But the smoking pack-years of 50 is roughly the same as it was before. The mean percent predicted FEV1 is around 50 percent of predicted.

I think from this we should note that 74 percent of patients who are represented here took the 15 mg twice a day dose of cilomilast. The remaining, less than 900, too doses somewhat less than that, 10, 5 or 2.5 mg.

[Slide]

This is a disposition of the asthma and COPD patients in the controlled trials. On the top yellow line, total withdrawn, the placebo patients had 19 percent withdrawal--percent here is given as percent of column total. The cilomilast 15 mg twice daily group had 26 percent withdrawals. I think we will concentrate on those two. The lesser doses that are shown in the total cilomilast group are of less interest.

So, sticking with the second and third columns, the placebo and the SB 15 mg columns, adverse events in the placebo group accounted for 9 percent of that group and accounted for 16 percent of the cilomilast group. When these are divided into adverse events that were COPD exacerbations and those that were not, the majority of them in the cilomilast group, 14 percent, were due to adverse events that were not COPD exacerbations and, in fact, were gastrointestinal adverse events,

as shown in the third yellow line. In the placebo patients only two percent of the patients withdrawn were withdrawn because of gastrointestinal adverse events. This is given in support of the statement that these adverse events are hardly trivial; they are causing people to withdraw from the study.

[Slide]

This is again a little complicated. Let me try to lead you through it. We were interested in those adverse events that might be dangerous to people receiving a new molecular entity. So, we focused on those adverse events where the frequency in the 15 mg twice daily cilomilast group was greater than the frequency in the placebo group. Thereafter, we put up those that were also ascribed to lesser doses to see if there was in fact a dose response or dose ordering.

I think you can see from this that with the criterion that the adverse events had to be greater in the 15 mg cilomilast group than in placebo, of the top six adverse events five of them are GI adverse events. If you look at nausea for example, just looking at the active treatments, 2.5 mg was associated with 3 percent nausea; 5 mg, 5 percent nausea; 10 mg, 8 percent nausea; and 15 mg,

15 percent. You can kind of see a hint of dose ordering through most, if not all, of the gastrointestinal adverse events as you inspect this. I think the point is that adverse events are largely dose related with this drug despite the hope that this drug would have very good efficacy with less side effects than theophylline.

[Slide]

This is deaths in all controlled asthma and COPD studies. There were two deaths during the studies in placebo patients, one during the placebo run-in period. It was a suicide; hard to blame anyone for that, and one as an MI during the double-blind phase.

During the double-blind phase in the cilomilast group six patients succumbed and though the frequency in the cilomilast group was probably greater than the frequency in the placebo group--in fact, it is; these are things to which old people succumb. They are not necessarily anything that would pose a unique signal that there might be something associated with cilomilast. During the post-therapy section of the trials about similar numbers of people died and they died for similar reasons, things elderly people succumb to.

[Slide]

Now we are looking at serious adverse events. Again, this is looking at those that are more frequent in the 15 mg cilomilast group than the placebo group. The one salient point here is that there are very few serious adverse events. How exactly that equates to events serious enough to cause withdrawal is not exactly clear. In any event, I think very little can be gleaned from this in terms of dose ordering of events. Virtually all of them have a frequency of less than an integer amount.

[Slide]

These are the withdrawals due to adverse events once, again, where the frequency in the cilomilast twice daily 15 mg groups exceeds that of placebo in all controlled asthma and COPD trials. I think you can see, just focusing on the ones in the yellow which are the gastrointestinal adverse events, arrayed in descending order of frequency in the last column on the right, that these are the leading causes of withdrawals. This is what is causing the withdrawals in the cilomilast group, once again speaking to the seriousness of these events.

[Slide]

GI adverse events of concern is something we come to find in the middle of these studies, in partnership with GSK. Once again our problem was with clinical arteritis. It was mostly mesenteric in distribution, although not exclusively. It was seen in two species. There is no safety margin between animals and humans. Early on GSK made an effort to find biomarkers by which we could track this. Regrettably, they were unsuccessful.

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It is fair to let you know that GI adverse events are thought to be centrally mediated for phosphodiesterase inhibitors. But, because we have seen results in animals and now some publicly acknowledged results in humans, mesenteric arteritis certainly may be a consequence of this class of drugs. Certainly, the GI adverse events were severe enough to cause premature patient termination and did, in fact, account for the majority of the early terminators in the cilomilast groups. In order to permit continued drug development we required a plan for evaluating patients for arteritis.

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We settled on or tried to find a prospective evaluation. The plan was to single out cases with gastrointestinal adverse events for thorough evaluation. We were to search for a pre-fatal and possibly monitorable manifestation, fecal blood loss, and by valuating that clinically establish a database of colonoscopies from which human safety could be inferred.

The justification for this rationale was that colonoscopy is becoming a standard of care for adenocarcinoma surveillance in asymptomatic adults over the age of 50. I won't embarrass anyone by asking them to raise their hands to acknowledge how many have had them. Certainly, symptomatic individuals of the same age range with GI blood loss would be candidates for the same procedure.

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Initially it was agreed that all pivotal controlled trials, 039, 042, 091 and 156, that we analyzed in depth for efficacy, both uncontrolled trials, the cardiac safety study and all three mechanisms of action studies would be evaluated for the GI adverse events of concern. These were defined, as previously stated, as symptoms that caused the patient concern, specifically bloody or

black stools, pain, cramps, diarrhea and vomiting, and/or things that interfered with patient's daytime activities or sleep.

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Within 24 hours a physician evaluation was to include examination of the patient and fecal occult blood. Either the patient could have used the previously distributed fecal occult blood test, or a digital rectal exam with fecal occult blood testing to be done on examination. This was obviously intended to signal the need for further clinical evaluation. Orthostatic vital signs were to be gotten on these same patients within 24 hours to signal acute volume depletion from blood loss or fluid third-spacing.

[Slide]

In terms of the follow-up of these gastrointestinal adverse events, we encouraged the company to evaluate each of them on a daily basis with clinical examination, fecal occult blood and orthostatic vital signs. They were unable to do that and, instead, agreed to the daily monitoring in study 039 and 156, the two pivotal trials, and 168, the cardiac safety study. They also agreed to daily monitoring in two mechanism of action studies

and the long-term safety extension. These were all the North American trials.

As time went on it was apparent that we were not getting that safety database of colonoscopies that would permit us to have a feeling of safety about the non-presence of arteritis. So, we requested, and the company kindly acquiesced to requiring complete colonoscopies within two weeks in two of the studies for melena or fecal occult blood positive stools. Unfortunately, this amendment was done midway between beginning and ending of these studies and it didn't allow for very many patients to be included under this particular mandate.

[Slide]

Well, what were the GI adverse events of concern? Again, the percentages in parentheses do represent the percent of the column totals. There were 56 placebo patients and 264 COPD patients who had GI adverse events of concern, and now the denominator is COPD trials, not COPD and asthma trials. You can see the relative types of adverse events associated with the GI system in the left-most column.

[Slide]

How well were these eventually evaluated? Now the column totals have the number of patients with GI adverse events in it from the placebo group and those in the cilomilast group. Fecal occult blood was gotten at some time after the GI adverse event of concern in 82 percent of the placebo patients and 90 percent of the cilomilast patients. Although mandated within 24 hours, it was gotten within 14 days in 55 percent of the placebo patients and 58 percent of the cilomilast patients. It was, in fact, positive in 11 percent of the placebo patients and six percent of the cilomilast patients. The conjoint event of a GI adverse event of concern and fecal occult blood positivity, regardless of how many times it was sought, as well as colonoscopy performed on those individuals at some point in time was a total of six patients.

[Slide]

The colonoscopy results showed in the placebo patients common things, diverticulae, polyps and internal hemorrhoids. In the cilomilast-treated patients, diverticulae, villotubular adenomas, polyps and internal hemorrhoids. In fairness, none of these showed ischemic colitis.

[Slide]

Fecal occult blood tests were also determined at baseline and endpoint for all patients as a matter of course. This table doesn't really show that. What it shows is the patients who were baseline negative, positive or missing and who became positive or negative sometime in the double-blind period. Sixteen patients that were negative at baseline became positive during the double-blind period in the placebo group and 33 patients became positive in the cilomilast group. Percentages are calculated on the row totals for each treatment. So, we have 49 patients here who are positive who previously were negative, and these are the total patients, 16 and 33.

[Slide]

Fecal occult blood positive stool samples were not unique. There were on the average two fecal occult blood positive stool samples per patient, 31 for the 16 placebo patients and 67 for the 33 cilomilast patients. Among those, a total of 22 patients, 7 placebo and 15 cilomilast, had a positive GI adverse event of concern. The number of patients receiving colonoscopy was 2 in the placebo group, 3 in the cilomilast group, and these

3 were previously presented to you because this represents a duplication of information.

[Slide]

Here are the demographics and disposition in uncontrolled trials. The uncontrolled trials had feeder studies from the pivotal trials so it is really no surprise here, again, that the demographics mimic those seen in the feeder trials. These were 76-79 percent male. Caucasians represented 96 or 97 percent of the group. They were of the same age, 64 years of age; 50 percent FEV1 percent of predicted, and close to 50-pack years of smoking history on the average.

[Slide]

Now we look at dispositions in uncontrolled trials and this slide is a little bit misinforming because "prior to treatment" refers to the placebo and SB 15 mg groups, and total SB represents a combination of the two. So, just looking at the total withdrawn from placebo, there was 46 percent withdrawals. For cilomilast 15 mg it was 38 percent withdrawals. Recall those declines in FEV1 over time in the long-term trials; just imagine what 40 percent withdrawals will do to that number.

Adverse events in patients who previously received placebo accounted for 24 percent of the total and in those patients previously treated with cilomilast, 15 percent of the total patients. So, I think you can see from the percentages and the second yellow line and the first yellow line that more patients were withdrawn from the placebo group than the previous cilomilast group because of adverse events. In fact, those adverse events, again, were gastrointestinal for the previous cilomilast group. The implication here is that there is something about having made it to the end of the feeder studies and being enrolled in the uncontrolled trials that perhaps selected for patients who were not responsive to GI adverse events. Certainly when exposure was continue they had a very small percentage, four percent, of their group withdrawn because of gastrointestinal adverse events as compared to the placebo, who were relatively naive to the drug at the time they entered the uncontrolled trial and had the same large number of withdrawals, or percentage of withdrawals, that was seen in the feeder trials.

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This is the treatment exposure in all

uncontrolled trials including the feeder trials. I show it simply to demonstrate that greater than 180 days exposed was given by 973 patients, and there were 865 patients who were exposed for greater than a year. This certainly lives up to the criteria of the International Committee on Harmonization for minimum required safety.

[Slide]

These are the adverse events in uncontrolled trials, and there were relatively fewer of them that are gastrointestinal adverse events, which is shown in capital letters, and they were prior, possibly because of the preselection for those folks who could tolerate them.

[Slide]

These are deaths on therapy in uncontrolled trials. There were eight deaths and one reported late, just prior to going to press. These deaths were caused roughly by things that elderly people succumb to. The last death reported was a 68-year old male with ischemic colitis who became ill, had an intestinal perforation; had a colon resected and died several hours thereafter. The pathology specimens at autopsy did not section the mesenteric arteries, regrettably, and the

pathology from the resected transferase colon was not supplied.

[Slide]

This is the number of patients and percent of patients with serious adverse events. Here, the serious adverse events were few in number and less in frequency, much as we saw with the feeder trials. Here we have withdrawals from the uncontrolled trials due to various reasons. I think you can see that leading the list for the top five are gastrointestinal adverse events. So, even in the uncontrolled trials we again have the recurring theme that these are meaningful to patients regardless of how they were thought to look to the investigators.

[Slide]

These are the gastrointestinal adverse events of concern in uncontrolled COPD trials. There was a grand total of 141 or 13 percent of the total patients exposed in the uncontrolled trials, which is approximately the amount in the feeder trials. They include abdominal pain, diarrhea, nausea, vomiting, dyspepsia, melena, etc.

[Slide]

How did we implement the plan for fecal

occult blood monitoring of the GI adverse events of concern in the follow-up and uncontrolled COPD trials? Now the column total on the right is the number of patients with GI adverse events in the uncontrolled trials, and 91 percent had fecal occult blood at some time in the follow-up period following the adverse event. Nine of these patients were positive. In fact, less than half of these people had fecal occult blood tested within 14 days of the GI adverse event. The conjoint event of a GI adverse event of concern and positive fecal occult blood and a colonoscopy occurred in four patients.

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On treatment four patients had colonoscopies and they showed polyps, diverticulae and hemorrhoids. There was one post-treatment colonoscopy in such patient and that was totally normal. In fact, these patients did not have ischemic colitis.

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So, the conclusion to the integrated summary of safety is that gastrointestinal adverse events were a feature of treatment with cilomilast. They were of sufficient severity to cause most of

the withdrawals in patients treated with cilomilast.

In terms of GI adverse events of concern that were to help us build our colonoscopy database, only 50-60 percent of the patients with them were tested for fecal occult blood within two weeks, and fecal occult blood positive patients with GI adverse events of concern were not all evaluated for ischemic colitis by colonoscopy.

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Hence, our database for colonoscopy patients with GI adverse events and fecal occult blood devolved to four patients in controlled trials treated with cilomilast, five patients in uncontrolled trials treated with cilomilast, and two placebo-treated patients, for a grand total of 11 patients.

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Overall, to remind you what we saw with efficacy--it is kind of anticlimactic, isn't it? FEV1 as the trough was the primary endpoint and, in fact, the target of the indication in four 24-week trials, not three to five-year trials. The change over time in FEV1 for any of the treatments was contaminated by the 25-30 percent dropouts. Where

a placebo decline was seen, it arguably occurred over the first two weeks. Two of the four pivotal trials were statistically significant with mean changes from baseline that were small.

Support for effective of cilomilast was found in one of four of the co-primary endpoint trials, the St. George's Respirator Questionnaire. Two showed statistical significance but only one showed statistical significance and slight efficacy. We feel support for the efficacy for cilomilast was also four in one of five secondary endpoints, the post-exercise Borg scale dyspnea.

