AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS

ADVISORY COMMITTEE

Tuesday, May 1, 2007

8:00 a.m.

The Hilton Washington DC/North
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

Mark L. Brantly, M.D., Chairman
Teresa Watkins, R.Ph., Executive Secretary

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS
(Voting)

I. Marc Moss, M.D.
Lee S. Newman, M.D.
Calman P. Prussin, M.D.
David A. Schoenfeld, Ph.D.
Eleanor Thornton, M.S., Consumer Representative

TEMPORARY MEMBERS
(Voting)

Mark Eisner, M.D.
Polly Parsons, M.D.
James Stoller, M.D.
William Vollmer, Ph.D.
James W. Gillett, Ph.D., Patient Representative

INDUSTRY REPRESENTATIVE
(Non-voting)

Theodore F. Reiss, M.D.

FDA PARTICIPANTS
(Non-voting)

Robert Meyer, M.D.
Badrul Chowdhury, M.D.
Carol Bosken, M.D.
Feng Zhou, M.S.
Lydia Gilbert-McClain, M.D.

C O N T E N T S

Sponsor Presentation
GlaxoSmithKline

FDA Presentation

<u>P R O C E E D I N G S</u>

Call to Order and Introductions

DR. BRANTLY: Good morning. Let's get started.

My name is Mark Brantly. I am from the University of Florida. I am Chairman of the nPulmonary-Allergy Drugs Advisory Committee.

I would like to remind everybody to please silence your cell phones and other electronic media if possible, so we are not disturbed during this meeting.

Today's meeting we will have a lot of discussion which will result in recommendations at the end of the day from the committee for the Food and Drug Administration. We are aware that members of the media are anxious to speak with the members of the committee and the FDA about those proceedings, however, both the committee members and the FDA must refrain from discussing the details of this meeting with the media until its conclusion.

I call this meeting to order. Let me

introduce the members of our committee at the present time. Bob, will you introduce yourself.

DR. MEYER: I am Bob Meyer. I am Director of the Office of Drug Evaluation II in which the Division of Pulmonary-Allergy Products resides.

DR. CHOWDHURY: I am Badrul Chowdhury. I am the Division Director, Division of Pulmonary-Allergy Drugs, FDA.

MS. ZHOU: My name is Feng Zhou. I am the statistical reviewer for this application.

DR. BOSKEN: Carol Bosken, medical reviewer for the Division of Pulmonary and Allergy Products.

DR. GILBERT-McCLAIN: Lydia Gilbert-McClain, medical team leader, Pulmonary and Allergy.

DR. VOLLMER: Bill Vollmer, Senior Investigator, Kaiser Permanente, Center for Health Research.

DR. SCHOENFELD: David Schoenfeld, Professor of Medicine, Harvard Medical School, and Professor in Biostatistics at Harvard School of

Public Health.

DR. EISNER: Mark Eisner. I am a pulmonologist from the University of California/San Francisco.

MS. WATKINS: Teresa Watkins, Designated Federal Official for this committee.

DR. STOLLER: Jamie Stoller. I am Vice Chair of Medicine at the Cleveland Clinic.

DR. MOSS: Marc Moss, Professor of Medicine, University of Colorado.

DR. NEWMAN: Lee Newman, Professor of Epidemiology and Professor of Medicine, University of Colorado, Health Sciences Center.

DR. GILLETT: Jim Gillett, Professor Emeritus, Environmental Toxicology, Cornell University, and Patient Representative.

MS. THORNTON: Eleanor Thornton, Health Educator and Consumer Representative.

DR. PRUSSIN: Calman Prussin, Senior Investigator, National Institute of Allergy and Infectious Diseases.

DR. PARSONS: Polly Parsons, Chair of

Medicine, University of Vermont.

DR. REISS: I am Ted Reiss, Vice

President, Clinical Research, Merck Research Labs.

 I am the non-voting industry member.

DR. BRANTLY: Thank you very much.

Conflict of Interest Statement

MS. WATKINS: I will now read the Conflict

of Interest Statement.

The following announcement addresses the

issue of conflict of interest and is made a part of

the record to preclude even the appearance of such

at this meeting.

Based on the submitted agenda and all

financial interests reported by the committee

participants, it has been determined that all

interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for an

appearance of a conflict of interest at this

meeting with the following exceptions.

In accordance with 18 USC Section

208(b)(3), full waivers have been granted to the

following participants.

Dr. Polly Parsons for serving on a competitor's advisory board for which she receives less than $10,001 per year; Dr. David Schoenfeld for consulting for two competing firms for which he receives less than $10,001 per year per firm, also, for his employer's unrelated study for a competing firm, for which his employer received less than $100,001 per year; Dr. William Vollmer for his employer's related study, which is funded by a consortium of pharmaceutical companies that include the sponsor and two competitors. His employer received between $100,001 and 300,000 per year in aggregate. He also receives less than $10,001 for personal remuneration.

Waiver documents are available at the FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Theodore Reiss is an invited participant as a non-voting industry representative, acting on behalf of regulated industry. Dr. Reiss is employed by Merck.

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 that 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. BRANTLY: Thank you, Teresa.

Now, Dr. Chowdhury has remarks from the FDA.

FDA Introductory Remarks

DR. CHOWDHURY: Good morning.

Dr. Brantly, members of the Pulmonary-Allergy Drugs Advisory Committee, representatives of GSK, and members of the public, I welcome you to this meeting.

This meeting is to discuss the supplemental New Drug Application from GSK to add a COPD indication to the labeling of Advair Diskus 500/50.

Three dosage strengths of Advair Diskus are currently marketed in the United States; these are 100/50, 250/50, and 500/50, with different dosages of fluticasone propionate, and all with a single dosage of salmeterol.

All three dosage strengths are indicated for use in patients with asthma as maintenance treatment. Only one dosage strength, Advair 250/50, currently has a COPD indication and that indication is limited in scope.

The labeled indication is for treatment of airflow obstruction in patients with COPD associated specifically with chronic bronchitis.

Advair 500/50 does not have a label

indication for COPD, because the pivotal studies that formed the basis of approval of Advair 250/50 showed little additional benefit with Advair 500/50, but the higher dose of corticosteroid would have the potential for additional adverse systemic effects.

GSK is now proposing to add a broad COPD indication for Advair Diskus 500/50. The proposed indication that we will be discussing today includes increased survival, reduction of exacerbations, and improvement of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. The claims for increased survival and reductions in exacerbations are both novel for a COPD drug.

I would like to stress one thing that is important to bear in mind in your deliberations and advice to FDA today. Advair Diskus 500/50 is already an approved and marketed product. The outcome of the meeting today does not change the availability of a product for use in COPD patients, but impacts the labeling of an available product,

and FDA has exacting evidentiary standards for giving a specific indication to a product.

The materials that we will discuss today are either already published in the literature or are otherwise available in the public domain, and can be used to inform the practice of medicine irrespective of the results of this meeting.

Therefore, we are seeking your scientific input to decide whether the submitted data provide convincing and substantial evidence to change the labeling of Advair Diskus.

As you listen to the presentations, please keep in mind the questions that are in the briefing document and also posted with 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.

There is an additional thing I want to mention. As you all know, advisory committee

members come on the committee for a period of time and then are rotated out.

We have one committee member whose term is expiring, Dr. Lee Newman, who has been commissioned to service to the advisory committee for the last couple of years.

I would like to present this plaque on behalf of the Agency. The plaque reads: "In recognition of distinguished service to the people of the United States of America."

[Applause.]

DR. BRANTLY: We will miss Lee.

We are now going to move into the next section, which is our sponsor presentation by GlaxoSmithKline. The first presentation will be by Christine Elaine Jones, Vice President, U.S. Regulatory Affairs for GSK.

Sponsor Presentation

Pulmonary-Allergy Drugs Advisory

Committee Meeting

Christine Elaine Jones, Ph.D.

DR. JONES: Good morning.

[Slide.]

My name is Elaine Jones and I am Vice President of Regulatory Affairs at GlaxoSmithKline. On behalf of GlaxoSmithKline, I would like to thank the Agency and the Advisory Committee for this opportunity to share the data we have generated on Advair Diskus 500/50 for the treatment of patients with COPD.

This morning I will start GSK's presentation by giving some perspective to this serious disease, and I will then introduce your speakers for today's presentation.

[Slide.]

The disease currently affects an estimated 20 million Americans and is associated with significant health care costs. During the past year, direct and indirect costs associated with COPD were estimated to be over $37 billion in the U.S. alone. The direct health care costs were over $20 billion, and almost half of that resulted from hospitalizations due to COPD.

COPD is currently the fourth leading cause

of death and does not discriminate between men and women. This means that the disease kills more than 120,000 Americans each year, which equates to one death every four minutes. Most people die every day from COPD than from breast cancer and diabetes combined. Disturbingly, deaths due to COPD are expected to rise and it is anticipated to become the third leading cause of death by the year 2020.

[Slide.]

The burden of COPD on patients is high. Patients experience poor physical functioning and live with the distressing symptoms which progressively worsen. They are frequently unable to work and may become socially isolated.

As well as living with the daily symptoms of a stable disease, patients live with the fear of exacerbations. Exacerbations are the driving force in a downward spiral of decline in lung function, increased symptoms, increased frequency of exacerbations, worsening quality of life, and increased risk of hospitalization.

For those patients hospitalized with an

acute exacerbation of COPD, the prognosis is grim
with a 1 year mortality of 22 percent. Even worse,
for those admitted with respiratory failure, they
have a 1-year mortality of 43 percent.

[Slide.]

Looking at COPD in the context of other
major causes of death in the United States
highlights the significant impact of this disease.
These data collected from 1970 to 2002 show the
age-adjusted death rate from heart disease and
stroke declined while, sadly, death due to COPD has
more than doubled over the same period.

[Slide.]

Increased morbidity and mortality are
significant unmet needs in the management of COPD,
and despite the serious concern, limited treatment
options are available for these patients. In fact,
to date, improvement in lung function, as measured
by FEV_1, has formed the basis for the approval of
all medications for COPD. The products are
indicated to address only the airflow obstruction
associated with the disease, and have not been

shown to address the progressive nature of COPD.

[Slide.]

Currently, Advair 250/50 is approved for patients with COPD associated with chronic bronchitis as maintenance treatment of airflow obstruction as measured by the improvement in FEV_1.

Although Advair 500/50 data were also considered when the 250/50 was approved, the 500/50 dose was not approved as it did not appear to offer a greater improvement in FEV_1 over the Advair 250/50 strength with a higher inhaled corticosteroid dose although no particular safety concerns were identified.

Since our previous submission, we have generated a substantial amount of data including the evaluation of additional endpoints beyond FEV_1, which has enabled us to further characterize the efficacy and safety of Advair 500/50 and has defined the benefit of the higher inhaled corticosteroid dose.

There are, however, no data comparing Advair 250/50 to Advair 500/50 in a single study.

Today, we are here to share the new data on Advair 500/50 in the treatment of patients with COPD, and we are seeking approval for this strength.

[Slide.]

The clinical development program we will share with you today had over 8,000 patients in three pivotal studies including over 2,100 in the U.S. These data will demonstrate how Advair 500/50 addresses some of the unmet medical needs that patients with COPD face including reducing exacerbations and, more importantly, improving survival, and these clinical advances are reflected in our proposed label.

Because this clinical program included a broader population of patients with COPD, including those who may have emphysema alone, the proposed indication is not limited to patients with COPD associated with chronic bronchitis.

[Slide.]

This is the indication for which we are seeking approval and it goes beyond the improvement of airflow obstruction to include an increase in

survival and reduction in exacerbations in patients with COPD including chronic bronchitis and emphysema.

We certainly believe the data you will see this morning will support this indication for Advair Diskus 500/50.

[Slide.]

Following me this morning will be two other speakers starting with my colleague, Dr. Katharine Knobil, who will review the efficacy and safety data from our clinical trials.

Next, Dr. Bart Celli will provide a clinician's perspective into what these data mean for the treatment of patients with COPD. I will then return to the podium and give some concluding remarks and introduce the additional experts we have with us here today, and we will respond to your questions.

Thank you.

Efficacy and Safety Data from the Advair

Diskus 500/50 Clinical Program

DR. KNOBIL: Thank you, Dr. Jones.

[Slide.]

I am very pleased to have the opportunity to share the results of the Advair 500/50 clinical development program for COPD.

The clinical program consisted of 3 pivotal studies which enrolled over 8,000 patients with COPD.

SFCA 3006 was conducted in the United States and formed part of the original submission for Advair in COPD.

TRISTAN, or TRial of Inhaled STeroids ANd Long-Acting Beta Agonists, was conducted primarily in Europe. TORCH, or TOwards a Revolution in COPD Health, was a global study that was conducted in 42 countries with approximately one-quarter of the patients enrolled in the United States.

TORCH was the largest of the three pivotal studies, so I will focus most of the presentation on this trial.

The studies ranged from 6 months to 3 years in duration. All were four-arm studies and evaluated Advair 500/50, which is fluticasone

propionate or FP 500 mcg with salmeterol 50 mcg together in one device, FP 500 mcg alone, salmeterol 50 mcg alone, and placebo.

All study medications were delivered in Diskus device twice daily.

The primary endpoint for SFCA3006 and TRISTAN was FEV_1. All-cause mortality was the primary objective in TORCH.

[Slide.]

The amount of data is quite extensive, so I will provide a summary of the data from the clinical development program in the order that you see here. Further detail is available in your briefing documents.

For the efficacy assessments, I will start with the more conventional measure of FEV_1 and then move on to the other important endpoints in the clinical program including health-related quality of life, exacerbations, and mortality.

For safety, I will discuss the adverse events reported from our larger study TORCH since the large size of the study overwhelmed the adverse

event data from the rest of the clinical program,
and the adverse events reported in the two other
studies were not remarkably different from those in
TORCH.

I will then discuss the safety sub-study
from TORCH which included evaluations of bone
mineral density and eye examinations. I will then
discuss data from the other pivotal studies of
other prospective safety evaluations that were not
collected in TORCH.

Finally, there will be a discussion of the
benefits and risks of Advair 500/50 based on the
data that I will present today.

[Slide.]

Shown here are the baseline
characteristics of the patients enrolled in the
three pivotal studies. While the entry criteria
for the three studies were not identical, in
general, the baseline characteristics reflect
similar populations with moderate to severe COPD.

Small differences were seen in ethnic
origin and reversibility, but did not have a

significant impact on the clinical findings.

[Slide.]

Although a number of efficacy endpoints were evaluated in these three studies, I will focus on those that had been associated with increased mortality in patients with COPD. This slide shows the key efficacy endpoints that I will be discussing today and the studies that contribute data to each endpoint.

FEV_1 and health related quality of life were collected in all of the studies. TRISTAN and TORCH contributed to the exacerbation rate data, and TORCH was the only study designed specifically to assess all-cause mortality.

[Slide.]

I will now focus on the FEV_1 data. In patients with COPD, lung function declines over time and eventually can lead to respiratory failure. Therefore, it is not surprising that lower lung function is associated with worse outcomes including increasing exacerbation rates and mortality.

Spirometry is an important well-accepted and reproducible measure of the clinical status of patients with COPD. FEV_1 is well accepted by regulatory agencies as a robust endpoint and has formed the basis for approval for all COPD medication available today.

[Slide.]

Trough FEV_1 was the primary endpoint for Study 3006 and the data for this endpoint are shown on this slide. On this graph and throughout the presentation Advair will always be presented in purple, salmeterol in green, FP in orange, and placebo in gray. The Y axis shows the change in FEV_1 in milliliters, and the X axis shows the time in weeks.

Results from Study 3006 showed that treatment with Advair resulted in significantly greater improvement in trough FEV_1 compared with both salmeterol and FP, as well as placebo after 6 months. Post-dose FEV_1 was also measured in this study and showed a similar trend.

[Slide.]

In TRISTAN, mean change in trough FEV_1 was also the primary endpoint. Similar to Study 3006, the patients receiving Advair had significantly better improvement in FEV_1 than salmeterol, FP, and placebo.

The improvement in FEV_1 that was seen with Advair was maintained over the entire year of the study.

[Slide.]

FEV_1 was not the primary endpoint for TORCH, but over the first year of the study, the results were comparable to those seen in TRISTAN. Over the entire 3 years of TORCH, the improvement in post bronchodilator FEV_1 with Advair was significantly greater than both salmeterol and FP at each time point.

After an initial improvement in FEV_1 in each treatment group, it took approximately a year and a half for patients on salmeterol or FP to return to baseline, while it took approximately 2 1/2 years for patients on Advair to return to their baseline FEV_1.

In addition, a post-hoc analysis showed a significant difference in the rate of decline of FEV_1 from Week 24 between each active treatment and placebo with a 39- mL year decline on Advair versus a 55-mL decline on placebo.

These data are quite exciting since it is the first study that has suggested that treatment with Advair or its components can have an impact on the rate of decline of FEV_1.

[Slide.]

Overall, the data from the pivotal studies demonstrated very consistent results. Advair significantly improved lung function over salmeterol, FP, and placebo in all three studies.

It was also encouraging to see the decrease in rate of decline in lung function for Advair versus placebo which we have not seen in our previous studies.

While FEV_1 is a very important endpoint, it only measures one aspect of this very complex disease, and this is why we also measured other clinically relevant endpoints in our studies.

[Slide.]

Now, I will present some of the data on the health related quality of life, which was the secondary endpoint in all three studies, however, I will only present the data from TORCH, as it is the longest and most informative trial. The results from Study 3006 and TRISTAN showed similar results and the data are available in your briefing documents.

[Slide.]