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Overall, safety we considered a concern because of the preclinical findings of mesenteric arteritis. There were prominent dose-related gastrointestinal adverse events and prominent withdrawals in the cilomilast group due to them. There is a very limited safety database of colonoscopies in fecal occult blood positive patients with gastrointestinal adverse events of concern. Without beating a dead horse, there are only 11 patients in that database.

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So, we pose the following four questions

to the advisory committee, and I think we can let you chew on these as we take our break. They are:

Has cilomilast, at a dose of 15 mg twice daily, shown a magnitude and consistency of efficacy that is sufficient to support approval for the maintenance of lung function, FEV1, in patients with COPD?

Is the safety database, aside from the concern about vasculitis, for cilomilast for the maintenance of lung function, FEV1, in patients with COPD sufficient to support approval?

Do you feel that the concern about mesenteric arteritis has been adequately studied to be dismissed as a safety concern in humans?

Finally, do the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 medication twice daily for the maintenance of lung function, FEV1, in patients with COPD?

Thank you very much.

Committee Discussion and Clarification

DR. PARSONS: I am going to open it up now for discussion and clarification for both GSK and the FDA. I would actually like to clarify one thing quickly, Dr. Anthracite, before you sit down.

The last question, if I could just clarify very quickly, the question specifically ends with "in patients with COPD" and, yet, my understanding from looking at the documents is that the request is for approval for patients with COPD who are not responsive to bronchodilator. Is that correct?

DR. ANTHRACITE: Yes, that is.

DR. PARSONS: So, do we want to modify that last question, or do you want the question to stand as it is?

DR. ANTHRACITE: Either way, I have no objections. DR. PARSONS: Thanks. Other questions? Dr. Joad?

DR. JOAD: I would like to hear, from both the FDA and from the company, the GI physicians' interpretation of that patient who died. I don't know if the FDA has somebody who can comment on that but what is bowel ischemia with perforation? How suggestive is that of mesenteric arteritis? And also, just to double check that there were no other autopsy results of any of the other patients. I am assuming that is correct.

DR. ANTHRACITE: We will address the autopsy question to GSK. In terms of that individual patient, we have an autopsy report. I

believe GSK has no more than we do. Is that correct?

DR. WHEADON: Yes, that is all we have.

DR. JOAD: I guess what I am looking for is, is there an expert who has commented on how clinically suggestive this case is of mesenteric arteritis since that is not an area of expertise I think for the people on this panel.

DR. ANTHRACITE: Perhaps our gastroenterologist?

DR. SURAWICZ: I am a gastroenterologist and I review these cases. Dr. Laine is here as well as a consultant for the company. I am sure we would both be happy to comment.

DR. LAINE: Again, I think everybody has similar information. There were actually five cases of intestinal ischemia that were identified in the overall safety database of this. Three, as you saw, were in the active drug treatment and two were in the placebo control group. This particular case that you are asking about was basically somebody who came in with a COPD exacerbation and basically developed abdominal pain, was found to have a perforation and was taken to the operating room. We don't really have much information,

except that the autopsy report specifically stated that they felt it was consistent with ischemic colitis leading to the perforation.

I would just remind you again that people who have COPD, as we talked about, who are smokers and have concomitant cardiovascular problems have a fairly high incidence, compared to the general population, of developing ischemic colitis, probably about a four-fold higher incidence.

Again, you know, one of the tenets of evidence-based medicine, of course, is when you ask a specific question, that is, does intestinal ischemia occur, you look at the clinical outcome of interest. That is your primary outcome you want to look at and when you look at that, as was shown, there were three cases versus two cases. The incidence that was identified with the patients receiving Ariflo was the same as would be expected in the general population based on another epidemiologic study. As we mentioned, there was no evidence of any increase with the patients receiving after treatment so there was actually no suggestion at all of a signal in the entire safety database of patients having intestinal ischemia with the active treatment.

DR. PARSONS: Dr. Morris?

DR. MORRIS: Did you want to have a follow-up here? I was going to ask a different question.

DR. PARSONS: Yes, Dr. Surawicz, do you have a follow-up question?

DR. SURAWICZ: I thought that the analysis of the patients who had the colonoscopies was very well done and there was nothing worrisome at all in any of the colonoscopy findings of the patients who had any sorts of adverse effects.

One thing that was confusing to me was the upper GI symptoms and the lack of upper endoscopies. So, for all the people with evidence of lower GI bleeding, there were either normal colonoscopies or findings at colonoscopy that would have explained the lower GI bleeding. Until I looked at this sheet this morning that we just received, when I saw the term melena in a symptom, I assumed that that was upper GI bleeding and not lower GI bleeding because it is very, very rarely a cause of lower GI bleeding. So, I thought that many of those patients should have had an upper endoscopy.

Now, it looks as though four or five

patients did have upper endoscopies as part of their workup and half of them had gastritis. Now, gastritis is a very common abnormality but it did make me wonder whether some of that acute nausea, vomiting and abdominal pain might be due to upper GI side effects and there really isn't any information to address that. It may be that the gastritis is a more broad problem. Elderly people are more likely to have gastritis.

I don't know how to reevaluate my comments with the change in the fact that you apparently used the term melena for all kinds of GI bleeding. Can you clarify that? Because traditionally melena--for a GI doctor the definition is black, tarry stools because of blood from the stomach or the proximal duodenum.

DR. RICKARD: Unfortunately, due to our dictionary, I guess the small majority of people who had positive FOBs were actually coded to melena. So a large part of these just had a positive fecal occult blood and did not have melena. But there were lots of other terms used that were coded to melena, which include black, tarry stools but also include things like blood on the stool; blood on the toilet paper; blood around

the toilet, things like that. So, they were all coded to the dictionary for melena so it actually over-reported melena and the actual incidence of melena was very low and was not different between placebo-and Ariflo-treated patients.

DR. SURAWICZ: Then, for the few people who did have gastritis, did you have any information on whether that might be due to their other medications? I am sure lots of them were taking non-steroidals or aspirin, or they were probably in an H. pylori group as well.

DR. RICKARD: Well, there was a significant number of people who took non-steroidals. If you look at the entire GI database, there were 70 other procedures performed in patients who had GI symptoms. Some of those were upper endoscopies. Some of them were other type of procedures. And, none of them really showed anything of significance. Now, I cannot tell you that a significant incidence of gastritis was actually found anywhere.

DR. SURAWICZ: Another question I had was in the people who had had GI blood loss, was any of that significant enough to require a transfusion?

DR. RICKARD: No. No, in fact, in all the

orthostatic vital signs there were no differences in hemoglobin hematocrits at any time performed throughout the study. There were no differences at all to show that there was any effect on either hemoglobin hematocrit or orthostatic vital signs.

DR. SURAWICZ: Good.

DR. PARSONS: Dr. Morris?

DR. MORRIS: I have a question for Dr. Knobil and then a follow-up for Dr. Rickard. If you could, could you clarify for me the belief of what the mechanism of action is of this agent for its effect in COPD patients?

DR. KNOBIL: Well, I did talk about that a bit. For a PDE4 inhibitor many of the cells that we think are important in COPD have phosphodiesterase-4 in them. The ones that have PDE4 as the predominant isoenzyme are the anti-inflammatory cells. So, we believe in this patient population the mechanism of action is predominantly an anti-inflammatory one.

DR. MORRIS: My follow-up question for Dr. Rickard would be could you help us understand the mechanism of action of the GI toxicity?

DR. RICKARD: So, for GI toxicity I assume you mean the symptoms of GI intolerance, which was

nausea, vomiting and diarrhea. We are not really sure of the mechanism of action. We believe it may be central mediated. I would ask one of my colleagues to further comment on that if they can discuss it further.

DR. DOWN: Geoff Down, clinical pharmacology, GSK. Looking at kinetic profiles when nausea commences, it appears to occur around Cmax or at attainment of Cmax. There is also an effect where with continued dosing you get attenuation of the effect. This will go through the central mechanism. There is evidence with other PDE4 inhibitors in dogs and ferrets that inhibition of that enzyme in the area post-treatment at the base of the fourth ventricle causes emesis. So, we are fairly certain that this is predominantly a central effect. There may be some augmentation by afferent vagals but we have no evidence for that.

DR. PARSONS: I have a question that may help clarify things since I just realized, obviously, that not everybody on the committee is an adult physician and all of us that are adult physicians are certainly not gastroenterologists. I was wondering, Dr. Surawicz and maybe somebody

from GSK, if you could just help the committee understand what are the presenting manifestations and symptoms of mild mesenteric arteritis, and what would you look for, and what do you do as a practicing clinician, so that we may maybe put some of this data in perspective?

DR. SURAWICZ: Well, the major reason why mesenteric ischemia is of such concern is because the presentation can be very vague and there is really no good clinical diagnostic tool, especially for mesenteric ischemia involving the small bowel. For the large bowel we do have colonoscopy and the symptoms are a little bit more obvious. But for small bowel mesenteric ischemia, which would be involvement occasionally of the celiac access but usually the superior mesenteric artery, it is supposed to be pain that occurs after eating in elderly people, 50 or greater. We just had a case in my hospital in someone 45.

The problem of this diagnosis is pain after eating, presumably because the blood is shunted away from those vessels because it is going to the stomach to help with digestion, so the compromised vascular system, then you develop ischemic small bowel pain. But when it is chronic

it is very hard to diagnose. There is no good diagnostic test. There are some non-invasive tests like ultrasound Doppler which frequently are falsely positive. The gold standard then is angiography, which is a relatively invasive test. So, clinically we are often in the setting of making this diagnosis when the bowel is already dead and already ischemic.

Happily, that is not as common as colon ischemia, which is what was looked for here where there is compromise of the interior mesenteric artery. In this case, the presentation is a little bit more obvious because usually there is diarrhea and bleeding. The pain is not such a big part of that; it is usually diarrhea and bleeding. Because of the ease of the flexible sigmoidoscopy and colonoscopy--I guess as Loren and I are both endoscopists, we consider it the ease of the procedures, and this is usually readily diagnosed when it is suspected.

Also, the course of colonic ischemia usually is milder than small bowel ischemia, maybe because the delay in diagnosis for small bowel ischemia means that it is through and through, whereas in colon ischemia usually it has a more

mild course although, obviously, if the diagnosis is delayed there can be sever through and through perforation as well. Colon ischemia is more likely due to an acute drop in flow as opposed to chronic, either embolic or thrombotic or narrowing of the small bowel. I don't know at all how common this is in children, but I suspect not very.

DR. PARSONS: Thanks. Now we will jump back to the regular order. Dr. Apter?

DR. APTER: Changing the subject a little bit, I wanted perhaps Dr. Knobil to tell us how adherence to the study protocol drugs was monitored. Because if the side effects are significant and patients in the active arm stopped taking the drugs side effects will be underestimated. Likewise, the effect of the drug will also be underestimated.

DR. KNOBIL: Well, compliance was monitored by pill counts at each study visit. So, that was the main mechanism by which compliance was monitored, as well as looking at the diary cards that were filled out in the three studies, 039, 091 and 042.

DR. APTER: I am sure you know that there is no good way to really measure adherence and

patients could conceivably dump their pills before they come to see you.

DR. KNOBIL: Well, yes, that is a possibility but in general I think that we have to trust the patients and what they tell us, and we have to take everything at face value. I guess we could have asked whether the patients dumped their pills but I am not sure we would have gotten any more accurate than we already have.

DR. APTER: Right. There are no blood levels or any other tests?

DR. KNOBIL: There was pharmacokinetic monitoring but that was not used to check compliance.

DR. PARSONS: Ms. Schell, you had a question?

MS. SCHELL: Yes, I guess I want a little bit of clarification and also if you had other studies from the current studies. The FEV maintenance was looked at as the difference between the Ariflo group and placebo group. Correct?

DR. KNOBIL: That is correct.

MS. SCHELL: I wondered if there was a subset of patients you looked at, since the drop occurred in the placebo group of FEV in the first

four weeks or so, did you look at an individual group of patients, say, on Ariflo that had their FEV1s and looked at their FEV1 as individual? Do you understand what I am saying? I am just wondering. You looked at the difference between the two groups, but did you look at individual patients? Did they maintain their FEV1 across the line, or did they improve on the individual basis?

DR. KNOBIL: Well, we had patients who improved, who stayed the same and probably a minority who went down as well but on average the results are as we have shown you. One point that you brought up about the drop occurring in the first two to four weeks, I am not sure that I necessarily agree with that analysis because the graphs that Dr. Anthracite did show you showed the absolute FEV1 at each week and compared back to the baseline for the whole group. I don't know if it is completely appropriate to compare the patients that are in the study at the time with the total number of patients that were at the beginning of the study, just as it would be inappropriate for me to subtract the FEV1s at week 24 from the total baseline raw means because that would give a much larger treatment effect than we would expect.

MS. SCHELL: Well, I was just curious because of the dropout rate and I just wondered, on the individual basis, if there was a group looked at for individual FEV maintenance. I am confused on the differences. You looked at the difference between the groups but I want to know on the individual, was there a steady maintenance?

DR. KNOBIL: You mean individual treatment group or individual patients?

MS. SCHELL: I just wondered if there was a subset or groups where you just looked at the individuals that were on the drug like, say, 50 patients you looked at and did they maintain their group that weren't dropped out? I just wondered if there was a substudy. I am confused.

DR. KNOBIL: I guess I don't entirely know what you are asking because we didn't look at each patient individually; we looked really at group means.

MS. SCHELL: Okay, that is what I was asking.

DR. KNOBIL: One other point is that the level of dropouts was actually quite similar to other COPD clinical programs. We do have a lot of experience with patients with COPD and we generally

have about 30 percent dropouts.

DR. PARSONS: Dr. Cross?

DR. CROSS: I was confused about the anticholinergics. Were these patients taking or not taking anticholinergics as a group? You emphasized the albuterol, that they were allowed to take their maintenance scheduled albuterol and they were allowed to take extra albuterol. Is that right?

DR. KNOBIL: No, that is not quite correct. If a patient was on scheduled epitropium prior to entry into the study they could continue that throughout the study. However, they were given albuterol for use as needed. There was nobody on scheduled albuterol.

DR. CROSS: That clears it up. Thanks.