Health-related quality of life was measured in the clinical program because it is important to determine the impact of COPD on patients and whether this changes with treatment. In patients with COPD, health-related quality of life is known to decline over time and poor scores are associated with worse outcomes including increased exacerbation frequency and mortality.

[Slide.]

An improvement in the SGRQ is reflected by a decrease in score. Advair significantly improved health-related quality of life versus salmeterol,

FP, and placebo. There was a 3.1 unit difference in the SGRQ for Advair versus placebo, which approached, but did not reach the minimally important difference of 4.

The differences between Advair in each treatment arm were sustained over the three years of the study. While it is well accepted that health-related quality of life declines over time in patients with COPD, the SGRQ in the patients receiving Advair had not yet returned to their baseline value even after 3 years of treatment, unlike the patients treated with salmeterol and placebo.

In the pre-specified responder analysis, patients receiving Advair 500/50 were nearly twice as likely to have significantly better health status than those on placebo and were 1 1/2 times more likely than those on salmeterol.

[Slide.]

Even though the MID was not met when compared with placebo, the data from all three studies showed consistent improvements with Advair

and health-related quality of life, and similar to the FEV_1 data, Advair demonstrated a significant improvement over salmeterol, FP, and placebo.

The data from TORCH showed that Advair maintained health-related quality of life for three years in the setting of this debilitating and progressive disease.

[Slide.]

Next, I will discuss the exacerbation data. I will be presenting the data from TRISTAN and TORCH as Study 3006 was not designed to evaluate exacerbation rate.

[Slide.]

Reducing exacerbations in patients with COPD is an important goal of therapy. Exacerbations are common and often have serious consequences. Once a patient begins to experience exacerbations, the likelihood of further exacerbations increases, and the recovery from each exacerbation may be prolonged or even incomplete.

A higher rate of exacerbations is associated with a more rapid decline in lung

function, declining health status, and an increased risk of hospitalization. A higher rate of exacerbation has also been linked to mortality.

[Slide.]

It is generally accepted that an exacerbation is a worsening of symptoms beyond day-to-day variation that requires a change in management.

The primary exacerbation endpoint for both TRISTAN and TORCH included all moderate to severe exacerbations. Since it is the patient who usually seeks help for a deterioration and perceived help, it is reasonable to use a definition of an exacerbation that did not imply etiology, but rather the level of health care utilization.

In the clinical program, a moderate exacerbation was defined as one requiring treatment with antibiotics or systemic corticosteroids, while a severe exacerbation was one that required the patient to be hospitalized. This is a clinically relevant way to define exacerbations because it is reflective of how physicians manage their patients

in a clinical setting.

[Slide.]

As I mentioned previously, exacerbations are common and this is supported by the data from TRISTAN and TORCH. As you can see here, in the one-year TRISTAN study, there were almost 1,500 exacerbations and there were more than 13,000 exacerbations reported from TORCH.

In both of these studies, the primary analysis of exacerbations was the determination of rate per patient per year. This analysis is clinically meaningful as it takes into account those patients who may have had more than one exacerbation during the study, and also accounts for the varying time the patients remained on treatment.

[Slide.]

On this and the next few slides, the annual rate of exacerbations is shown in the box on the right. The bar graph represents the percentage reduction in exacerbations with Advair compared with the other treatment arm.

The first bar compares Advair to placebo, the second bar shows the added benefit of Advair over FP, and the third bar shows the benefit of Advair over salmeterol.

Shown here are the results for the exacerbation rates from TRISTAN. As mentioned previously, this study was a year in duration and there was a requirement for patients to have had at least one exacerbation in the year prior to entry.

The exacerbation rates ranged from 1.47 per patient per year in the placebo arm down to 1.00 in the Advair arm. This translated into a reduction in exacerbation rate of 32 percent when compared with placebo, shown here by the first bar.

There were also reductions in exacerbation rate with Advair when compared with components. Although these reductions were not statistically significant, Advair showed a favorable trend over salmeterol and FP.

[Slide.]

In TORCH, patients were not required to have a history of exacerbation prior to entry, but

the long duration of the study made it ideal to look at exacerbation rates over time.

In this study, the overall exacerbation rate was slightly lower than seen in TRISTAN with 1.13 exacerbations per patient per year in the placebo arm and 0.85 in the patients receiving Advair. This difference in rate translated into a 25 percent decrease in the rate of exacerbations with Advair versus placebo, which was highly statistically significant.

In addition, Advair significantly reduced exacerbations by 12 percent compared with salmeterol and 9 percent compared with FP. Even though patients were not required to have a history of exacerbations prior to entry, and only 57 percent reported an exacerbation in the year prior to the study, we see a substantial decrease in exacerbation rates with Advair.

Approximately one-quarter of the exacerbations required hospitalization. Advair significantly reduced these exacerbations by 17 percent when compared with placebo. There were no

significant differences between Advair and
components for this endpoint. It is likely that
because of the low number of severe exacerbations,
differences were not discernible between Advair and
components.

[Slide.]

Systemic corticosteroids are associated
with a number of adverse clinical outcomes
including osteoporosis and cataracts. Therefore, a
reduction in the administration of systemic
steroids should be of benefit to patients.

[Slide.]

Here, we see the results of pre-specified
analysis from TORCH showing that treatment with
Advair reduced the rate of exacerbations that were
treated with systemic corticosteroids by over 40
percent over placebo and nearly 30 percent over
salmeterol.

TRISTAN showed a 45 percent reduction with
Advair compared with placebo and a full description
of this analysis is available in your briefing
document.

These two large clinical trials have shown a consistent reduction in exacerbation rate even in TORCH where patients were not required to have a history of exacerbations prior to entry into the study.

In TORCH, Advair also significantly reduced moderate and severe exacerbations in those requiring systemic corticosteroids when compared to both salmeterol and FP, and when all moderate to severe exacerbations were taken into account across both studies, the greatest benefit was always seen with Advair.

Advair has consistently demonstrated an improvement in lung function, health-related quality of life, and exacerbations, which are some of the key predictors of mortality in patients with COPD, so an important question is whether treatment with Advair had an impact on the endpoint of survival since there are no other prospective studies of pharmacotherapy apart from oxygen that address this endpoint, TORCH has broken new ground for the study of COPD.

[Slide.]

Before I get to the results, there is some background that will be important to be aware of to understand the conduct of the study and the context of the results.

There were three external committees that were necessary for the execution of TORCH. The Steering Committee worked with GSK to design, implement, and manage the study.

In order to have consistent assignment of cause of death across this very large study, TORCH had an independent Clinical Endpoint Committee. The CEC was blinded to study treatment allocation, and assigned a primary cause of death and whether the death was COPD related.

The Safety and Efficacy Data Monitoring Committee independently conducted the two planned interim analyses and performed safety reviews every six months.

[Slide.]

TORCH was a challenging study to design and run. It was a very large study that was

conducted in over 400 centers in 42 countries, and enrolled over 6,100 patients.

In order to remove the potential uncertainty around the assessment of the cause of death, all-cause mortality was chosen as the primary endpoint. It was also chosen to ensure that treatment was not reducing mortality from one cause while increasing mortality from another. COPD-related mortality was also assessed.

Since the study was three years long, it would have been unethical to withhold all COPD care, so patients were allowed to take any COPD medications during study treatment except for long-acting bronchodilators, inhaled corticosteroids, and systemic corticosteroids.

[Slide.]

All patients were included in the primary analysis of mortality at three years regardless of the time on study treatment. In addition, patients who withdrew early from the study could go on to take treatment, such as Advair, but were still counted in their original treatment group.

Therefore, the analysis is a conservative one and probably underestimated the treatment effect. It is important to have complete follow-up in a mortality study in order to achieve the most robust results. Patients had survival status assessed at three years even if they had withdrawn from study medication.

After three years, only one patient out of 6,112 had an unknown survival status. This patient was known to be alive at two years.

[Slide.]

This graph shows the rates of withdrawal from study medication over time using ascending Kaplan-Meier curves with Advair having significantly lower withdrawal than salmeterol and FP and placebo.

Withdrawal from the placebo group was 44 percent, while only 34 percent of patients on Advair withdrew early from treatment. In the United States, this difference was even larger with 52 percent of patients on placebo and 39 percent of patients on Advair withdrawing.

As I mentioned on the previous slide, patients who withdrew could have taken any COPD medication after withdrawal including Advair, but were still counted in their original treatment arm when survival status was assessed at three years. Thus, the magnitude of the treatment effect is likely underestimated.

It is important to consider the effect of premature study drug discontinuation for all analyses from TORCH and that the more severe patients tended to withdraw earlier. Therefore, those patients remaining in the study tended to be healthier than those who withdrew.

[Slide.]

Shown here are the results for the probability of death from all causes from the placebo group in TORCH.

[Slide.]