DR. PARSONS: Dr. Morris?

DR. MORRIS: I have a question looking across the four pivotal studies. Am I right that the percent of people completing the 24-week study was similar in the two groups for the European studies but there was a difference between placebo and treatment arms in the North American studies?

DR. KNOBIL: For those that went into the long-term? Yes, that is correct. About 70 percent

of patients from the European studies in both arms went into the long-term extensions, whereas 85 percent of the placebo group in the North American trials went into the extension whereas it was somewhat lower in the Ariflo-treated group, about 68 percent.

DR. MORRIS: I don't know if that is exactly what I meant. Let me ask you in a different way. Could you give us some idea of the demographics of the patients not completing the 24-week study?

DR. KNOBIL: We haven't actually looked at the demographics of the patients who dropped, but we looked at the demographics at the beginning of the pivotal trials and at the beginning of the long-term extensions. They are quite similar. So, I don't think that there can be a huge difference in those that dropped or else that would change the composition of those that went into the long-term extensions.

DR. PARSONS: We have Dr. Kercsmar next.

DR. KERCSMAR: I wondered, since there is a pretty significant imbalance in white versus black enrollment in all your pivotal studies and also male versus female, do you have any evidence

that this drug will be metabolized differently in a minority population, or in females, or if there is any difference in response to the drug in those two populations?

DR. KNOBIL: Yes, there was no difference in metabolism in men versus women. One patient population that we did look into was Japanese and Chinese individuals and they had slightly higher serum AUCs and it was felt to be more due to the smaller body size and lower body weight, but there were no other differences noted. There were no differential tests between Caucasians and other ethnic groups.

DR. PARSONS: Dr. Joad?

DR. JOAD: I am still looking at the mechanism of action and if you could explain what we know about bronchodilators. I am trying to figure out how much those changes in FEV1 represent bronchodilation and how much don't. So, what is the evidence that you have for the amount of bronchodilation you get with this drug, especially at trough levels?

DR. KNOBIL: Well, overall, as we have already seen from the data, there is really no bronchodilation. The most we get is about a 10 ml

increase from baseline, except for study 042 which had a little bit higher, between 20-30 ml from baseline. So, there doesn't appear to be any bronchodilator activity. We have looked at serial FEV1--

DR. JOAD: Is that at Cmax where you get the 10 percent?

DR. KNOBIL: That is at trough.

DR. JOAD: Well, that is my question. As a bronchodilator at its maximum serum concentration, what is the change in FEV1?

DR. KNOBIL: Right, and we have looked at serial FEV1 after dosing and there does not appear to be a bronchodilator response in this patient population. Again, you have to remember that this patient population was chosen not to have a bronchodilator response so it is not unexpected that we don't see that. We do have some preliminary data in a broader population that shows a little bit greater FEV1 response that may be due to bronchodilation.

DR. PARSONS: Dr. Apter and then Dr. Newman?

DR. APTER: Dr. Knobil, you have hypothesized that the proposed mechanism is

immunologic and that it is an anti-inflammatory drug. Could you review for me what the evidence is, BAL or things where the number of anti-inflammatory cells decrease, where there is decrease in CD8 cells or cytokines or products of these cells?

DR. KNOBIL: Yes, there were two studies, study 110 and study 076 which I referred to briefly. Study 110 mainly looked at sputum neutrophils. There were no large studies of BAL cellular counts. But in study 110 there was a trend toward a decrease in sputum neutrophils. In study 076 there was no difference in sputum neutrophils, however there was a trend toward a decrease in subepithelial neutrophils. Also in 076, in biopsies there was a significant decrease in subepithelial macrophages and there was a trend toward a decrease, a 40 percent decrease, in subepithelial CD8 positive T-lymphocytes, which has not really been seen with any other medication for patients with COPD.

DR. APTER: How many patients were in those trials?

DR. KNOBIL: There were about 100 patients per arm.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: I guess you might as well stay up there--save you the trip. A lot in this study seems to hinge around what happens at baseline. I wonder if you could go over with us how, in fact, the baseline FEV1 was generated and what, if anything, was done with the spirometry data that were obtained at screening and at the two-week prior to baseline visit.

DR. KNOBIL: Well, the baseline FEV1 was done in a very rigorous fashion, as per ATS guidelines, with three efforts, taking the most appropriate effort. The screening FEV1 and the visit two weeks prior were not included in the analysis for the study. It was mainly included to make sure that there was not a great variation and that patients weren't rapidly deteriorating as they came off their other COPD medications.

DR. NEWMAN: I think that speaks to my question then. What, in fact, did you find when you looked for that variability? Potentially you had people who could have stopped using any variety of medications that the day they came in for their screening visit and you might have only two weeks or potentially four weeks of them coming off other

medications.

DR. KNOBIL: So, you would like to see what happened to FEV1 over that time as they came off?

DR. NEWMAN: Yes.

DR. KNOBIL: Yes, we do have a slide to support that. Just one second. While we are waiting, there was not a large decline in FEV1 over time. Of course, if someone did have a precipitous decline, then it was felt that they would not be appropriate to continue in the study.

DR. NEWMAN: Perhaps, while they are looking into this, could I ask a related question?

DR. KNOBIL: Sure.

DR. NEWMAN: It has to do with covariates. I know that the smoking status in terms of pack-years didn't differ among the groups, but could you tell us about what information, if any, you collected and what you found regarding change in smoking status? Were there any differences in people becoming former smokers or changing smoking status either up or down during the course of the study?

DR. KNOBIL: As we have seen in all of our clinical trials including these, the number of

patients who changed smoking status is incredibly small and it didn't differ between treatment groups.

[Slide]

So, this is for study 039, and I think this is representative of all the clinical trials, screening at baseline FEV1 is shown here. There is a small decline which is not unexpected, given that patients were discontinued from their medications, including inhaled steroids, but it wasn't a very large one.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: I have a couple of questions for Dr. Knobil. One is that, say, the two North American studies, were they the same set of clinical centers that were involved with both?

DR. KNOBIL: I don't believe that there was. There might have been overlap of a few centers but, for the most part, they did not overlap.

DR. CHINCHILLI: So, the same question for the European studies?

DR. KNOBIL: Yes, since the European studies did run concurrently the centers did not overlap.

DR. CHINCHILLI: Then a question about the spirometry, what did GSK have in place in terms of training and certification for the spirometry technicians? Did you have any type of training and certification program?

DR. KNOBIL: Yes, we did. We had large investigator meetings during which the coordinators and pulmonary function techs would come to make sure that we had consistent procedures at all of the sites. If there were sites that were unable to come to the investigator meeting, then we would go to each site and train sites.

DR. PARSONS: Dr. Apter?

DR. APTER: This is a question for either the FDA or GSK. I am confused. You chose the endpoints together of FEV1. You chose patients that didn't have a variability in FEV1 as an entrance requirement and then, as an endpoint, you didn't have any variability. You are postulating another mechanism is possibly the way it works. It seems like the design has--what do you have to say about the design here?

DR. ANTHRACITE: I must confess to not quite understanding what you are asking. Could you just repeat it in more simple terms?

DR. APTER: You chose patients who didn't have any variability in the endpoint at the beginning, having no bronchodilator reversibility. Then, at the end of the study, after randomizing them, there wasn't any change.

DR. ANTHRACITE: Are you doing any better with this than I?

DR. PARSONS: See if this helps and see if this is what you are actually asking, the initial study, as designed, was looking for a change in FEV1 of 120 ml.

DR. ANTHRACITE: Yes.

DR. PARSONS: And that apparently was between treated groups versus placebo. So, the question I think Dr. Apter is asking is since you specifically picked the patient population that you did not anticipate would have a change in FEV1, how was the study designed to look for a change that big in a 24-week period? Does that clarify it?

DR. APTER: Thank you for interpreting for me.

DR. ANTHRACITE: Considering that wasn't my choice, let me turn it over to Dr. Knobil.

DR. KNOBIL: Well, I think that based on the Phase II clinical trial, which you have already

seen, we actually did expect a little bit larger change in FEV1 than was actually seen. However, we did not expect the placebo group to decline so consistently, as we saw. So, even though we designed our trials to see a particular result, we did get another result which was clinically significant.

DR. PARSONS: Dr. Morris?

DR. MORRIS: Could you go over for us, please, how the notion of exacerbation-free from COPD over the 24-week period was defined and thought about?

DR. KNOBIL: The four-panel slide? Would you like to see that again?

DR. MORRIS: No, just tell us what went into that definition, percent of exacerbation-free days or percent of exacerbation-free time in the 24-week period.

DR. KNOBIL: Is that from the briefing document, exacerbation on any given day or the exacerbation-free days? I am sorry if I am complicating it.

DR. MORRIS: The exacerbation-free days.

DR. KNOBIL: Okay, the exacerbation-free days is really a Kaplan-Meier plot so that as soon

as someone has an exacerbation they are censored from the analysis. So, what we see over time--actually, if we could just show the four-panel slide from the core--is that over time patients tend to exacerbation at a certain frequency.

DR. MORRIS: More specifically, what went into the definition--

DR. KNOBIL: Oh, the definition. I apologize.

DR. MORRIS: That is okay.

DR. KNOBIL: This is exacerbation-free time to moderate to severe, and moderate to severe exacerbations were defined as exacerbations that required physician intervention and medication, including oral steroids or antibiotics. A severe exacerbation was one that required hospitalization.

DR. MORRIS: Could you tell us about what percent required hospitalization in both arms?

DR. KNOBIL: It was actually quite low, less than ten percent. Actually, much less than five percent, I should say.

DR. MORRIS: And what happened to study medication during the hospitalization?

DR. KNOBIL: Well, that varied from

patient to patient. I don't know the particulars for each patient that had an exacerbation but I would guess that some patients stopped taking their medication just because they were in the hospital but we do know that some patients did continue. I don't have any information to be able to differentiate between the two about outcomes or anything else.

DR. MORRIS: Were the hospitalization records reviewed for AEs and SAEs?

DR. KNOBIL: No, they were not.

DR. PARSONS: We have Dr. Joad, Dr. Surawicz and Dr. Cross. Dr. Joad?

DR. JOAD: Did you measure weight? Did these patients lose weight with all this GI symptomatology?

DR. KNOBIL: We measured weight at the beginning but we did not measure weight at the end.

DR. PARSONS: Next I think is Dr. Surawicz.

DR. SURAWICZ: I want to go back to the ischemia because we have been reassured by the colonoscopy findings in the patients who had symptoms but we haven't really talked about the ischemic cases that were in the briefing document,

and Dr. Laine I think mentioned five ischemic cases but there are only two here, which were both in placebo. Then we have this one death on treatment. Who were the other two patients and should we perhaps know which groups those were in?

DR. RICKARD: As we showed earlier, there were two patients in the placebo group and three patients in the long-term extension trials that had a diagnosis of ischemic colitis. Now, the particulars--I think the narratives should be in the briefing document. The three patients for Ariflo--one patient was admitted for rheumatoid arthritis exacerbation and his diagnosis really was only based on a comment from the x-ray; we don't even know what type of x-ray it was, saying it looked like he had ischemic bowel. So, we don't know much more about that patient but he continued in the study on the drug and had no further problems for that.

The other two patients, one had a COPD exacerbation with a bowel perforation, which you heard about. One patient underwent vascular procedures, you know, vascular dye procedures, and subsequently had significant complications after that, and at the time of his death also was

shown--whether it was due to the procedures or not--to have ischemic colitis.

The other two patients were in the placebo population. I think what we showed earlier was that you need to keep in mind that the patients on placebo only had six-month therapy and the patients who were on Ariflo had a much longer time and, in fact, one patient was on it for two and a half years at the time of his incident. The others were on it for about 18 months for over two years. So the exposure was quite a bit longer in the Ariflo patients.

DR. SURAWICZ: So, one way you might look at it is that this is probably a significant problem that develops de novo but it is possible that it exacerbates underlying vascular disease.

DR. RICKARD: I think we need to keep in mind the fact, as mentioned earlier by Dr. Laine, that there was a significant increased incidence of ischemic colitis in COPD patients. Maybe we can show the M-7 slide which looks at the study in the UHC database that looked at COPD patients versus non-COPD patients and what the incidence could be expected to show.

[Slide]

As you can see here, if you look at COPD patients there was a 1.75 incident rate compared to 0.44 for patients who did not have COPD. So, I think we need to realize, as I said earlier, that these are elderly patients who have a lot of problems and though this is a rare event--it really is rare, it is not uncommon to see a couple of cases.

DR. PARSONS: Dr. Cross is next.

DR. CROSS: Was there any difference in the pharmacokinetics in smokers versus not smokers?

DR. RICKARD: Smoking had no effect.

DR. CROSS: Second, at the beginning you did a bronchodilator response and you found an average in all of these studies--what was it?--it was less than 200--it was 60 or 70 ml or something like that. Is that right? It was two or three times--

DR. RICKARD: It was 80.

DR. CROSS: It was 80. So, that is quite a bit different than what you found as your endpoint on your FEV1. Were any examinations done for the bronchodilator response at the end of your study, looking to see if that was the same 80 or whether you bit into some of that not very

significant in terms of pulmonary function, but you are trying to make significance out of 30 ml in terms of the efficacy on the FEV1 side?

DR. KNOBIL: Right. Yes, in some of the studies we did do bronchodilator response at the end of the study and the bronchodilator response was the same at the end as it was in the beginning. So, it was comparable.

DR. CROSS: So, the data that is presented is, of course, all without the bronchodilator.

DR. KNOBIL: That is correct.

DR. CROSS: All right. Another one, your symptoms of GER were a little bit more in the treated group, as I remember. Is there any effect on the smooth muscle, the esophageal-gastric junction? That is pretty easy to look at in terms of zero and max, like is done with theophylline where there is relaxation of that muscle. You have not clarified too much whether smooth muscle has a significant effect. You think it doesn't in the airway.

DR. DOWN: I will take the question. Geoff Down, clinical pharmacology. We performed one study with esophageal manometry and there was some increased relaxation of the lower esophageal

sphincter in cilomilast-treated subjects compared to placebo. It was only a small effect and this is probably a class-related effect. Does that answer your question?

DR. CROSS: Yes, it does but I would like to then push into the cardiology questions. You had more PVC by quite a bit in this study on the drug, and you had some cardiologic rule-outs for who you didn't take into the study. I know you have a cardiologist. I was just wondering if you had abnormalities on your baseline EKGs, or you were looking at long 2s, or 3s, etc. With theophylline there is quite a bit happening to that cardiogram on a Holter monitor, and I wanted to get a little bit more detail of what type of cardiac patients you excluded from the study because, as we all know, there is a fair amount of cardiac active patients in the COPD population.

DR. RICKARD: Well, patients were excluded from the study if the physician thought they had significant underlying cardiac disease. Certainly, they were also excluded if they had significant QTc prolongation present before entering the study. They may not have been excluded if they had other type of background cardiac abnormality like

evidence of an MI on EKG, or things like that.

When we looked at the analysis we looked at people who did not have significant issues at baseline, and we looked at the number of people who had changed during therapy and what we saw was that there were no significant differences in those people who had changed. We also looked at people who had some issues at baseline and, again, when we looked at those people we didn't see any significant differences in what we saw in the EKG or the Holter monitor analysis for that.

DR. CROSS: So, patients with significant CAD, and you are looking at a little bit younger population of COPD if they averaged around 60 to where you would find the maximal cardiac problems--I am just wondering, for instance, on the cardiogram you had more PVCs but were more sophisticated tests, heart rate variability, etc., etc., looked at on your Holter monitors?

DR. RICKARD: Well, if you are talking about QTc intervals, as we discussed, we did correct them by Bazett correction and Fridericia's. I certainly would have our cardiologist actually answer that for you, if you would like.

DR. CROSS: Yes, the concern I still have

is the mechanism of any cardiac activity of this drug and whether you have a population of cardiac patients with coexisting coronary disease or angina, etc., that were studied.

DR. RICKARD: Well, certainly anybody with unstable angina would not have been put into the study at the time that they came into the study. We can have Dr. Ruskin discuss his analysis of the cardiac data.

DR. RUSKIN: Jeremy Ruskin, Mass. General, Boston. Based on the patients that were included in the data that is available, which is all that I can speak to, there was no signal of a cardiac risk based on a conventional evaluation, and this includes effects on vital signs, a very rigorous ECG analysis, 7,000 electrocardiograms, almost 10 percent of them at Cmax, serious adverse cardiovascular events and mortality. So, based on those parameters there certainly is no signal that I can see. In particular, obviously recent concern has focused on ECG intervals and there were no detectable changes there, particularly with regard to effects on repolarization.

DR. CROSS: Lastly, in the basic studies was there any potentiation of, let's say, albuterol

cardiac toxicity by this drug? In other words, there is overlap between even some of the betas and with theophylline which increases the toxicity of the betas a couple of orders of magnitude. I am still trying to get at are there any effects on the heart of this drug in terms of either rhythm or heart muscle, etc?

DR. RICKARD: No, we studied albuterol and theophylline. In addition, we used them both together and we saw no differences in the cardiac assessments that we obtained.

DR. CROSS: At the toxicity level?

DR. RICKARD: Right.

DR. PARSONS: Dr. Newman, then Dr. Joad, then Dr. Kercsmar.

DR. NEWMAN: One of the questions that I wanted to ask, putting this in the perspective of figuring out that approximately 30 percent of patients are not going to tolerate the drug after a few weeks and trying to integrate this with what the statisticians have said about the repeated measures analyses, weighting for the 24-week study goes more heavily to the earlier time points. I guess what I am wondering from the statistical standpoint or from the clinical design standpoint

is, is there a way to understand what the likelihood is of people who can tolerate the drug showing stability of FEV1. If we were to subtract out the 30 percent of people who in the first month, because of various toxicities, stopped using the drug, has there been an analysis to tell us that the people who can tolerate it for 24 weeks either improve or stay the same in FEV1?

DR. KNOBIL: Yes. Actually, we have done all kinds of sensitivity analyses on all the studies. When you look at just the patients who are in the study for a significant period of time, either 8 or 16 weeks, the results in FEV1 are the same or better than when the dropouts are still in the study. In fact, I can show you one example of this for 039. Can we look at the graph from 039 from the core, please?

[Slide]

This is the slide that I showed you before, looking at the effect of Ariflo over time with the maintenance of FEV1 and the decline in the placebo arm of this trial. Now, the concern has been raised that most of the decline occurred in the first two to four weeks, whereas when we did the repeated measures analysis we see that the

decline is pretty steady over the course of the trial.

[Slide]

However, when we take out the patients who dropped out in this early part of the trial, we see the following result which is nearly an identical graph. So, really when you take the dropouts into account you see the same result.

DR. PARSONS: Dr. Joad, you had a question?

DR. JOAD: This is for the FDA. Do you have any other information about your PDE4 inhibitors with regard to vasculitis that you can share? You said it was a class effect.

DR. MEYER: There is really very little information we can share. We can say that it has been seen with others. There apparently has been public acknowledgement that one manufacturer has stopped development because they had a case of colitis in humans and that caused them to stop development. That is something of a web page but, unfortunately, that is very little of what we have seen that we can share with you because it is not public data.

DR. PARSONS: The last question will be

from Dr. Kercsmar.

DR. KERCSMAR: I might have a similar question that was just asked of GSK. You looked for a biomarker or something to try to predict serious GI adverse events or arteritis, but can you identify responders from non-responders? Do you have subgroups that will respond favorably to the drug and those that won't? Are there any biomarkers, or is it age related, FEV1, co-morbid conditions so that you can predict responders to the drug? I am not looking for adverse effect.

DR. KNOBIL: Yes, there are some things that are correlated with a better response, although none of them is very definitive in terms of defining a very specific population. For example, in the North American studies, for SGRQ a lower FEV1 is correlated with a better SGRQ response, the most severe patients. Also, again for SGRQ a history of chronic bronchitis is associated with a better response, as well as a longer smoking history, a higher pack-year history of smoking is actually correlated with a better response for SGRQ. Most of these things don't really have any effect on the FEV1 response.

DR. PARSONS: We still have lots of

questions on the list so I am not trying to ignore anybody, but we need to let people break for lunch. We do need to meet back here at exactly one o'clock and we will start with the open public hearing.

I have an additional announcement that there is a table reserved at the front of the restaurant for members of the committee so that we can meet there. So, we will resume again at one o'clock and start back with questions.

[Whereupon, at 12:00 noon the committee recessed for lunch, to reconvene at 1:00 p.m.]

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

DR. PARSONS: I would like to welcome everybody back. We are getting ready to resume the meeting. The first item on the agenda this afternoon is the open public hearing. We currently don't have anybody scheduled to speak but if there is somebody from the audience who would like to speak, they can stand up and come to the microphone. Do we have anybody? No? We will then close that part of the public hearing and we will move on.

We are going to resume now where we ended this morning. We are going to go back to general discussion with both clarification and questions to both GSK and to the FDA. We actually had a list of people who still had questions. We were going to start with Ms. Schell and Dr. Apter, and we can go from there.

MS. SCHELL: I have a clarification again. It was my understanding that both the company and the FDA met early, before the trial started, on the protocol for testing of the safety issue regarding the fecal occult blood and the protocol to be followed. It is also my understanding that the FDA thought there was discrepancy in following that

protocol. I was just wondering, from the company, if there was a particular reason or why it wasn't followed.

DR. RICKARD: Well, I think we have a slightly different perspective and I think, on the contrary, we did follow the protocol to the best of our ability in a clinical trial setting. I know we have talked a whole lot about fecal occult bloods and we talked also about colonoscopies. Actually, the number of colonoscopies that were done in this trial, if you look at the point when the studies were amended and you go from that point forward, 39 patients would have qualified to have undergone a colonoscopy and there were actually 25 colonoscopies done. Again, none of those 25 colonoscopies showed anything, not even a hint of evidence of ischemic colitis.

So, I think that in fact in this protocol we actually did a pretty good job of doing what was fairly difficult as far as getting people to follow procedures and doing procedures such as fecal occult blood and colonoscopies.

DR. PARSONS: Dr. Apter?

DR. APTER: I guess, Dr. Rickard, you mentioned that this drug is not to be used with

erythromycin. Could you clarify that and then talk about the other macrolides, clarithromycin and azithromycin?

DR. RICKARD: Right, for erythromycin, in the studies that we have done, if you initiate both of the drugs at the same time so you start them at the same time, you see an increased incidence of GI intolerance and you see more nausea and vomiting, something that you probably would expect. However, if you already have Ariflo at a steady state and then you add erythromycin you don't see as many GI adverse events. So, it seems to be the initiation of the two at the same time for that.

Now, we don't have any other data I could talk to you about any other types of those drugs. We do have one study that has been done but we don't have any other significant data I can tell you about at this point.

DR. PARSONS: I just have a quick follow-up question about some of the GI side effects, and this would be probably for either of the gastroenterology experts. Since a number of the patients that did drop out that got the drug had GI side effects, is there any preclinical data or any reason to suspect that those GI

manifestations were manifestations of early mild ischemia that would ultimately be reversible? In other words, the question I am asking is I know it is very difficult even to diagnose full-blown mesenteric ischemia but are there early signs that people were exhibiting that cause them to drop out based on preclinical data? What is the likelihood that that reflects mild vascular impingement that may or may not be reversible?

DR. SURAWICZ: I will let Dr. Laine go first.

DR. LAINE: I guess I would say two things, it is hard to answer it directly. One, in the preclinical data even in the rodent model where there was this vasculopathy there was no ischemia of the intestine seen. So, there wasn't evidence of a downstream decreased perfusion. So, that is one bit of information.

I think the other information, as Chris mentioned, when you are talking about mesenteric ischemia, arterial ischemia of the small intestine at least, usually it tends to be they get severe disease and they probably go on to have something bad if it continues for a while. But different than that, in ischemic colitis there is a group of

people, at least half the people who get ischemic colitis, who actually get abnormalities that are probably only for the mucosa and the submucosa so only the superficial part, and that can resolve in a matter of weeks or months with no sequelae.

So, I would think, if Chris agrees, that would be the main place where there can be, in the colon at least, transient abnormalities but there are no great studies because, you know, if a tree falls in the forest nobody is there kind of idea--do you know it is really there?

DR. SURAWICZ: I had pretty much the same thought. It may be that I am misinterpreting the data that most of the early dropouts were nausea and vomiting and that didn't seem like those would be ischemia type symptoms. It would be more if it was abdominal pain. Perhaps you ought to answer that, is it that the dropouts were more nausea and vomiting and diarrhea?

DR. RICKARD: Yes, in fact the major ones were nausea and vomiting that people would withdraw for.

DR. LAINE: The other thing, of course, as we heard rectal bleeding is one of the other major features of ischemic colitis and one of the

problems that Chris did mention is that there was a whole bunch of different things that all fit into the same descriptor of melena, most of which really weren't rectal bleeding. It was only a small proportion that actually had the rectal bleeding, and I think those people had a higher incidence, although not 100 percent, for getting colonoscopies.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: I want to ask the company about the proposed indication for use of this medication. I guess my question is that it is fairly broadly stated this would be for people with COPD who have poor reversibility. When I look at the studies, it seems that the category of patients who were enrolled in the four pivotal studies are not in the most severe form of COPD and, yet, the application of the medication in practice could potentially be used by clinicians with this indication for more seriously affected individuals. For example, you excluded people who were on any form of long-term oxygen therapy. I am wondering what is the company's thought about the ability to take these data and extrapolate them to the universe of severe COPD patients without

reversibility.

DR. KNOBIL: Well, severity of COPD is generally defined by FEV1. So, we have a wide range of severity of disease in our trials. Additionally, as you have already mentioned, they are poorly reversible. Even in the other long-term trials of patients with COPD, even the milder patients have declines in FEV1 and would benefit from maintenance or stabilization of their therapy. So, I don't think that this should be relegated to more severe or less severe. I think right now we have the data in a broad population of moderate to severe patients who are poorly reversible and, as we have seen by these other trials, they can benefit from maintenance of their FEV1. I don't know if I answered your question.

DR. NEWMAN: Well, maybe there isn't a direct answer to it but I think from my way of reading this the kind of exclusion criteria you had, even if it wasn't a direct impact on severity, it would have an indirect impact on the severity of patients that we see. I am thinking mainly about looking back, and maybe you can comment on this--looking back at study 168 where you showed the difference in those who had more reversibility

responding better in terms of FEV1 response compared to the ones with poor reversibility. I started thinking about what about the most severely affected COPD patients in my practice who have truly the least degree of reversibility and the worst DLCOs and the worst FEV1, the worst emphysema?

DR. KNOBIL: Well, you mentioned 168 and for reference for everyone else we can show the data that you just referred to.

[Slide]

In study 168 any patient was allowed to participate--well, not any patient but they weren't excluded on the basis of their reversibility, and it turns out the baseline characteristics were similar in this study except for the degree of reversibility, which was about 16 percent in this patient population versus the 6.5 over the four pivotal trials. Overall, we see a 16 ml increase in the total population, a 30 ml increase in the poorly reversible by the same definition as we said before, and 130 ml increase in the more reversible patients. This is on a par with what we have seen in the other studies. Just bear in mind that this study was small and not powered to detect a

difference.

But I think you have to look at a couple of things, one is that for patients who do have the ability to have a bronchodilator effect, they do have a larger effect. For patients who are poorly reversible to bronchodilators we have seen a consistent effect in FEV1 versus placebo. And, any patient who has COPD and has increased rate of decline of FEV1 would benefit from stabilization whether or not they are on the lower end of severity or on the upper end of severity. That is really all; I don't know how else to say it based on the data that we have.

DR. PARSONS: Dr. Morris was next.

DR. MORRIS: I have a question for Dr. Ruskin. Could you comment, please, on any preclinical or clinical data that might shed some light on the likelihood of this agent to cause dysrhythmias?

DR. RUSKIN: I can't comment on any preclinical data because there is very little available with regard to the profile of the drug in preclinical models. The usual approach to profiling a drug with regard to cardiovascular risks involves the things that we have talked

about, that is, an assessment of the drug's effect on heart rate, blood pressure, EKG parameters, and then looking at some outcome parameters within the confines of a clinical development program, that is, serious adverse cardiovascular events and mortality. If one uses those various parameters there are no signals of a cardiovascular risk.