The primary comparison in TORCH was between Advair and placebo for all-cause mortality. The primary analysis was a log-rank test stratified by smoking status. Advair demonstrated

an absolute reduction in all-cause mortality of 2.6

percent versus placebo over the three-year study,

which translated to a 17.5 percent risk reduction.

These curves demonstrate that the

proportional risk reduction in mortality was

consistent throughout the three-year study. The p-

value was 0.052, which was just above the

predetermined level of significance after

adjustment for two interim analyses. This is the

first time a medication has demonstrated a survival

benefit in patients with COPD.

On-treatment mortality, which included

approximately one-half of the deaths, had a similar

magnitude of effect with 23 percent reduction for

Advair compared with placebo.

[Slide.]

There were also two pre-specified

supporting analyses of the primary endpoint. The

first accounted for clinical predictors of

mortality using a Cox's proportional hazard's model

adjusting for smoking status, age, sex, region,

baseline FEV_1, and body mass index. The hazard

ratio of 0.811 corresponds to a risk reduction of 18.9 percent with a p-value of 0.031.

A second analysis was performed in response to a request from the FDA in order to more fully account for the stratified nature of the randomization. This was a log-rank analysis stratified by smoking status, country, and participation in the safety sub-study. The hazard ratio of 0.815 corresponds to a risk reduction of 18.5 percent with a p-value of 0.036.

These pre-specified analyses accounting for the clinical predictors of mortality and for the stratified randomization were statistically significant and therefore support our confidence in the magnitude and the relevance of the treatment effect seen in the primary analysis.

[Slide.]

Here are the data that I previously showed you for the primary comparison of Advair versus placebo. Here are the results for all four treatment arms for the mortality endpoint. It is important to note that TORCH was not powered to

detect a mortality effect between active treatment,
but the component arms were included in the study
to help determine the relative contribution of each
to the effect of the combination.

The statistical comparisons for Advair
versus components and components versus placebo are
shown on the next slide.

[Slide.]

When we designed the study, it was powered
to compare Advair versus placebo, and we also
expected favorable trends for salmeterol and FP
versus placebo, as well as for Advair over
components.

When compared with placebo, salmeterol
behaved as we expected, while FP was slightly lower
than placebo. While the FP curve crossed the
placebo line, as shown on the previous slide, the
hazard ratio was 1.06, indicating no survival
difference for FP alone versus placebo, and as
expected, Advair showed a favorable trend over
salmeterol, and in addition, there was a
statistically significant improvement when compared

with FP.

So, both components of the combination were needed to achieve the greatest benefit and survival.

[Slide.]

We wanted to see if there were consistent treatment effects for all-cause mortality within patient subgroups. It is important to remember that whenever we cut the data into subgroups, we expect to see some increased variability in the results and, of course, any subgroups will have smaller numbers of events than the overall data, thus reducing the power to detect differences.

When we listed the variables that are known to have an effect on mortality by themselves, we found that there was no interaction with treatment. In other words, the survival benefit with Advair went in the same direction within each of these subgroups.

[Slide.]

For example, when we look at mortality by age, we see that predictably the highest mortality

was in the older patients, however, the improvement
in mortality between Advair and placebo was seen
consistently in each of the age groups.

[Slide.]

Furthermore, we looked at the hazard ratio
for all-cause mortality after excluding each
individual country. The blue dot on this graph
represents the overall hazard ratio for mortality
with all countries included.

When we looked at the hazard ratios with
each individual country excluded, shown by the
orange dots, the p-value only changes very
slightly. More importantly, the hazard ratios
remained remarkably stable, ranging from 0.79 to
0.84, resulting in reductions in mortality from 16
to 21 percent.

We believe that the mortality data are
robust because within all of the subgroups that we
looked at, we have seen very consistent results.

[Slide.]

For each death that occurred in the study,
the Clinical Endpoint Committee gathered all

available documentation and made an assessment of the primary cause of death and whether the death was COPD-related by a set of a priori criteria.

These criteria were that COPD was the primary cause of death, or the terminal event was hypercapnic respiratory failure or failure to be liberated from a ventilator, or if the patient likely would have survived if COPD was not present. While the death may have been related to the patient's COPD, it may not have been the primary cause of death.

There were 875 deaths by the end of three years. Patients with COPD usually suffer from other comorbid conditions and COPD is often not the primary cause of death in these patients.

[Slide.]

Shown here are the primary causes of death as adjudicated by the CEC. As one would expect, cancer-related deaths were similar across the treatment groups, while cardiovascular and pulmonary deaths generally followed the same pattern as all-cause mortality.

Interestingly, cardiovascular deaths were lower in the salmeterol-containing groups. There was a higher number of pulmonary deaths in the FP arm, and so we looked further at the causes of death within this category.

[Slide.]

This is the adjudication of deaths within the pulmonary category. As you can see, the majority of deaths were due to COPD. Most of these resulted from COPD exacerbations, with the lowest number occurring in the patients receiving Advair, which is consistent with the data that I have already shown you.

There was a higher number of pneumonia-related deaths in the FP arm, and I will discuss this further in the Safety section of the presentation. Overall, Advair had the lowest number of pulmonary deaths compared with placebo, salmeterol, and FP.

[Slide.]

In this study, it was important to also look at COPD-related mortality. Approximately,

one-half of the deaths in this study were related to COPD, which includes more than just those adjudicated to the pulmonary category.

Although the study was not powered to detect the difference in COPD-related mortality, a notable trend in favor of Advair versus placebo was observed. The hazard ratio for Advair versus placebo was 0.776 representing a 22.4 percent reduction in risk of dying at anytime within three years from a COPD-related cause.

[Slide.]

When we look at the components, there was a 23 percent reduction in the risk of dying for Advair compared with salmeterol, and a 33 percent reduction in risk of dying for Advair compared with FP.

This analysis supports the results seen with all-cause mortality by demonstrating a consistent magnitude of response for reducing the risk of dying from a COPD-related cause for Advair compared with placebo.

[Slide.]

Treatment with Advair led to a 17.5 percent reduction in the risk of dying over three years versus placebo. The magnitude of the effect was corroborated by two supporting analyses that incorporated clinical predictors of mortality, and COPD-related mortality also showed a similar trend.

We believe that the 17.5 percent reduction in all-cause mortality seen with Advair represents a clinically important improvement in survival. The magnitude of the treatment effect is similar to other studies of mortality seen in patients with COPD and in other therapy areas.

The results of all the analyses are affected by the fact that patients could have taken any COPD medication after withdrawal, including Advair, and this conservative estimate of the treatment effect likely underestimated the magnitude of the mortality benefit.

Therefore, we believe that having a p-value of 0.052, that is just above the conventional cutoff, should not detract from the clinical importance of these results.

[Slide.]

In summary, I have shown you that Advair improves lung function, and this was replicated in all three pivotal studies.

We have also seen exciting new data in which Advair reduced the rate of decline in lung function, a result that may have important implications for disease progression. Advair consistently improved health status across all three studies and, in TORCH, health status was maintained over the three years of the study.

I have shown you that Advair consistently decreased the rate of moderate to severe exacerbations, as well as reducing the need for systemic cortical steroids, and most importantly, Advair reduced the risk of dying.

For the first time ever, a medication for COPD has demonstrated the ability to improve survival in a large, well-controlled study. The number of patients that we have treated in these three clinical trials is significant and offers the largest body of evidence yet generated for a

medication for the treatment of COPD.

For the data that I have shown you today, the greatest benefit was always seen with Advair. We believe that these results will be very encouraging to patients with COPD and to the physicians who care for them.

That concludes the efficacy portion of the presentation. I will now share with you the safety results from the Advair pivotal studies.

[Slide.]

Extensive safety monitoring has been performed to specifically assess the long-term safety of inhaled corticosteroids. This has been done by focusing on events of special interest including lower respiratory tract infection, bone disorders, eye disorders, and HPA axis disorders.

We have also studied cardiovascular adverse events which have been of interest for inhaled beta agonists. Bone and eye disorders were also evaluated by prospective assessments in the TORCH Safety Sub-study and HPA-axis and cardiovascular assessments from the other pivotal

studies.

The safety exposure from the three pivotal studies is extensive and consisted of over 8,000 patients with COPD, over 2,000 of whom were treated with Advair. This slide shows only the time on study medication from TORCH as this was approximately 10-fold higher than from TRISTAN and Study 3006 combined.

There were no remarkable differences between the adverse event reporting from TORCH and the other two studies, so I have only discussed the adverse event data from TORCH.

[Slide.]

In TORCH, the adjusted total time on study medication was higher with active treatment compared with placebo. There was a 13 percent increase in the time on treatment for Advair compared with placebo and an 8 percent increase for both salmeterol and FP.

This difference in time on treatment reflects the differential withdrawal across the treatment which should be kept in mind when

reviewing the adverse events collected from TORCH,

because a longer time on treatment increases the

opportunity to report adverse events.

To account for differential withdrawal,

rates of adverse events per 1,000 treatment years

of exposure were calculated to adjust for time on

treatment.

[Slide.]

Adverse events of special interest were

defined upfront and included the adverse events

shown on this slide. These events were reported

from the sites as part of the normal adverse event

reporting process.

[Slide.]

There was a higher number of patients with

lower respiratory tract infections including

pneumonia and bronchitis in the Advair 500/50

group. When the lower respiratory tract infections

were examined, it was found that the increased

reporting was predominantly due to pneumonia.

As a result, a further investigation of

physician-reported pneumonias was conducted to

allow for a more complete summary. This included

several different types of adverse events preferred

terms for pneumonia, which are listed in your

briefing document, and these analyses will be

discussed further in a moment.

I will also discuss the bone and eye

disorders in greater detail later in this

presentation. However, I will not talk further

about HPA-axis adverse events since the incidence

was quite low. There were only 4 reported events,

2 on placebo and 2 on FP. Later in the

presentation, I will discuss the serum cortisol

data that was collected in the other pivotal

studies.

[Slide.]

To better understand the impact of

pneumonia on patients in TORCH, a more detailed

summary of pneumonia adverse events is shown here.

 The increase in reporting of pneumonia as a single

term prompted a further investigation of physician-

reported pneumonias to be inclusive of all adverse

event pneumonia terms.

All reports of pneumonia were clinical diagnoses by the investigators and there was no requirement in the protocol for a chest x-ray or other diagnostic criteria.

An increased reporting of pneumonia adverse events and serious adverse events was observed for patients treated with Advair and FP. It is important to remember that adverse events and serious adverse events were only reported while the patient continued on study medication. As previously discussed, patients treated with Advair remained in the study longer than patients treated with placebo.

When the data were corrected for exposure to study medication, the increase in time on treatment did not account for the difference in pneumonia events, and there was still a larger number of events reported in the inhaled corticosteroid-containing arms of the study.

[Slide.]

This slide presents the probability of having a pneumonia reported at any time during the

study while patients were receiving treatment.
Pneumonias were not uncommon in patients with COPD
even in the placebo arm. The probabilities ranged
from 12.3 percent on placebo to 19.6 percent on
Advair.

The time to first event analysis shows a
hazard ratio of 1.64 for patients treated with
Advair when compared with placebo.

[Slide.]

Because pneumonias can have serious
consequences in patients with COPD, it was
important to determine if there were any serious
sequelae after pneumonia in the study. Here, we
see the numbers of fatal pneumonia adverse events.
 It was reassuring to see that there was no
corresponding increase in mortality with Advair due
to pneumonia although the numbers are small.

This can be seen in both the number of
fatal serious adverse events as reported by the
investigators, as well as the rate of pneumonia
death when corrected for exposure to study
medication. It was also true for deaths

adjudicated by the Clinical Endpoint Committee.

Deaths from pneumonia on FP were higher than the other groups, but due to the small numbers of events, the clinical significance of this finding is unknown.

[Slide.]

An analysis was undertaken to evaluate who would be at greatest risk of pneumonia. This analysis indicated that more severe disease or FEV_1 less than 30 percent predicted, male gender, older age, greater than 65 years of age, and lower BMI were associated with a higher risk of pneumonia across all treatment groups, however, the review of the data did not show any risk factors specific to the inhaled corticosteroid-containing groups compared with the non-inhaled corticosteroid-containing groups.

Although the patients in these subgroups were generally more prone to pneumonia whether receiving FP or not, these same groups of patients also derived benefit from Advair 500/50 in reduction in mortality.

The pathogenesis of increased pneumonia with inhaled corticosteroids is unclear. We do not know if local immunosuppression is occurring, but it was reassuring that of the cultures that were taken in the study, there was no evidence of an increased risk of opportunistic infections.

To better understand who may be at increased risk, we have utilized databases even larger than TORCH to help with these unanswered questions.

Five observational studies in U.S. and UK cohorts were designed, three to evaluate the natural history of pneumonia in patients with COPD including calculating incidence rates over time and identifying risk factors associated with pneumonia, and two further observational studies to specifically measure the risk of pneumonia associated with the use of Advair in patients with COPD.

The effect of dose and duration of therapy will also be evaluated.

[Slide.]

Pneumonia is serious and can be especially debilitating in patients who already have compromised lung function. In TORCH, there were more pneumonias reported in patients receiving Advair.

While there was an increase in pneumonias reported, there were significantly fewer exacerbations and hospitalizations. There was also improved survival with Advair and no apparent increase in pneumonia-related deaths.

To put these data into context, remember that there were over 13,000 exacerbation events in TORCH. In contrast, there were fewer than 1,000 pneumonias reported across the treatment groups.

It is generally recognized that exacerbations of COPD are associated with infection. In TORCH, all pneumonia events that were treated with antibiotics met the protocol definition of a COPD exacerbation. While there was an increase in the reporting of pneumonias, which were a subset of exacerbations, the overall rate of moderate to severe exacerbations was reduced with

Advair.

The current product labeling already has wording about the potential increased risk of pneumonia, and the proposed label has been expanded to include the findings from TORCH, and the medication guide will provide guidance to patients.

To ensure that the information in the label is properly communicated, we will educate health care professionals on the increased risk of pneumonia in patients with COPD treated with Advair. GlaxoSmithKline will work with the FDA in order to ensure this information is communicated accurately and effectively.

[Slide.]

Another adverse event of special interest is the incidence of fractures. Fractures are an important safety endpoint to address in a long-term study of an inhaled corticosteroid-containing medication.

The percentage of patients reporting a fracture was 4 to 5 percent across treatment groups. The rate of fracture per 1,000 treatment

years was low across groups with 19 per 1,000

treatment years for patients receiving placebo and

22 per 1,000 treatment years for patients receiving

Advair.

[Slide.]

Eye disorders were another predefined

adverse event of special interest that were

collected during the study. The rate of ocular

events per 1,000 treatment years was low across the

treatment groups. It was 14 per 1,000 treatment

years for patients receiving placebo and 19 per

1,000 treatment years for patients receiving

Advair. This corresponds to a difference of 5 eye

disorder events per 1,000 treatment years between

Advair and placebo.

[Slide.]

I have just presented the adverse event

data as reported by the investigators in TORCH. I

will now discuss the prospective evaluations of the

potential long-term effects of FP that were

conducted in TORCH as part of the TORCH safety sub-

study.

658 subjects from 88 sites in the United States participated in annual assessments of bone mineral density and eye examinations. This study included nearly one-half of all of the patients enrolled in the United States.

The sub-study required that all patients from each site perform all safety assessments as part of their participation in TORCH. I will begin by discussing the bone mineral density data.

[Slide.]

Osteoporosis is an important health concern for the elderly even if they don't have COPD. Even so, it was surprising to see that overall, over one-half of the patients had osteoporosis or osteopenia based on T score at baseline.

When broken down by gender, 55 to 67 percent of women and 44 of the 51 percent of men across the treatment groups had osteoporosis or osteopenia, so decreased bone mass not just an issue for women.

[Slide.]

This slide shows the results of the bone mineral density at the total hip. The percent change after three years ranged from 1.7 percent in salmeterol to 3.2 percent in Advair. While the salmeterol arm appears to be different from the other three treatments at the final visit, there was no significant difference in bone loss between any active treatment and placebo.

Now, I will move on to the results for the eye exams.

[Slide.]

Cataracts have been associated with the use of corticosteroids, so in the TORCH safety sub-study, we prospectively evaluated the risk of developing cataracts over the three years of treatment. As with bone mineral density, we were surprised by the high incidence of cataracts at baseline, with 61 to 71 percent of patients having cataracts seen on eye examinations.

[Slide.]

These are the numbers that I have just shown you on the previous graph, and since so many

patients had cataracts at baseline, there was approximately one-third of the original group available for further study.

The number of events in the study was low and when corrected for exposure to study medications, there was no difference between groups in the rate of developing cataracts.

[Slide.]

Few patients had glaucoma prior to randomization in the Safety Sub-study, with only 11 patients developing glaucoma during the study. This low number does not allow a robust comparison between the treatment groups.

[Slide.]

In addition to bone and eye assessments performed in TORCH, other prospective safety evaluations were conducted in a subset of patients in the clinical program.

HPA Axis assessments were performed by the measurement of 12-hour serum cortisol in TORCH and 24-hour urinary cortisol in TRISTAN. An assessment of short ACTH stimulation testing was performed in

Study 3006.

When compared with placebo, treatment with Advair resulted in an approximate 20 percent reduction in 12-hour serum cortisol AUC and in 24-hour urinary cortisol.

The incidence of abnormal short ACTH stimulation testing was low and similar across the treatment groups, indicating that patients with COPD were able to respond to acute physiologic stress without impairment.

[Slide.]

In addition, there has been extensive evaluation of cardiac events in the clinical program, which I will summarize here.