DR. MORRIS: Could I ask you to speculate, if serum concentrations of the drug rose, could there be arrhythmogenicity of this agent?

DR. RUSKIN: I can't answer that question. I just don't have the data to answer it, except to say again that one worries about high exposures usually in a situation in which there is some signal at standard therapeutic concentrations, for example a modest QT effect that might be amplified markedly if exposures go up markedly. There were no such signals in this program.

DR. PARSONS: Dr. Cross?

DR. CROSS: Can you give us a clue to say what percent of these patients were on ideal doses of anticholinergic inhalants? It is a little bit hard to say reversible and irreversible if they are already maxed out on anticholinergics.

DR. KNOBIL: Yes, about 40 percent of the

patients were on anticholinergics. When you say ideal doses--

DR. CROSS: Well, I mean properly administered.

DR. KNOBIL: And that would be two or three puffs three to four times daily.

DR. CROSS: Right.

DR. KNOBIL: And that was the definition of scheduled epitropium. Now, we didn't track compliance with that medication because it wasn't a study medication.

DR. CROSS: Did I read it right, you had over 40 percent smokers, 40, 45 percent smokers?

DR. KNOBIL: That is correct, yes.

DR. CROSS: Have you done any studies of airway challenging to see if you had, say, methacholine responsiveness, etc? Has there been anything done even in your asthma population in terms of are they more sensitive to airway reactivity when challenged in terms of this drug?

DR. KNOBIL: You mean more sensitive or less sensitive to challenge?

DR. CROSS: Correct.

DR. KNOBIL: Yes, we don't have methacholine challenges in patients with COPD. I

don't believe we have them in patients with asthma.

DR. CROSS: Because you would expect with 40, 45 percent smokers you would have quite a few that had abnormal challenge tests.

DR. KNOBIL: That is very possible, however we did not do methacholine challenges in these patients. It is important to note though that there was no difference in FEV1 response for current smokers--

DR. CROSS: Right. Now, you are presenting this as an anti-inflammatory and, of course, we are all aware that we are calling asthma a very inflammatory disease and we have recently been calling COPD a bit of an inflammatory disease. Can you say anything about this drug in terms of your asthmatic analysis of what is happening in terms of the drug? There are a couple of studies that were already mentioned in terms asthmatics studied. Can you give us any clue as to whether this is going to be doing anything in asthmatics?

DR. KNOBIL: We don't have similar studies that I showed you in the COPD patients in asthma patients. We do have some preclinical data in some of the cell types that are important in the pathogenesis of asthma. Dr. Barnett?

DR. BARNETT: Mary Barnett, GSK. What we did a lot during the development of the cilomilast program is to look at a lot of the inflammatory cells and asked the question how sensitive they were to PDE4 inhibitors. What we did find is that there is a variation in the level of sensitivity to suppressive effects of this class of drugs. Interestingly, in asthma one of the cell types, the mass cell type which is very important in at least allergic asthma, is one of the least sensitive cells to PDE4 inhibitors in general. So, it may be that the type of inflammation we see in COPD, with CD8 cells, macrophages and neutrophils, they are more sensitive to PDE4 inhibition than the type of inflammation that you see in asthma, which is more of a CD4, mass cell, eosinophil type of inflammation and that may be the reason why we are seeing such nice effects in COPD.

DR. CROSS: You focused a lot in the presentation on the decrease in the CD8 cells. Can you remind us what sort of evidence there is that decreasing the CD8 cells is going to be very helpful or not, and what role they are playing in immune reactions of the airway?

DR. KNOBIL: Do you want to do the

preclinical and then I will do the clinical?

DR. BARNETT: Well, the evidence is probably circumstantial right now in terms of the fact that they are present there. If you look at the cytokine potentials that people are beginning to measure in COPD bowel fluids, it looks like a TH1, T-cell cytolytic response rather than a TH2 response and the fact that we have evidence to suggest preclinically that we can affect CD8 cell function and recruitment into the lungs. That is basically what we have.

DR. KNOBIL: Also, I mentioned the clinical data that correlated increases and CD8 positive T-cells with COPD severity. Dr. Sciurba was one of the authors on the Retamales paper--

DR. CROSS: I guess what I am trying to ask is, is that good or bad?

DR. KNOBIL: Yes, I would like him to comment on the clinical significance of that finding.

DR. SCIURBA: I confess that I collaborate with basic scientists. I consider myself a physician and a physiologist but I have learned a little bit of the vocabulary.

There is data from the Italian group,

Saetta's group, and a lot of papers that CD8 cells are elevated in early, late COPD. CD8-CD4 ratios are elevated. The Retamales paper out of British Columbia that both Kate and I presented showed dramatic elevations in really all class inflammatory cells, dramatic increases in CD8 lymphocytes. There are a couple of papers that have been presented in abstract form that are currently in review, elaborating on potential mechanisms whereby in more chronic advanced COPD, in fact, there is low grade chronic colonization resulting in the ongoing deterioration; that it is a cytolytic type of response. There is no doubt CD8 cells are elevated in COPD. To say cause and effect, I guess this data is as good as any data that you can lower the CD8 cells and see an impact on lung volume and stabilization of FEV1, but the data is emerging and it is being looked at. I will tell you though that inflammation is an actor in COPD and there is a lot of research and a lot of work going on right now on that.

DR. PARSONS: Dr. Joad?

DR. JOAD: Yes, I wondered, if you have it available, if you could show us the graph of the hourly PFTs for four hours after the first and last

dose. I would just be curious to see if you have it.

DR. KNOBIL: Just a second.

[Slide]

Here is the first dose effect and the last dose effect, looking at serial PFTs over four hours. Again, the Ariflo group is shown in yellow and the placebo group is shown in blue. At the end of the four-hour period they were given albuterol. So, that is what we are seeing here. The response to albuterol was unchanged really from the first to last dose. As you can see, there is a small increase in FEV1 following the first dose but certainly not appreciable bronchodilator effect.

DR. PARSONS: I wanted to follow up on a question that Dr. Apter had this morning and that was about the original study design and what the initial anticipated results were compared to the results that you got. One question I had is when you initially powered the study and you were looking, hopefully, for an FEV1 change of 100-120 cc--I have two questions. One is was that based on the fact that you were anticipating that the group that received drug would improve 120 cc, or did you anticipate a fall in FEV1 in the placebo group as

well as an improvement? If so, based on data out there from the Lung Health Study and everything else, what degree of decrease in FEV1 were you thinking you were going to see in the placebo group at 24 weeks?

DR. KNOBIL: Well, to be perfectly honest about it, after looking at the Phase II clinical trial 032, we did expect to see an increase in FEV1 with cilomilast and we didn't really expect to see the drop in FEV1 in the placebo group. Perhaps we should have, given the data that is out there with these long-term clinical trials. However, even though we didn't see what we expected to see, I think we did see a very clinically important result, basically the stabilization of FEV1 over time while the placebo group did decline.

I think the other important thing to note is the decline in FEV1 in the placebo group was seen in three of the four clinical trials. So, the weight of evidence suggests that this is a real finding. The maintenance of FEV1 of improvement, again, was also seen in four out of the four clinical trials. So, I don't think we can ignore what we are seeing, still a very clinically relevant result albeit not exactly what we

expected, and supported by the lung volume reductions that we saw too. So, I do believe there is real activity going on in the lung.

DR. PARSONS: Dr. Morris?

DR. MORRIS: I have a question for Dr. Knobil. In thinking about how this drug would come to be used and in thinking about how, since there is some percentage of the people on the active arm who did have GI intolerances, was there any information gained from looking at the concomitant med list on those people within study drug arms who had GI intolerances? Was there anything by analysis of the concomitant meds that might give us a clue to say to Mr. Smith, or Mrs. Jones, or Mr. Jones, you are on this drug. We know those people get more GI intolerance?

DR. RICKARD: We looked in particular at one drug, such as non-steroidal anti-inflammatories which a lot of these people can be on at times. We didn't really see any difference in effect on GI intolerance if they were on non-steroidals or not. We really didn't have a lot of other concomitant meds that we looked at to see whether it was involved with GI intolerance.

DR. MORRIS: Do you know particularly if

diuretics were seen?

DR. RICKARD: Well, certainly diuretics were used in some of the patients based on their underlying diseases but I don't have an analysis to tell you whether it correlated with anything or not.

DR. SURAWICZ: Can I ask why you asked about diuretics?

DR. MORRIS: I am just worrying when someone has nausea and vomiting and persists in taking a diuretic. They would become more dehydrated.

DR. RICKARD: Again, I just want to remind you that we have done very many vital signs, hemoglobin hematocrits and laboratory values and at no time did we see any difference. So, we did not see any evidence of any type of blood volume loss per se or any effect of dehydration.

DR. MORRIS: What would be the recommendation for use during an acute exacerbation of COPD?

DR. KNOBIL: Well, the recommendation for use would be the same as what was done in the clinical trials, that patients should not stop taking their medication. There is no evidence to

suggest that they should stop taking it and there is, you know, probably more evidence to suggest that as a maintenance medication it shouldn't be discontinued unless there is a physical reason why they can't take it.

DR. MORRIS: In some of the safety studies there was some notion that in people with hepatic impairment there was an increase in serum levels.

DR. RICKARD: In people who have severe hepatic impairment or people who have severe renal impairment there is an increase in the unbound portion of Ariflo. Now, interestingly, in these studies we did not see an increase in side effects but what we are saying is that there is a potential for increase in GI intolerance because of the fact that the unbound fraction is increased.

DR. PARSONS: Dr. Kercsmar?

DR. KERCSMAR: Two things, I wonder if you could put that slide back up about the bronchodilator response, the first and last dose? The other question I had was if you give this drug to a patient with COPD who does have a reversible component is it an acute bronchodilator? In the 168 study, it looked like those patients who are reversible have a pretty sizeable response.

DR. KNOBIL: Right, and that is the only study in which we did not restrict reversibility and we did not do serial FEV1s. So, I don't know the answer to that question.

DR. KERCSMAR: You might expect drugs which are phosphodiesterase inhibitors to potentially in that patient population to have more of a bronchodilator effect. I want to see the magnitude of those responses.

[Slide]

Is that right, that you are still getting about 150 ml response in those patients to bronchodilator?

DR. KNOBIL: To albuterol. Remember, we are getting a little bit more than the 80 ml because that is the average for all clinical trials, and the reversibility was slightly higher in the North American trials and this is North American trial 039. Again, we don't see much of a bronchodilator effect acutely but we don't see any diminution of response to albuterol either.

DR. PARSONS: Dr. Joad?

DR. JOAD: Part of what we have to deliberate on today is whether 30 ml is a clinically important difference and I wondered if

you wanted to say why you think it is.

DR. KNOBIL: Well, I think the clinical picture is very clinically significant because in the clinical trials we do see the stabilization of FEV1 over time whereas we do see this steady decline in the placebo group, albeit in three of the four trials. We also see the stabilization of FEV1 of up to 84 weeks in the open-label trials.

So, I think that the clinical significance is quite compelling in that if we can potentially stabilize FEV1 over time, that would be one of the things that we haven't been able to do in patients with COPD.

The other thing to remember is that we have seen significant decreases in lung hyperinflation which also are associated with improved exercise tolerance. Also, even though we didn't see a large increase in FEV1 in the cilomilast-treated groups, we did see a significant increase in quality of life. So, I think all those things taken together tell me that for patients this would be a clinically relevant medication for them, and I would invite also Dr. Sciurba to comment.

DR. SCIURBA: I guess what I would ask the

committee and the agency to consider is what would be the outcome you would expect with the broad class of anti-inflammatory agents that are currently in various stages in the pipeline, or at least being speculated upon in the literature. What response would we expect to see? It is not going to be in irreversible COPD 200 cc acute changes, yet there is a lot of effort, a lot of money, a lot research, basic science research developing products that we can then translate and test clinically.

You know, when I look at it from that perspective, if we can stabilize COPD and prevent the decline and the symptoms, then I think we are doing the right thing for our patients. Do we have evidence here that that is occurring? Within the length of the trial we do see stabilization. We see other factors that I think are very important if we don't just focus on FEV1, things that I talked about in my formal presentation--drop in hyperinflation, residual volume.

The surrogates, while they are surrogates and I don't have absolute evidence, I don't know if in the next ten years we will have the absolute evidence that, in fact, drops in CD8 and

neutrophils and macrophages do translate into the things that we think they will translate into, but there is pretty strong surrogate evidence that we are doing the right thing if we--as the strong trend in our area of research is--believe that, in fact, inflammation is the key agent resulting in progressive decline in COPD.

DR. PARSONS: Dr. Cross?

DR. CROSS: Did you do any subgroup analysis, or can you remind us what you found when you took that beginning FEV1, 20, 30 percent of predicted, 60 percent of predicted--can you tell us that improvement that you are trying to show, did it cross over all degrees of severity of the FEV1? Obviously, 30 ml is a lot more impressive to somebody whose FEV1 is 400 than somebody whose FEV1 is 1.9. I am sure you did some subgroup analyses because you had so many patients, and almost all these studies do subgroup analyses, to tell when you pegged it to the severity of the COPD.

DR. KNOBIL: When we looked at severity of COPD, that by itself did not have significant impact on the FEV1 response. But as I mentioned before, the more severe patients, that is, less than 35 percent of predicted, tended to have a

greater response in SGRQ than the less severe patients. So, just by looking at FEV1 severity, it really had more of an impact on the SGRQ.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: I just wanted to follow-up on something you said a few minutes ago about why you think this is an efficacious medication. I am trying to reconcile what is the proposed indication, which says the efficacy of the drug has not been established in clinical trials beyond 24 weeks and what you are inviting us to do here is to accept the open-label work that carries on for a few years thereafter.

In light of the fact that you are making the statement, I think correctly, that you have efficacy data for 24 weeks, I have a two-part question. One is what would be the recommendation to patients and to their physicians in terms of prescribing this drug beyond 24 weeks? And, why were the studies as originally designed only 24 weeks in length?