ECGs were performed in all patients in Study 3006 and in TRISTAN, and did not identify any clinically significant abnormalities including QTc at prolongation. Holter monitors from a subset of patients in Study 3006 showed no differences in ventricular ectopic events or arrhythmias in the salmeterol-containing treatment groups.

During the three years of treatment, there

was no increase in cardiac adverse event reporting in TORCH. These results are consistent with previous clinical trials of salmeterol and Advair, as well as supported by the lower numbers of cardiovascular-related deaths in the salmeterol-containing arms in TORCH.

[Slide.]

Based on the efficacy and safety data that I have just presented, I will now discuss the overall benefit/risk profile for Advair 500/50 in patients with COPD.

[Slide.]

Advair and its components, salmeterol and FP, have been extensively studied in both asthma and COPD. There are risks and benefits of any treatment that one gives to patients and how these are weighed is dependent on the complexity and the severity of the disease being treated.

COPD is a very serious condition that has had few options that have been approved for indications other than for the improvement of lung function.

There are several potential risks of treatment with Advair. The first is the risk of HPA axis suppression with only 4 events reported in TORCH and no clinically significant changes in prospective assessments, we do not believe that this is of major clinical concern.

Next, based on pharmacology, there had been a concern that beta agonists could increase the risk of cardiac events especially in a population that is already at risk for cardiac comorbidities.

In the entire clinical program, we did not see any increase in adverse events or deaths related to cardiovascular events in any treatment arm. Bone and eye effects are important when considering the long-term use of corticosteroids. It was reassuring that we did not see any clinically relevant differences between the treatment groups especially when adjusted for time on treatment.

Osteoporosis and cataracts are common in patients with COPD as we have seen in the baseline

data from TORCH, but they are also monitorable and treatable, and the potential for these defects are already contained in our current labeling.

Pneumonia is the most serious risk that was identified in TORCH in patients who were in the inhaled corticosteroid-containing arms. There was an increase in the risk of pneumonia in the patients receiving Advair versus placebo, however, because pneumonia presents similarly to COPD exacerbations, and exacerbations are so common, pneumonias are usually detected early and appropriate treatment is often given empirically at the first sign of worsening symptoms, and treatment with Advair did not lead to an increase in pneumonia-related death.

Finally, the proposed label has detailed information for physicians and patients, so that they will be able to recognize the deterioration that requires intervention, so that the risk of pneumonia can be minimized.

[Slide.]

There were also demonstrated benefits with

treatment with Advair, and these improvements were on endpoints that have been shown to be key predictors of mortality.

The improvement in FEV_1 is well recognized and was significant with Advair compared with placebo, FP, and salmeterol in all three studies.

In addition to the improvement in lung function, there was a decrease in the rate of decline of FEV_1, which may have important implications for slowing the progression of this disease.

Quality of life was also improved for Advair in all three studies, which is an important goal from a patient's perspective.

Overall exacerbation rates and exacerbations requiring systemic corticosteroids were decreased with Advair compared with placebo, FP, and salmeterol, and this may also have implications for reducing the progression of disease.

Finally, and most importantly, there was a 2.6 percent absolute reduction in mortality, which

translated into a 17.5 percent reduction in the risk of dying for Advair compared with placebo, a magnitude of effect that is clinically relevant and compares favorably with other well-accepted treatments that reduce mortality in other diseases.

Advair also trended favorably versus salmeterol for both all-cause and COPD-related mortality. Based on the strength of these data, we believe that the benefits clearly outweigh the risks of treatment with Advair 500/50 relative to salmeterol, FP, and placebo, and the data that I have shown today supports the proposed indication.

[Slide.]

Dr. Jones has already shown you this slide of the proposed indication for Advair 500/50 for patients with COPD. As she mentioned at the beginning of the presentation, this indication goes beyond just the improvement of airflow obstruction to include the increase in survival and reduction in exacerbations seen in this clinical program.

[Slide.]

Now, I would like to invite Dr. Celli to

the podium for his perspective on these very important data.

Clinician's Perspective

DR. CELLI: Good morning. My name is Bartolome Celli and I am a pulmonary physician in Boston. I head the Critical Care Pulmonary Division at Caritas St. Elizabeth's and I am a Professor of Medicine at Tufts University, but with a long-standing interest in this disease.

I am very happy to be here. There is always a first and this is my first appearance in front of the FDA. I enjoy it very much and I see a lot of friendly faces, people that I know, and I trust that you will make decisions that are of importance to our patient population.

I would like to provide you with one clinician's perspective. Having said that, I must tell you that I am a member of the Steering Committee and as impartial as I will be, I am excited with the data that I will be presenting.

So, let me start with the outline of the 10 minutes that I am proposing that I will share

with you.

[Slide.]

The first one is I would like to share with you the view of a clinician in terms of what COPD mortality represents.

Second, I would like to propose to you that we can change mortality in COPD. We have had a negative approach to this disease, oxygen therapy, smoking cessation, and TORCH.

Thirdly, I would like to expand our lessons from this field into those of cardiovascular and make some comparisons. I would like to then make some clinical comparisons using those areas, and finally, provide you with a summary.

So, let me start by sort of sharing with you that some of these are lessons that we have known for a while and some of these are lessons that we have from today.

Let me go back to the same graph that Dr. Knobil presented a few minutes ago, changed a little bit, so we can represent it in time.

[Slide.]

During my lifetime, my professional
lifetime, this is what our brothers, the
cardiologists, neurologists, and internists have
done to mortality from coronary heart disease and
stroke. As a person reaching that age at which I
am at risk, I am grateful to them that have allowed
me to reach this age with that possibility dropping
over time.

Even my other cousins, the oncologists,
and those that deal with diseases that we think are
irreversible, having impacted on mortality over the
same time by 32 percent. I know most of you are
not at risk for any of these diseases because you
look younger than I do, but I believe that we must
give credit to those individuals who have been able
to make those curves possible.

In the same time, a little shamefully, I
am showing you that for the disease that I care a
lot about, and some of you do, too, there has been
this increase over time affecting both men and
women, and it is something that we have to face and

try to change.

[Slide.]

Now, we have lessons that we can impact on this disease, and I am going to take you through some of them, not all of them, but the ones that I consider more important, and I will start with the first one, the oxygen trial.

[Slide.]

There were two prospective randomized trials and from those trials I have taken the extremes to show to you that we can impact on survival even if we don't change the underlying lung function.

On the Y axis we have survival, on the X axis time in months. The purple line represents patients included in the randomized trial done in the UK by the MRC where they were high hypoxemic and did not receive oxygen.

[Slide.]

These lines represent what we know. People who have low oxygen do not do well. If then the same group is randomized to receive oxygen, we

get the line depicted up above, and this is the biggest difference and the biggest impact we have had on the disease. There was an absolute risk reduction of death of 21 percent and the relative risk reduction, this is magnified to a 34 percent.

So, there is no question that we can impact on mortality and COPD with minimal changes on the lung function. This is the greatest benefits to risk ratio, and I would like to use this as the highest standard that we can achieve.

[Slide.]

Let us look at smoking cessation in an intent-to-treat design. For that I am using Nick Anthonisen's Lung Health Study. This was a study in which patients were randomized to receive therapy and amongst other things, they were randomized to receive a good advice to stop smoking and the best available therapy for smoking cessation at that time.

[Slide.]

On the Y axis we are going to be using again survival, on the X axis time, and now we have

a 14.5 year follow-up, the longest we have had for any cohort.

In yellow, we have the intent-to-treat special intervention group, in orange, the usual care group. At the end of 14.5 years of therapy--I am sorry, of the beginning of the study--there was a drop of relative risk reduction of 15 percent in favor of the smoking cessation intent-to-treat.

Now, what I have done on the next portion of the slide is to trace a line, an arrow at 3 years to see what would have happened if we look at smoking cessation intent-to-treat at 3 years, and, yes, there is a difference in favor of implementing the therapy at the magnitude as reduced over that period of time.

The reason why I think it is important from the clinician's point of view is that patients with COPD have a long course, 3 years will be long in terms of study, still perhaps doesn't represent the real 20, 30 years that the disease has as a horizon.

[Slide.]

Now, let me turn around and see what we can learn from TORCH. I call them New Lessons because they are right off the press, but they are very exciting in terms of being a large study and the kind of study that we need for our patient population suffering from this disease.

[Slide.]

I am taking again, just as Dr. Knobil did, the placebo versus Advair survival curves to show to you that there was again a difference of -17.5 percent, and I acknowledge the p-value to be 0.052.

However, if we look at it differently, if I looked at it as accepting that that was a valid percentage, the number of patients needed to treat to perhaps save one life, we have a number of 39, and I want you to remember this as we extrapolate some of these findings to the ones that come from other areas of medicine.

As a person who deals with a lot of exacerbations or patients who exacerbate, they tend to exacerbate usually on Friday as I am leaving the hospital. Those of you that do pulmonary find this

a frequent situation. You make sure there is no
resident or fellow around you, and you order your
systemic steroids and antibiotic and pray that they
don't call you on Saturday and Sunday.