DR. KNOBIL: Well, I think I will answer the second part first. They were originally 24 weeks in length to establish efficacy and a six-month trial is what we have generally been

using for our medications for COPD. Generally we also do longer-term trials mainly for safety and that is why we have the long-term extensions.

As I mentioned before, what we were expecting to see and what we actually did see was slightly different. I think if we had expected what we saw we would have had a longer-term trial, placebo-controlled trial to fully look into that.

I am sorry, now I have forgotten the first part of your question.

DR. NEWMAN: Is it advisable for a patient to be prescribed this medication for more than 24 weeks?

DR. KNOBIL: Well, certainly from a safety standpoint there are no issues seen, as you have heard, for up to three years in patients with COPD. The potential to stabilize FEV1 beyond the 24 weeks is very real. So, I would certainly expect that there would be no issues to prevent a physician from prescribing this beyond the 24 weeks. The reason that the label has been proposed that way is because that is the duration of the placebo-controlled trial but, again, with the safety information that we have there is no reason to limit it only to 24 weeks. The patients should

be reevaluated periodically however.

DR. PARSONS: Dr. Joad?

DR. JOAD: Theophylline has been shown to increase excretion of calcium. Did you look at that at all with this drug, urinary excretion?

DR. RICKARD: We did not look at urinary excretion of calcium. We did look at all the standard things you would look at--electrolytes, potassium, glucose, and so forth and so on, and saw no differences in that. We did not specifically look at urinary excretion of calcium.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: This one is for Dr. Anthracite. I want to get a clarification on something that you said this morning when you were discussing adverse events versus serious adverse events. I thought I heard you suggesting, and I just want a clarification on this, that if a person had an adverse event and dropped out of the study in your way of thinking that would push it into the category of being a serious adverse event. Did I understand you correctly or could you clarify that, please?

DR. ANTHRACITE: Something like that, I was commenting on the paucity of serious adverse

events in the controlled and uncontrolled trials. I was kind of wondering if withdrawal from the study then moved it from the category of serious. There was, however, no way to ask that at the time.

DR. PARSONS: I have one question, I think just one question left but you never know, I am afraid; I am sorry. The two pivotal trials that clearly showed statistical significant differences in efficacy were the two North American studies. The European studies were less significant. You just mentioned, and I just looked back in the book, and actually the degree of reversibility in the North American trials is actually very different than the European trials. Is there a statistical difference between those baseline values between the studies? It may be difficult to compare.

My second part of the question is, is that why there is a statistical significance in the North American trials, because the reversibility is actually greater?

DR. RICKARD: Could you please show the baseline characteristics?

[Slide]

As I mentioned, there are some differences between the populations, not just reversibility.

You know, in the North American trials baseline reversibility is between 7.5 and 8 percent whereas ion the European trials it is about 5 percent. I don't believe this was statistically significant. I am not even sure that it was actually tested. It is hard to really say that that is a clinically significant difference just because there is some variability in reversibility testing, but it seemed to be pretty consistent across the trials.

The other things that were different were the degree of DLCO impairment, the numbers of women, as well as history of chronic bronchitis. So, there are a number of differences between the populations that may have contributed to the differences that we have seen. Now, we have done analyses to try to tease this apart and, as I have mentioned before, we haven't come up with the one answer that explains all of this so, unfortunately, I can't give that to you. But I wouldn't doubt that some of these baseline characteristics have something to do with it.

DR. PARSONS: Just doing quick math in my head, which is never very reliable, the difference is about 30-40 ml if you look at North American baselines and European baselines.

DR. KNOBIL: Yes.

DR. PARSONS: Which is the effect size that you are using for your efficacy in the two pivotal trials. Is that correct? That is approximately the effect that you saw?

DR. KNOBIL: Yes.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: I have a question that pertains to the non-clinical evaluation of the drug in animal species. I know there has been nothing found in terms of carcinogenicity. I am just curious has there been any look at co-carcinogenic effects with animals that were exposed to tobacco smoke, since that is kind of the unique thing about this patient population?

DR. RICKARD: No, there has not been.

DR. PARSONS: Are there additional questions from the committee? Dr. Morris?

DR. MORRIS: One last quick question, the Holter monitor data that we discussed before, you mentioned in your presentation that it was done at week 1 and then--was it week 12 and week 24? Were any histories taken that you remember while people were experiencing GI intolerances?

DR. RICKARD: You question is were any of

the Holters done while they were experiencing GI intolerance. I don't believe I have the data to answer that question.

DR. PARSONS: Any further questions from any committee members?

DR. KNOBIL: Can I just make one clarification? You asked the question earlier about whether or not hospital records were reviewed when a patient had been hospitalized. While we did not review records, if an adverse event or a serious adverse event occurred during the hospitalization or prior to or after, that was reported by the site personnel to GSK. So, while we did not personally review hospital records, any event that occurred during hospitalization would have been reported to us.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: I want to come back to a question I asked earlier today which had to do with the baseline data. In terms of your randomized criteria, you would allow people into the study if the difference between their screening FEV1 and their baseline FEV1 was less than 20 percent. I wonder if you would give me a clarification on the rationale for allowing that wide a range of

potential variability during the pre-randomization period.

DR. KNOBIL: The wider range of variability than reversibility?

DR. NEWMAN: Yes, you basically would allow a 20 percent variability between those numbers. I just wanted to get a little better sense of how that number was picked and why that was picked.

DR. KNOBIL: Well, I think it was a relatively arbitrary number, mainly chosen for safety purposes. We didn't want people who were rapidly declining because they had been removed from medications during the run-in period. Also, it was sort of a quality measure because if there was some variability in how FEV1 was done we didn't want to have unreliable FEV1s all over the place from patients potentially having an impact on the study. We wanted to have very strict rules for how FEV1 was performed and making sure patients who were deteriorating weren't getting in.

DR. PARSONS: Dr. Joad?

DR. JOAD I just had one question about that graph you had, A-72, in which you showed that people who were going to have GI adverse events

were going to have them early. It was an incidence graph I think. My question is if they had GI adverse events did they quit having them, or did they continue to have them? As far as I understand, that is incidence of new patients presenting with adverse events on that graph.

DR. RICKARD: Right. So, you question is if patients experienced it, in some patients did it go away?

DR. JOAD: Like with theophylline--

DR. RICKARD: Right.

DR. JOAD: --if they had it early it usually went away.

DR. RICKARD: Yes.

DR. JOAD: And that wouldn't be reflected on this particular graph.

DR. RICKARD: That is correct, but you are correct in saying when patients did experience GI intolerance many patients were able to tolerate them and they went away, and they continued in the studies. So, if you look at the withdrawal rates it was about 17.5 percent that withdrew from the study. Most of those were due to GI effects. But then greater than 80 percent of the patients were able to continue into the study and tolerate the

medication.

DR. JOAD: Did you formally look at that, you know, when they occurred and the people who had them?

DR. RICKARD: As far as time--

DR. JOAD: To show that it really did go away and the people who initially had GI events later on didn't have them?

DR. RICKARD: I don't think we have a specific analysis on that data but, certainly, the number of patients who did have it continued on. Otherwise, we would have had a much larger withdrawal rate from the study for it.

I also just antibody to clarify something for Dr. Morris and when you asked me about the Holter. The first one was done at week one. As you know, in the early period when you are likely to see GI intolerance, certainly there were a lot of Holters done at week one when patients were having those symptoms but we didn't actually pull those patients out and look at them separately.

DR. PARSONS: Dr. Cross?

DR. CROSS: I would just like to ask what the strategy and thinking was in having patients not take Combivent, which must be one of the more

frequent drugs in this country that is used to treat COPD, in other words, the combination of an anticholinergic and a symptomatic.

DR. RICKARD: Well, there are two reasons. One, when the first three pivotal trials were started Combivent was not available. So, when we designed the fourth one it was to be as similar as possible.

Also, I think it was felt that patients could use albuterol as needed anyway. So, if they were allowed epitropium on a scheduled basis they could also augment that if necessary.

DR. CROSS: Related to that, you probably had some discussions in comparing the post-bronchodilator FEV1s for your baseline versus the de novo or without bronchodilator FEV1s but allowing them to take anticholinergics. I just wondered when you went into the study you thought it was going to be an anti-inflammatory and not have any effects on airway reactivity? Was that the thinking?

DR. KNOBIL: Well, I have to admit since I wasn't around at the beginning when these trials were designed, I don't know what the discussions were about choosing post-bronchodilator FEV1 for

inclusion versus pre-bronchodilator, and I would welcome any other input. But to reiterate something that I said earlier, based on the dose-ranging study I think we were expecting a little bit more of a bronchodilator effect. So, that is sort of the answer to your second part.

Questions

DR. PARSONS: Are there further questions from the committee? Any comments? No further questions? If there are no further questions from the committee we are going to move on to asking the specific questions. We have four of those that the FDA has asked us to address. What I will plan on doing is read the first question, then we will open it up for discussion among the committee members and once discussion is complete we will take a vote.

We are going to start with the first question and we will go on from there. The first question that we have been asked to address is number one, has cilomilast at a dose of 15 mg twice daily shown a magnitude and consistency of efficacy that is sufficient to support approval for the maintenance of lung function, FEV1, in patients with COPD? If not, what further efficacy data

should be obtained?

I am going to open up that up for the group for discussion, comments.

DR. JOAD: I am always happy to start.

DR. PARSONS: Thanks!

DR. JOAD: In my opinion the magnitude is too small and the replicability between the studies was too poor to convince me that it is an effective drug. I am intrigued with the fact that it doesn't appear to be a bronchodilator in this group of patients and that there may be something that is anti-inflammatory that is really going to get at the underlying structural problems with the disease and preventing it from progressing. So, that is very exciting, that there could be such a drug for these people but I am not convinced of that.

What could convince me is really a longer study I think. If in the end all they ever get is a 30 ml, which is less than 3 percent, improvement of FEV1, that is never going to be clinically important. But if over the next six months or the next year it continues to widen then, of course, it would be just terrific. So, that is what I think.

DR. PARSONS: Other comments or discussion? Dr. Cross?

DR. CROSS: Yes, over a lifetime the 30 ml is going to cut a few months from disability and a few months from death I suspect if we take what the average yearly loss in FEV1 is and we relate the FEV1 to life expectancy, etc., etc. So, I think we are talking about something that might be in the long-run two, three months in terms of efficacy at the end that is critical where people are going on oxygen, etc. I otherwise agree with your comments.

DR. SURAWICZ: Can I ask a question of the committee, not being a pulmonologist? How do you determine the importance of one criterion like that versus all of the other outcomes that they measured functionally? I guess what I am asking is if I were a patient with lung disease what would I be expecting if I took this drug long term, besides just that 30 ml?

DR. PARSONS: Dr. Cross?

DR. CROSS: Yes, I will take a crack at that. The lung community as a whole is very interested in using studies other than the FEV1 for COPD, and the FDA has had these discussions too. As a chest community of pulmonary docs, we have probably been too dependent on physiology and there are other things that we would like to measure in

COPD. That has been pretty prevalent in our recent literature.

DR. PARSONS: I think in part too, you know, the quality of life scores that were obtained--that is another feature you would like to see in your patients. I can comment here. I think part of me is a little bit swayed by the change in FEV1. The study was not originally designed to look at what we are being asked to approve it for now, and that is just because the results were different than originally anticipated, and that happens, but I think the trial, from my point of view, if we were looking to stabilize lung function to start with, it would have been designed differently and for a longer period of time.

I share Dr. Joad's concerns about the minimal efficacy, and that has further sort of hampered me because there is so little improvement in the other potential outcome, which is quality of life. Based on those scores there was really minimal improvement in only one of the trials. But I would like to hear from the other committee members. Dr. Apter?

DR. APTER: Well, I agree with the other speakers. I am not convinced at all that FEV1 is

the right endpoint. I think quality of life should be part of it. Therefore, I am not convinced of the efficacy of the drug.

On the other hand, I am not sure that there is significant toxicity to hold it up and we have no good drugs for COPD, and that is the problem. The FDA perhaps could tell me how you could get what we all say is needed, a longer trial. How can you get a longer trial with economic considerations, aside from allowing the drug to be marketed?

One other comment that you brought up is that there may be effect seen at a lower dose, 10 mg b.i.d., that may have less side effects.

DR. PARSONS: Ms. Schell?

MS. SCHELL: I was interested in the fact that the more severe the patient the better quality of life rating they gave from the drug. I know from a patient's point of view that is very important for the more severe patient because they don't have much to go on but the quality of life. But I was disappointed in that the less severe didn't see that same improvement. So, from a patient's standpoint, there is a large group of patients out there that don't see a quality of life

improvement even though the more severe do. It is just a comment that sometimes the more severe can see little improvements so much better than the less severe, so how compliant are they going to be about taking the drug?

DR. PARSONS: Dr. Meyer?

DR. MEYER: I just wanted to address Dr. Apter's question to us about the long-term data. There are a couple of pathways. Part (a) of this question is, if not, what further efficacy data should be obtained? So, the committee could, in theory, recommend that the drug not be approved until longer-term data are obtained.

Another pathway, as I think you were getting to, is that the drug could be approved with what is called a Phase IV commitment, which is a commitment on their part to do a longer-term study. Or, it could be approved without such but the long-term study could be done otherwise.

DR. APTER: We can propose a number of studies postmarketing. Right? For adverse effects, for long-term follow-up, for different doses?

DR. MEYER: I think the intent of question 1(a) would be to have the committee give us their

opinion as to what further efficacy data would be obtained the way the question is posed, that is particularly if you feel like there are not sufficient data currently, but I think we would be happy to receive that kind of input in any case.

DR. PARSONS: Dr. Meyer, can you clarify for the committee in terms of Phase IV trials ongoing. In the past we have discussed them and they have generally been discussed for safety issues as opposed to efficacy issues. Is that not the case?

DR. MEYER: They can be for either. In fact, for certain classes of drugs it is common to approve them for surrogate markers, for instance AIDS drugs, drugs for HIV will be approved based on biomarkers. Then, the Phase IV studies, in addition to getting more safety data, are actually to prove the efficacy on clinical endpoints such as mortality and progression to AIDS, and things like that. So, Phase IV studies are not just for safety. They can be for many, many reasons.

On the other hand, obviously if the committee were to feel there were not sufficient data now one might argue that you should then do the study before approval. So.

DR. PARSONS: Before we vote on this question, are there other committee members that have items for discussion or comments? Dr. Kercsmar?

DR. KERCSMAR: The situation I have some experience with is another disease, cystic fibrosis, and one of the goals of they there for patients is to also slow the rate of progression and decline in FEV1. A number of the trials there with therapies have been much longer term, a four-year study for ibuprofen that showed significant slowing in the rate in decline of FEV1 as opposed to improvement. There have been some similar data here, a brief rise and then a decline over time, and what looks like in some of the extension studies here, a regression to the mean in both groups.

So, I would agree that a longer-term study might give you a better idea if the current indication for approval of maintenance of FEV1 is true or not.

DR. PARSONS: I think the other factor we might want to consider as a group is, indeed, some of the data that was presented in terms of how many patients there are in the United States and in the

world who fit the definition of COPD that is not responsive or COPD.

Also, although the average life expectancy varies with FEV1, for the majority of patients in the trial the average age was 60 such that they still have many years to live. I think others would verify that just in terms of information to put on the table. Dr. Joad?

DR. JOAD: The design of the study seemed fine to me. I think if they do another study, a longer study, they would want to do lung volumes because they made a cogent argument but it was not part of their pivotal studies and I think it should be.

DR. PARSONS: Additional discussion? I am going to ask the FDA one question before we start to vote on question number one. If we vote on question number one, if the vote is, yes, it is efficacious, do you want us to go on to 1(a)?

DR. CHOWDHURY: The way the question is written, if the answer the question is that it is, yes, it is efficacious, then 1(a) would not apply. If the answer is no, then really what we are asking for is what should be required for approving the drug.

DR. PARSONS: I just wanted to clarify that before we asked the question and voted on it. A vote of yes to question number one means question 1(a) does not go back on the table. Correct?

DR. CHOWDHURY: Yes.

DR. PARSONS: Any further discussion before we vote on question number one? Dr. Apter?

DR. APTER: I would like to be able to say yes but with postmarketing recommendations.

DR. CHOWDHURY: I missed the question. Is it a question to us?

DR. APTER: I guess so. Given the alternatives you just gave us, I wanted another alternative, yes, but with these postmarketing recommendations.

DR. CHOWDHURY: I mean, that can be something which you can put out as a discussion and as a comment that we take, but the voting is really as it is. Am I clear on that?

DR. PARSONS: Anybody on the committee have further discussion? I have tried to encourage it to make sure we haven't cut anything up and truncated things. Dr. Meyer?

DR. MEYER: I was just going to suggest why don't we go through the voting and if the vote

comes out that the committee is on balance recommending approval, then, since we are ahead of schedule, after the formal voting is done there would be plenty of time to add thoughts about what other studies might be recommended even in light of recommended approval.

DR. PARSONS: So, if there is no further discussion, I will read question number one again and then we are going to vote. I am going to ask that we actually ask on this side with committee members that have been on the committee for more than their very first time having to vote initially. So, we will start with Dr. Morris, but let me read the question again.

The question on the table is has cilomilast at a dose of 15 mg twice daily shown a magnitude and consistency of efficacy that is sufficient to support approval for the maintenance of lung function, FEV1, in patients with COPD? Dr. Morris?

DR. MORRIS: My answer is no, and the answer to 1(a) would be that long-term follow-up type studies that would include quality of life, that did look at drug use, that did look at hospitalizations and used those as parameters to

say this drug had efficacy. Since we are targeting a population that might not have a lot of mobility in the FEV1, I would use those other parameters as efficacy.

DR. PARSONS: Dr. Cross?

DR. CROSS: My answer is maybe but I have to decide which way to go. Can I pass for now and listen to other comments as we go around the table?

DR. PARSONS: I am going to have to ask somebody how we do that procedurally. Yes, we can let you pass, but not everybody can pass.

[Laughter]

Ms. Schell?

MS. SCHELL: My answer is no. Are we answering (a) now too? I would recommend further or longer studies including greater populations.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: My answer is no to question one.

DR. PARSONS: My answer is no. I think there is potential but I would like to see different studies done. Dr. Apter?

DR. APTER: My answer is yes, but there have to be postmarketing studies to follow those patients long term for safety, efficacy, a more

diverse patient population, and other endpoints of physical functioning than COPD.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: My answer is also no for many of the same reasons that we have heard here already. I will come back and comment later when we get to 1(a).

DR. JOAD: No.

DR. KERCSMAR: My answer is no for the same reasons and I would like to see some other studies done.

DR. PARSONS: I made an error. Dr. Surawicz, you are a voting member of the committee today. I apologize.

DR. SURAWICZ: I vote yes, and I am swayed by the magnitude of the disease, the lack of other options, the notion that there may be additional benefits long term. That is it.

DR. PARSONS: Dr. Cross, we are back to you.

DR. CROSS: Yes, I am going to go with yes. I am impressed with the volume changes, the symptom relief in the sickest of the patients, and I am satisfied on the safety. I don't think it is necessarily going to be great but I think it needs

further study and I think it will get further study if it is approved.

DR. PARSONS: All the committee members have voted. The final vote is yes, three votes; no, seven votes. We are going to go on to question 1(a) for those that didn't answer it. I am going to go around the room again. We will start with Dr. Morris and go in the same direction for 1(a). What additional studies would you like to see?

DR. MORRIS: I think for this particular population a longer study period of time would be beneficial, and with the other parameters we discussed that might give light to this agent. The trends possibly are there but it wasn't sufficient enough to convince me that it is ready at this point. But looking at the secondary parameters presented here in more detail, looking at quality of life and the use of medications to supplement exacerbations would be useful in helping to determine efficacy.

DR. PARSONS: Dr. Cross, you voted yes but do you have additional comments?

DR. CROSS: Yes, I want to see further studies done. I don't think in this country we are going to get away from doing them the way they did

their first studies because people are taking Combivent. I think that is a tough one because it is sort of almost a standard of care in COPD to use both. I question the whole business of reversibility. If you have somebody on an anticholinergic you would have to pull them out of an anticholinergic and wash it out and then say they were irreversible. So, I have problems with the definition of irreversible disease that is being forwarded here, and would call for qualifications of that and say that irreversible is defined as somebody on effective cholinergics who also is having to show a significant effect to a beta sympathometic that was being given because I think you would have to look at those two groups differently because the response to an anticholinergic in the literature is better than the response to a sympathomatic and I don't think you can call it irreversible because we don't know what it was without the anticholinergic. I agree with other comments, there are a lot of Phase IV studies that should be done on this drug.

DR. PARSONS: Ms. Schell?

MS. SCHELL: As I stated earlier, I would like to see a greater diversity in populations

including older people and more non-Caucasian, and also I would like to see the quality of life issue maybe studied more for those patients.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: Yes, I believe that longer-term studies are necessary, but then I question whether or not it is ethical to use placebo in a longer-term study in this type of disease. The company may need to consider a non-inferiority type of design where there is some active control instead of placebo.

DR. PARSONS: I think what I would like to see, because of the magnitude of the disease and the duration that patients are likely to be on this medication, is a trial clearly designed to now address the question that we have been asked to approve the drug for, which is does this drug, indeed, stabilize FEV1 or lung function and quality of life, and ask that in a specific prospective, randomized design trial to specifically answer that question which, unfortunately, is going to be a long-term study, longer than 24 weeks I suspect. It is going to be expensive. There are a lot of issues with it. But I don't think that the current trial has actually specifically answered the

question that we have been asked to answer. Dr. Apter?

DR. APTER: I agree, long-term because I am concerned about the endpoint. We haven't really answered the question. Other populations, as I have already mentioned. Other doses.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: Just adding to what I agree with, and I agree with everything I have heard here so far, I think that there is an opportunity to also include people who are not only older but also who may have somewhat more severe disease.

I think the other thing that I would encourage people to attend to is the precision and repeatability of the baseline measure because, if everything is going to peg off that baseline, I think we want to have a great deal of confidence going forward from that baseline that we know where people started before the initiation of the trial.

DR. PARSONS: Dr. Joad?

DR. JOAD: Yes, it is repeating what others have said, longer, a more diverse patient population, include lung volumes in the study.

The other thing I would add is that I think once it is released people are going to want

to use it for everybody, which means a big population of COPD that does have reversibility. So, especially with their preliminary data showing that reversibility may be more successful in patients who have reversible airways disease, at the time of this study they should just go ahead and address that issue so people would know who to apply it to.

DR. PARSONS: Dr. Kercsmar?

DR. KERCSMAR: The beauty of going at the end is you can agree with what everybody else has said, which I do. A couple of points I think bear greater emphasis. I would agree with Dr. Chinchilli about if you are going to do a long-term study, perhaps not using a placebo design, and also the measurement of lung volumes might be very, very useful and should be included.

DR. PARSONS: Dr. Surawicz?

DR. SURAWICZ: I have no additional comments.

DR. PARSONS: We can move on to question number two unless the FDA has further issues regarding question number one, further comments or questions.

I will read question number two and then

we will open it up for discussion. Question number two, is the safety database for cilomilast, aside from the concern about vasculitis, for the maintenance of lung function, FEV1, in patients with COPD sufficient to support approval? If not, what further safety data should be obtained?

I will open it up for discussion. So, this is safety database for all side effects, not vasculitis. Comments from the committee? Dr. Morris?

DR. MORRIS: I think overall the data presented appears very clean. I think the design of the study allowed for patients to be seen often and for people going through the trial there was a minimum of adverse side effects. So, in that light, I think for those people who were stable there was not, in my mind, a concern.

However, I think there was a great area of potential safety concerns that we did not have an opportunity to see or to evaluate and that is when people do become ill with the COPD exacerbation and do become ill enough to go to a hospital, I would think that we are going to see toxicities. Now, because the number of those in this particular study is small, we didn't have the opportunity to

see it very often, but in considering moving this agent out to a more ill population of COPD patients who do go into the hospital often we have to have more data on what does this look like when people get sick; when they are in the hospital; when they have new liver dysfunction or renal dysfunction, what does that do; and they have hypoxemia that is severe. What does that do to the arrythmogenicity? I am not sure but I do have concerns.

So, in the sense of what we saw and the data that was presented, I do think it is clean and I have no safety concerns there but I would say there is a caveat. I think there is an area of study that has not been evaluated that should be evaluated more carefully, and that is when people do get sick. Then we could have a better recommendation to say do we continue this drug during acute exacerbation or not.

DR. PARSONS: Dr. Cross?

DR. CROSS: I echo all of Dr. Morris' comments. I think the studies would need to be done in Phase IV with those with cardiac disease, and I am also concerned about hypoxia and arrhythmogenicity and cardiac manifestations, including Holter monitors done on patients that

weren't excluded because they had coexistent active heart disease.

DR. PARSONS: Additional comments regarding the safety? If there are no additional comments we will vote on this one. We are going to start with the initial question and then we will go to 2(a). I think that would be the best way to do this.

Question number two again, is the safety database for cilomilast, aside from the concern for vasculitis, for the maintenance of lung function, specifically FEV1, in patients with COPD sufficient to support approval?

This time I will go in the correct order; I apologize. Dr. Surawicz?

DR. SURAWICZ: Yes.

DR. PARSONS: Dr. Morris?

DR. MORRIS: No.

DR. CROSS: Yes.

DR. PARSONS: Ms. Schell?

MS. SCHELL: Yes.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: Yes.

DR. PARSONS: For myself, the answer is yes.

DR. APTER: yes.
DR. NEWMAN: Yes.
DR. PARSONS: Dr. Joad?
DR. JOAD: Yes.
DR. PARSONS: Dr. Kercsmar?
DR. KERCSMAR: Yes.
DR. PARSONS: The vote on question number two is nine yes and one no. In light of the one no, I think we should just go through the group and address "if not, what further safety data should be obtained." Dr. Surawicz?
DR. SURAWICZ: I pass.
DR. PARSONS: Dr. Morris?
DR. MORRIS: I would just reiterate I think dealing with people who have more critical illness so we could have recommendations as to what to do when they become more severely ill.
DR. PARSONS: Dr. Cross?
DR. CROSS: Ditto.
DR. PARSONS: Ms. Schell?
MS. SCHELL: I agree with Dr. Morris.
DR. PARSONS: Dr. Chinchilli?
DR. CHINCHILLI: Nothing to add.
DR. PARSONS: I have nothing to add. Dr. Apter?

DR. APTER: Nothing to add.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: If the study design in the future were to be broadened out to include somewhat more severe patients, then I think Dr. Morris' point would be especially important. I think it is important already but it would be even more important because you could expect that there would be more admissions to the hospital and you would want to track those data.

DR. PARSONS: Dr. Joad?

DR. JOAD: All of the GI side effects that they had were not particularly safety concerns but they certainly were very annoying and people had to drop out based on them. I don't know if the company has done this but, certainly, when we used to use theophylline all the time if you started low and worked the dose up slowly, then there were many, many fewer GI side effects and it became a tolerable condition. So, if the company hasn't really considered this or looked into it for this phosphodiesterase inhibitor then they should consider that in a future study.

DR. PARSONS: Dr. Kercsmar?

DR. KERCSMAR: Nothing else to add.

DR. PARSONS: We are going to question number three. Question three for the committee is do you feel that the concern about mesenteric arteritis has been adequately studied to be dismissed as a safety concern in humans? Then 3(a), if not, what further data should be obtained?

I am going to open this up for discussion. I think for many of us, our eyes are on Dr. Surawicz.

DR. SURAWICZ: Do you want me to make a comment?

DR. PARSONS: Yes.

DR. SURAWICZ: All right. I think that I am satisfied that the drug is safe, however given the experience that we had with lotronex a couple of years ago, I think it would be really important to monitor after the drug is marketed to make sure that nothing comes up. Certainly in that case there were some clues but it became really widely apparent when the drug was released and used widely, and sometimes in inappropriate patients. So, it is something I would keep an eye on but I am not worried and I would recommend yes as an answer to the question, for myself.

DR. PARSONS: Other additional comments

from the committee? Further discussion regarding this issue?