[Slide.]

Decreasing exacerbation rates is
important. This is our angina, this is our
possible MI. If you look at this table, again
taken from the TORCH trial, there was a significant
reduction in the Advair compared with placebo,
salmeterol and fluticasone had an impact, not as
big as the one provided by the combination.

[Slide.]

Post-bronchodilator FEV_1, I am using again
the same slide, but I want you to concentrate
mainly on the rate of decline of the lung function,
the point between the 24 weeks and the 156 weeks.

This is the placebo line and I want you to
compare it with the combination line, and there was
a difference in the rate of decline of FEV_1. For
those of us brought up on the FEV_1 anchoring of
COPD, this is the first time that this is shown.

The individual components also behaved positively. The slopes were different from the placebo, but the absolute magnitude of change of FEV_1 was lower than that achieved by the combination.

Quality of life was already presented.

I am using the same slide to highlight that at the end of the study, the patients on the combination had not returned to baseline, and although three years in a progressive disease is not as good as it would have been 15 years, I do believe that if I am a patient who started on a therapy and I am better three years later than I was at the beginning, to me, that is an important clinical outcome.

I would like to take all three outcomes in the context of the final observations on mortality

Let me just make in a graphic representation, the thinking process that goes through the mind of a doctor who orders a medication. What are my risks? Patients on Advair or inhaled corticosteroids will get hoarse and they

will have thrush in some instances, and all of us who deal with those patients have seen that problem.

We do and are aware of eye effects and I am reassured that the TORCH trial provided us with (a) an indication that a lot of people have eye problems before they get started on anything, and (b) that when we put them on therapy, things are not as bad as I thought they would be.

The same thing can be said about bone effects and I am surprised, worried, and hopeful that we will find out what the reasons in possible patients that may be a risk are for the development of pneumonia.

On the other hand, the benefits of an improvement in FEV_1 with a change in the rate of decline, an improvement in the quality of life that does not return to baseline at three years, a decreased number of exacerbations, and an improvement in survival in my opinion outweigh the risks if used with caution.

[Slide.]

Let me translate the findings from other areas. My heroes all my life have been the cardiologists. They have impacted on the diseases that affect a lot of us with very good thinking, simple measures, and superb studies.

I want to compare some of the cardiovascular trials toward the end come back with a summary. Let me start with the beta blockers compared with placebo.

[Slide.]

I am taking one of several trials mainly because this is one that I know well. It was in a reputable journal and what I am showing you here is the survival rate on patients on carvedilol compared with placebo. Notice that the overall mortality was relative low. There was a difference of 4.6 percent when translated by the magnitude of the study on the time, this was a 65 percent reduction in mortality. Excellent for the six months that is given for a bad disease.

[Slide.]

I like the study, the GUSTO trial, which I

also pulled out of the New England Journal of Medicine because it involved four arms, and I would like to describe the study a little more in detail.

It's a randomized trial in several countries. They have four thrombolytics in acute myocardial infarction. They require large numbers of patients and cardiologists know how to do that better than anyone, 41,000 patients, 30 days follow-up, with a very small death rate of 7.4 percent.

[Slide.]

On the Y axis I will have mortality again. In the inverted Kaplan-Meier curves, on the X axis base, streptokinase plus heparin sub-Q, streptokinase plus heparin IV, streptokinase plus tPA, the same mortality, and tPA showing a 1 percent difference at the end of 30 days.

However, the relative risk reduction of 10 percent is larger than the 1 percent would suggest, and you need to treat about 100 patients to save one life over 30 days.

The reason why I like the study, it is

four arms, and it does show a small effect, but one that has some impact in how we view medicine and treat our patients.

[Slide.]

Finally, I have chosen statins. I don't think anyone in this room but me is on statins, but statins are something that have become the mainstay of therapy. Let us look at some of the data.

There are five trails against placebo, all of them within the range of the TORCH trial, 4- to 9,000 patients to total 30,000 patients.

Mean follow-up not too far from what we are talking on this trial that we are presenting, and the mean relative reduction in mortality was 21 percent, in some trials zero, in other ones 31 percent. The mean absolute risk reduction is 1.6, but I want you to look at the numbers within the brackets. Even though there are some showing 3.3, which is a very decent result, there are some trials that were actually negative.

Now, as a clinician, it may be interesting to use the number needed to treat, and what I have

done for the trial, what I have shown you, is plug

them in one single graph, what are the numbers of

possible patients that you need to treat to try to

save one life.

[Slide.]

The best ratio comes from oxygen. It

proves what we know. Lack of oxygen is bad for

you. If you put it back in, you do very well. You

need to treat 5 patients for 36 months to save one

life.

Beta blockers are also a block buster.

You put patients on beta blockers, you need to put

20 of them for 6 months if you have CHF, and you

will save one life. In a single grouping, I have

put three that I think may represent more or less

the ball park of what we are talking about.

Intent-to-treat, smoking cessation, 62

patients, you have to attempt to make them quit for

14 years to save 1 life; statins, 61 patients for 5

years; Advair, 39 patients for 3 years.

Within that, I am giving you the other

extreme, which is the tPA, which you need to treat

100 patients, once in the emergency room, to save 1 life in 30 days.

[Slide.]

Now, I promised you I was going to give you a summary, and when I was asked to do this a year and a half ago, the best I could do is try to imagine how to represent this.

[Slide.]

I have drawn a figure. I took this three-legged stool. On top of it is the survival and I am not here to tell you whether that is clinically significant or statistically significant. There was some impact on survival. It is up to you to judge in your own soul what you think is the impact.

However, when you look on the three legs on which that stool is resting, I believe the change in FEV_1 with a 92-ml difference at the end of 3 years when the patients were compared to placebo, the decrease in exacerbation rate around 24 percent requiring systemic steroids or antibiotics, and a better quality of life at the

end of 3 years does support, but taken in the whole overall context of the study, the results are positive.

[Slide.]

What do I hope the future will hold? Not just for this trial, but more trials to come and our approach to the disease in a proactive way is the following.

As I get a little older, I hope my brother cardiologists and strokologists will continue to impact on those. As I get a little older, I hope cancer rates are also impacted and I tend to live longer.

But my real dream as a clinician is that as we develop more therapies along the lines of what we are discussing today, we can impact on this deadly disease.

Thank you very much for the time. I have clinic tomorrow morning. I hope our deliberations will only last today. I thank you for being here with us today.

Thank you very much.

Dr. Jones.

Closing Remarks

DR. JONES: Thank you, Dr. Celli.

We have just heard from Dr. Knobil and Dr. Celli how the data we have generated around Advair Diskus 500/50 has a positive impact on the treatment of patients with COPD.

We have presented results from three studies, the most substantial of which is TORCH. One important point I would like to address before taking questions is why we believe the results from this single study are persuasive and impractical to support the proposed indication for survival.

[Slide.]

In the TORCH study, while the primary endpoint was just above the predetermined level of significance, the other endpoints, predictors of mortality, such as FEV_1, quality of life, and exacerbations demonstrate the significant improvement.

The totality of the data confirms that the effect we are seeing on mortality is real, and not

due to chance. In addition, TORCH was a large
multicenter trial and no single investigator or
country was disproportionately responsible for the
effect.

Evidence of this was provided by the
analysis of the all-cause mortality where the
results were remarkably stable when we individually
exclude each country.

Furthermore, the data were also analyzed
to determine if there were consistent treatment
effects for all-cause mortality within patient
subgroups. When we look at variables that are
known to have an effect on mortality by themselves,
we find no interaction with treatment, and the
overall survival benefit demonstrated with Advair
was consistent with the results in each subgroup.

Finally, for mortality trials, it is often
accepted that we have to rely on evidence from a
single trial, and indeed, based on the strength of
the data we have just presented, to conduct another
study would present certain ethical issues.

[Slide.]

I would now like to introduce four additional experts here with us today. Peter Calverley is Professor of Pulmonary and Rehabilitation Medicine at the University of Liverpool in the UK, and Honorary Consultant Physician at the University Hospital Aintree in Liverpool. Professor Calverly is Chairman of the TORCH Steering Committee.

Paul Jones is Professor of Respiratory Medicine at St. George's Hospital, University of London. Professor Jones is also a member of the TORCH Steering Committee.

Anne Whitehead is Deputy Director of the Medical and Pharmaceutical Research Unit at the University of Reading in the UK. Professor Whitehead was the statistician on the TORCH Safety and Efficacy Data Monitoring Committee.

Gary Koch is Professor of Biostatistics of the University of North Carolina.

This ends our formal presentation and I thank you once again. I would now like to invite my colleagues back to the podium, so we can address

any questions you may have.

Thank you.

Questions from the Committee to Sponsor

DR. BRANTLY: We are ahead of time at the present time, so we have approximately 30 minutes for questions from the committee members to the sponsor.

Questions? I guess I will start off with the first question.

One of the interesting concepts that has been developed over time has been the concept that COPD is an inflammatory disorder.

In any of the studies that you have done in the past or in data, is there any evidence of reduction in CRP in individuals treated with Advair 500/50?

DR. KNOBIL: There are published data with FP. There aren't any data yet with Advair, but the data with FP, published by Don Sin, showed I think it was approximately 50 percent reduction in CRP in patients with COPD.

We also have other biopsy data with Advair

versus placebo and Advair versus components that

also show a reduction in inflammatory cells in lung

biopsies.

DR. BRANTLY: What type of inflammatory

cells were reduced?

DR. KNOBIL: Mainly lymphocytes and some

eosinophil reduction, but that was less of an

effect.

DR. BRANTLY: Dr. Prussin.

DR. PRUSSIN: So, in the number needed to

treat analysis of 33 patients for 1 life saved, I

mean any of us probably would take a medication

like that if we could live forever, but these

patients are eventually going to die.

Certainly, I saw one analysis, I think it

was in the FDA document, that there was a 132-day

difference at the 10 percent death level between

the placebo group and the combination group.

Again, a simplistic way of thinking about it, that

is 132 days for 10 percent. If you normalized it

for all, would that be 13 days per patient?

I mean how much does each patient buy I

guess is my question, because they are not going to

live forever, they are going to die at some point,

right?

DR. KNOBIL: I am not sure I understand

the question about how much each patient buys.

DR. PRUSSIN: In other words, if you are

going to treat somebody, how much longer are they

going to live? We are saying that it prolongs

survival. Is that prolonged survival a few weeks

or a month? I think that is an important question

because they are not going to live forever. So,

the number needed to treat is sort of perishable.

David, maybe you have some thoughts.

DR. SCHOENFELD: The problem is that you

should always realize about clinical trials is they

aren't reality, they are just a model for reality.

You do a clinical trial for three years in a

lifetime disease, you are not really measuring the

true treatment difference. You are just modeling

it basically.

You would like to do a trial for 15 years,

but you can't really, because people, it is too

much to ask people to take a placebo for 15 years,

and you have too many people dropping off. So, you

are really not--you know, 100 days is not really an

estimate of the improvement in life. I mean it is

again very, very hard to estimate that because you

have to take into account normal mortality, as

well, and mortality over the course of the disease.

DR. KNOBIL: We have done an analysis,

because when we looked at the 90 percent mortality

difference that was done in the briefing document,

it was hard to understand the clinical relevance,

because that is to 90 percent survival when most

patients are still alive, so we don't know what the

clinical relevance of that is.

What we did is we modeled it for median

survival or 50 percent survival, and when we looked

at that, the difference was about 1.5 years.

DR. SCHOENFELD: I actually did that

calculation, I repeated that, I did the same

calculation just before I came for the fun of it

because I was curious as to what it actually is.

My figure is actually fairly similar.

          I used normal life expectancy and then

back calculated the excess risk due to COPD, and

then I don't know if they did it the same way, but

basically, a 63-year-old male has a life expectancy

of about 18 years, which being that age it is not a

nice thing to know, but on placebo, in this study,

they would have about a life expectancy of about

12.5 years with COPD, and on Advair it would be

13.7 years, so my calculation is about 1.2 years

difference, but this is again based on a model over

time and sort of a back-of-an-envelope model that

you might do better if you had long-term follow-up

on COPD.

          DR. KNOBIL: The calculation that we did

was based on all-cause mortality, so it was all

causes in there.

          DR. SCHOENFELD: This is based on all-

cause mortality also, but I had to sort of make

modeling assumptions to do the calculations.

          DR. BRANTLY: Dr. Parsons.

          DR. PARSONS: I actually will ask a

clinician question, which will be, so now I have a

patient who currently has COPD who is on Advair 250/50, and can you tell me how I decide now what to do with my patients regarding the 500/50 data that has only been compared to placebo and its components?

DR. KNOBIL: As we mentioned earlier, we don't have any head-to-head data, so I don't think that I could speculate on what the mortality benefit would be with the 250 strength.

DR. PARSONS: Can you explain how the study was designed to not have that arm? Was there a reason that arm was excluded?

DR. KNOBIL: When the study was started, it was before we had any data with the 250 strength. As you can imagine, a three-year study takes a long time to run. So, the study was actually started before we had any of the clinical trials with the 250 strength in the United States.

When the study was designed, it was felt that in order to have the best opportunity to see a mortality benefit, the higher strength would give us that opportunity to do that.

DR. VOLLMER: Just a couple questions. I grant that there is an awful lot of very positive messages coming from this. I would ask your take on what I see as a somewhat different way of spinning the results, if you will.

There are times when you take a small absolute difference and you characterize it very strongly as a percentage basis and make a lot of it, even though some things are significant and some things are not significant, so, for instance, you have, what is it, a 17 percent reduction in mortality, borderline significant, and yet you fairly readily discounted on the FP alone arm, an increase as not significant without talking about the fact that neither one of them technically is statistically significant, and you have a 33 percent increase in side effects, ocular side effects, that would discount it as being small and not significant.

I would just like your take a little bit on how one looks at the results. It seems to me that depending upon whether we choose to look at

absolute differences or percentage differences, the results are very different, and you seem in some cases, where benefit is applied, to be looking at things on an absolute basis, and not worrying about the statistical significance, and saying this looks clinically relevant, where it doesn't necessarily benefit the product as well, sometimes looking at it the other way and putting it aside.

I am just wondering your take on how you look at the results.

DR. KNOBIL: Well, let me start with the ocular effects first, because I think that when you look at effects over time, and because the patients on Advair were in the study longer, you have to look at that endpoint corrected for time on study medication.

When we did that, there was only a difference of 5 ocular events per 1,000 treatment years between the steroid-containing groups and the nonsteroid-containing groups. So, you can't just look at the percentage of patients that have that reported.

When you go back to the all-cause mortality--and actually, can we just show the core slide on all four arms--you mentioned that we don't address that FP was less than placebo, when, in fact, we did say it was less than placebo, it wasn't statistically significant, and, in fact, it wasn't what we expected.

As I mentioned in the presentation, we expected that just like all the other clinical endpoints, the components would be somewhere in between Advair and placebo. FP wasn't where we expected it to be, but we don't interpret that as a significant increase in mortality.

I did not say that Advair was significantly greater than salmeterol, but it is in the right direction, it is what we expected, and the study wasn't designed to show a difference between Advair and salmeterol, but we were pleased that it showed a favorable trend in that direction.

DR. VOLLMER: Could you also speak to the smaller effect sizes that you saw in the U.S. population?

DR. KNOBIL: I am sorry?

DR. VOLLMER: Could you also speak to the smaller effect sizes that you saw in the U.S. cohort that is not really addressed in your presentation?

DR. KNOBIL: For mortality? Yes. The effect size for the United States by itself is a little bit smaller. I knew I would have this question. There was a mortality of 13.9 percent in placebo versus 12.3 percent in the Advair arm, which is a difference of 1.6 percent versus the 2.6 percent we saw in the entire population.

However, when you look at that, the all-cause mortality for Advair was remarkably similar between those two. It was 12.3 percent for Advair in the U.S. population and 12.6 percent for the entire population.

What was different was actually the all-cause mortality in the placebo arm in the U.S., which was 13.9 percent in the U.S. versus 15.2 percent in the overall population. I think a lot of that has to do with the fact that there was a

lot more dropout in the U.S. in the placebo

population, and patients could go on to take

whatever they wanted including Advair.

The other point to consider--and I don't

have to tell you this as a statistician--is that

when you cut the groups into smaller and smaller

pieces, you are not going to see the exact same

result in all of those subgroup analyses, so I

don't think that it is remarkably different

results. It goes in the same direction, and it

goes in the same direction in nearly all the

subgroups that we looked at.

DR. BRANTLY: Dr. Stoller.

DR. STOLLER: I have several questions.

One regards the calculation of the FEV_1

slope. As I understand, the rate of change of FEV_1

was calculated as a post-hoc analysis, and picked

the slope between 24 weeks, the nadir, the zenith

value, and 103 years.

Characteristically, we think of the FEV_1

slope as change from baseline, so I am curious what

was the rationale for picking the change in the

FEV_1 slope from the zenith value and what would the slopes be if calculated from baseline to 3-year follow-up.

DR. KNOBIL: This is the slide that you are talking about, looking at slope of FEV_1. The reason that we calculate slope of FEV_1 from 24 weeks is that we do see an improvement in lung function with Advair, as well as the other active treatment.

So, if you took the slope from baseline and don't take into account the effect on lung function that you are seeing, then, it is going to be difficult to know. You are not comparing apples to apples.

So, you want to compare the slope with the patients on the medication over time.

DR. STOLLER: And if the slopes were recalculated from baseline, would those slopes differ?

DR. KNOBIL: Actually, I think they would look better, but I would like to ask Julie Anderson to step up here, who is the statistician on the