DR. JOAD: Are we going to get to talk about what further data can be obtained? I think autopsies on people who die, their vessels should be looked at. I think that is a really important omission.

Then the other thing is it seemed like what they were trying to do with colonoscopy seemed cumbersome and a lot of effort for not a very definitive answer.

DR. SURAWICZ: But look at all those polyps that were removed and that cancer that was diagnosed! Everyone needs a colonoscopy after age 50.

DR. PARSONS: That would certainly make our clinical trials easier in the future if we just do colonoscopy routine on everybody and then start trials. Dr. Newman?

DR. NEWMAN: I guess I have a question for the members of the committee, especially for our GI consultant. Do we think that if they had been more successful in performing more colonoscopies and if there had been an inspection of vessels as available that we would know more? Would we have

greater confidence?

DR. SURAWICZ: Are you asking about the quality of the colonoscopies? Because we don't really look at vessels but we look at the mucosa as a result of whether the vessels are abnormal. I think the quality of the colonoscopies was probably quite good. I know there was one comment in one of the briefings that perhaps the transverse colon wasn't looked at appropriately, but most colonoscopists, I am pretty sure, would look at everything; they would look at absolutely everything because we don't want to miss a little polyp or a little lesion. So, I think if there was anything there mucosally, I think it would have been found.

DR. NEWMAN: Not just quality but quantity. Not that many people actually ended up getting the procedure done.

DR. SURAWICZ: No, but they were the highest risk people because they had blood in their stools or they had symptoms. So, I think it is unlikely you would have found anything in the asymptomatic people so I think it certainly made sense, what they were doing. There was nothing in any of these colonoscopy reports that bothered me

at all. They were all findings that you would expect to see that had nothing to do with this drug whatsoever.

DR. PARSONS: We know from experience that when drugs get approved for a patient population that was studied, it is frequent that we, as physicians, broaden out those indications to older people, people that are sicker, and people that have different FEV1s and maybe even have some of the exclusion criteria. That is not uncommon practice for all of us. Is there any reason to believe that in a patient population that is a little bit sicker that we would like to be giving this drug to, because there aren't really good drugs for COPD, that they would be more likely to be at risk for mesenteric vasculitis? Is there a specific patient population that you can describe to the committee who are actually at more risk to start with and that might be included in a different COPD population?

DR. SURAWICZ: Not really. They already were studying old, sick people in this study--not old but relatively old, older, sicker people in this study and with age you are more at risk to get mesenteric ischemia but we don't have any way to

pick out a particular population. So, I think the best way to do it would be to approve the drug, postmarketing look for ischemia, follow people in the hospital to make sure that that is not what they develop because often for mesenteric ischemia you pick up the diagnosis after the patient has been in the hospital a few days; you don't tumble to it on diagnosis all the time. I think that would be reasonable so that if there is a problem it would show up that way. I think it is unlikely.

DR. PARSONS: Further discussion or comments from the committee regarding this question?

DR. CROSS: Were the animal studies oral dosing? They were? Then, there were deliberations on this committee with this same company 20 years ago on the most common drug we use for obstructive airway disease, salbutamol or albuterol, which caused tumors in the mesovarian ducts of rats and that probably held up approval a significant period of time, and we decided that we couldn't translate that easily to humans. I find great difficulty here. I mean, the older population is going to have atherosclerosis of these vessels and they are going to have a higher incidence, because they

smoke, of ischemia of bowel vessels. But with this thing here we have absolutely no mechanism to propose because the rat didn't have atherosclerosis. I just have to take the data that is there and say that the rat doesn't translate to people and we don't have any clue of a mechanism of why one vessel bed that really isn't getting a higher dose of drug because it is the artery is susceptible to inflammation when we administer an anti-inflammatory drug.

DR. PARSONS: Additional comments? We are ready to vote on question number three then. The question on the table is do you feel that the concern about mesenteric arteritis has been adequately studied to be dismissed as a safety concern in humans? We selective start with Dr. Surawicz.

DR. SURAWICZ: Well, if I read the question carefully I vote yes but to be followed. Is that clear? I mean, I wouldn't dismiss it entirely. So, I don't think it is a concern now but I can't promise that it isn't going to be a concern in the future so it is something that needs to be watched. Is that unambiguous enough?

DR. PARSONS: Dr. Morris?

DR. MORRIS: I viewed it as something that would not be asymptomatic and it did not seem like these people were symptomatic with this particular illness. So, I think it has been addressed.

DR. CROSS: I vote yes, and I do think I would do a certain amount of autopsies, carefully looked at for arteritis in the mesenteric vessels. This population has a large number dying off from different diseases so it should be no problem to get a certain amount of autopsies performed on a patient population that has been on this drug.

DR. PARSONS: Ms. Schell?

MS. SCHELL: Yes, with continued monitoring.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: Yes, I agree, yes, with continued monitoring.

DR. PARSONS: I would vote yes as well, although I just realized something I should have asked before, which is the two safety questions are actually worded very differently. The one we voted on before says is the safety database sufficient to support approval, and this is have the concerns been adequately studied enough to be dismissed. So, the word "dismissed" is bothersome to me for

the same reason I think maybe they are for other people on the committee. So, my answer is definitely yes but I certainly would continue to watch.

DR. APTER: I share the reservations of my previous colleagues, yes, but watch.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: The way I read the question I think everyone's answer should be no with the caveats, but to go along with what I have heard here so far I would say yes, with the stipulation that there be the kind of follow-up that Dr. Surawicz and Dr. Cross both mentioned.

DR. PARSONS: Dr. Joad?

DR. JOAD: Maybe we could restate the thing so we don't go on record as saying it should be dismissed because I would like to vote yes also, but I don't really think it should be dismissed. My concern is not enough to affect approval, or something. That is the way I would prefer to vote on that.

DR. MEYER: The discussion is captured in the public record. That will be part of the transcript.

DR. JOAD: Okay. So, I will say yes, but

like everyone else.

DR. PARSONS: Dr. Kercsmar?

DR. KERCSMAR: Yes, and I agree with all the previous comments.

DR. PARSONS: So the vote on question number three is ten yes and none no. That means we won't specifically go on to 3(a). I think it is important that most of the committee members did indicate that the dismissal is not what they voted on and that continued observation would be important. Does that capture the discussion? Is everybody on the committee comfortable with that?

We are going to go on to question number four, do the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 mg twice daily for the maintenance of lung function, FEV1, in patients with COPD?

So, this question combines both the efficacy and safety questions. I am going to open it up for discussion.

DR. CROSS: Just a question, we have already voted on one. I just wonder what in the world we need to vote on for four because it is 10-0 on safety.

DR. PARSONS: I can ask the FDA to address that. My impression would be we should vote on it because it is the combined. There were people who voted yes for efficacy and some who voted no.

DR. CHOWDHURY: Question number one is on efficacy, whereas question number four is efficacy, safety and indication. So, the whole picture comes together here. Based on the data that we have on efficacy, the data that we have on safety and the indication which we have heard a couple of times, does the whole picture come together for you to vote yes or no?

DR. PARSONS: I just want to clarify the question one more time. This is not the exact indication that is in our brochure. The indication in our brochure is for patients with COPD not responsive to albuterol.

DR. CHOWDHURY: The question is shortened but it is meant to be the full indication that the company has asked to obtain approval for, which is COPD which is not reversible to albuterol.

DR. PARSONS: So, not the patient population that we may all end up treating but the actual indication is what we are voting on. We are going to open that for discussion. Dr. Newman?

DR. NEWMAN: I think that when you have a disease that affects as many people as this does, if you take a public health perspective it is possible, with longer-term studies, that even a small effect could end up as a net benefiting a lot of people a little. From a public health perspective, that would in the long-term be beneficial to all of us.

Likewise, I want to just go on the record of complimenting the company for the thoroughness with which much of the safety data has been addressed because, again, you are looking at a large population being potentially placed at risk given how common COPD is. I think reflected in the vote so far has been the sense that there has been good attention paid to most of the safety issues. I know where I am going to come down. It is based on the efficacy issue that has to be proved with longer-term studies.

DR. PARSONS: Additional comments and discussion? Dr. Surawicz?

DR. SURAWICZ: I agree with that and also what sways me is that it is a new type of drug and often the first may not be as efficacious as the others, but the others may not follow if the first

is held up. Then the final point is that apparently there isn't anything else for these folks. So, that is a huge plus. I mean, even if you are just going to enhance the placebo effect, you know, it is sending a message to patients that things may come along.

DR. PARSONS: We may want to have some discussion. There already has been the issue raised by Dr. Cross, who probably wants to jump in here, regarding that there are other treatments available for these patients. Dr. Cross?

DR. CROSS: I just want to say that there is a lot of emerging literature on inhalation steroids in COPD and you have to call that anti-inflammatory. We will probably also run into problems with an older population with absorption and osteoporosis and all the problems we see in younger people that get inhaled steroids. But, certainly, that is pending.

DR. PARSONS: Dr. Joad?

DR. JOAD: Well, I would argue that if committee members felt it should not be approved based on efficacy, then this has to be a decision not to approve it when you weigh the risks, for instance, and the benefits. There are no

convincing benefits. Even if we hope there are going to be, I can't see how you could approve the two together if you don't approve effectiveness in the first place.

DR. PARSONS: Additional comments? No further discussion? Yes, please, Mr. Kennedy?

MR. KENNEDY: I am sitting here and I am trying to get a handle on what your thoughts are, and the thing that is coming to mind is I keep hearing postmarketing commitments of Phase IV commitments; and we are hearing a long-term study; we are hearing a study designed to show stabilization of FEV; and we are talking about this longer-term study that would include a more diverse population. We haven't heard from the agency whether that would be one study or two studies, and that may present something that would be a commitment on the part of the company of five or six years. With the safety profile that the drug is exhibiting now, would you be disappointed with your decision of this marginally positive efficacy if they declined to undertake that five- or six-year obligation? Or, is it a part of your assumption that they would automatically do it?

DR. PARSONS: I did not necessarily make

an assumption that the studies would get done. For me, the efficacy is small and the patient population that would likely have this drug prescribed is huge and I would like to see a better study to show that it really is efficacious, that it really does have a significant clinical difference, such that when the drug is available to patients and they are going to be taking it for years we can feel confident that, indeed, they are going to have a benefit. But I would like to hear other committee members. Dr. Newman?

DR. NEWMAN: Likewise, I didn't make any assumption that a study would be done. I think we all would like to have a medication to treat our patients with COPD but I just would reinforce that I was underwhelmed by the efficacy data.

DR. PARSONS: Ms. Schell?

MS. SCHELL: Looking from the patient's perspective and the possibility of a large number of patients being treated with this medication, I would hope to see better results for them so that they don't have a false hope that this drug is going to help them, and we don't see a lot of improvement with it. So, just from the patient perspective, I think right now I would like to see

more data that supports the drug.

DR. PARSONS: Dr. Cross?

DR. CROSS: Yes, I think the long-term data is critical. I mean, these patients will lose 35 ml a year from just getting older every year and with the average COPD patient it is over 100. In the general 20 million that have COPD it may be closer to 60. The company has done a half-year study and shown 30. I have more confidence in my colleagues, in the increased money, NIH is paying on COPD, the organization of the COPD Society, and I suspect there is going to be a large number of COPD clinical studies that are going to be done from unbiased viewpoints in the next few years. I take the comment that these are very expensive studies to do. They will be over prolonged time. I, myself, would like to see an inhaled steroid versus this drug done and this company is not going to do it; it is going to be somebody else. Those are my reasons for wanting it to go ahead with a lot of provisos on postmarketing surveillance by the company, but I also have confidence that our respiratory medicine community and the COPD societies and government funding will also look at this issue in some detail.

DR. PARSONS: Dr. Apter?

DR. APTER: I understand that we can recommend and the company may not want to take on the commitment, but I am hoping that our comments on the record will make a very strong case that this happen.

DR. PARSONS: Additional comments and discussion?

DR. CROSS: I wish this had said volume change as well as FEV1 because I agree with the comment that the volume change is very symptomatic in terms of the quality of life issue. When we think of how much reduction surgery is done and how equivocal that is and how much it costs and the fact that it is not maintained for the duration, that the rate of loss is equal at the end of a year. I have to say that I am as impressed with the volume change as the FEV1.

DR. PARSONS: Further comments or discussion? Anybody need further clarification of the question? No? Then I will read the question and we will vote. Question four is do the efficacy and safety data provide substantial and convincing evidence that support the approval of cilomilast at a dose of 15 mg twice daily for the maintenance of

lung function, FEV1, in patients with COPD?

We are going to vote and we are going to start with Dr. Surawicz.

DR. SURAWICZ: Yes.

DR. PARSONS: Dr. Morris?

DR. MORRIS: I vote no, briefly to explain it, based on what we saw as not having the consistent trends in the primary and secondary endpoints in the four pivotal studies. That is the majority of my answer and a minor aspect of it is the safety concerns I previously mentioned.

DR. PARSONS: Dr. Cross?

DR. CROSS: It is not very convincing and it is hard to go zero versus 1 on this issue, but I have to vote yes.

DR. PARSONS: Ms. Schell?

MS. SCHELL: No.

DR. PARSONS: Dr. Chinchilli?

DR. CHINCHILLI: No.

DR. PARSONS: My vote is no for the issues I described before. Dr. Apter?

DR. APTER: My vote is yes, I agree with Dr. Cross and if the drug is approved I strongly recommend postmarketing studies.

DR. PARSONS: Dr. Newman?

DR. NEWMAN: No.

DR. PARSONS: Dr. Joad?

DR. JOAD: No, and I would encourage the company to do the longer study.

DR. PARSONS: Dr. Kercsmar?

DR. KERCSMAR: No.

DR. PARSONS: I am going to ask at this point if the FDA has further questions for the panel, not limited just to the four.

DR. CHOWDHURY: No.

DR. PARSONS: I am sorry, I forgot to announce the result of the last vote. I apologize. On question number four we have three votes for yes and seven votes that are no. Any additional questions from the FDA?

DR. CHOWDHURY: No.

DR. PARSONS: Any final comments from the committee? I think then that concludes the meeting. I would like to thank everybody for being here.

[Whereupon, at 2:40 p.m., the proceedings were adjourned.]

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