FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC)

Virtual Meeting

Monday, August 31, 2020

10:03 a.m. to 3:57 p.m.

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C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
James Stoller, MD, MS	13
Conflict of Interest Statement	
Philip Bautista, PharmD	22
FDA Introductory Remarks	
Banu Karimi-Shah, MD	26
Applicant Presentations - GlaxoSmithKline	
Request to Amend the TRELEGY ELLIPTA Label to Include Data on the Reduction in Risk of All-Cause Mortality in Patients with COPD	
C. Elaine Jones, PhD	30
Clarifying Questions to the Applicant	47
FDA Presentation	
FDA Summary Presentation	
Banu Karimi-Shah, MD	73
Clarifying Questions to the FDA	92

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Open Public Hearing	114
Clarifying Questions (continued)	124
Questions to the Committee and Discussion	156
Adjournment	253

P R O C E E D I N G S

(9:02 a.m.)

Call to Order

Introduction of Committee

DR. STOLLER: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

Good morning. My name is Dr. Jamie Stoller, and I will be chairing today's meeting. I will now call the August 31, 2020 Pulmonary-Allergy Drugs Advisory Committee meeting to order. Dr. Phil Bautista is the designated federal Officer for today's meeting, and he will begin with introductions.

DR. BAUTISTA: Good morning, everybody. My name is Phil Bautista, and I am the designated federal officer for today's meeting. When I call your name, please introduce yourself by saying your name and affiliation, and for those voting members,

please also state for the record that you have viewed the FDA and GSK prerecorded presentations in their entirety.

Ms. D'Agostino?

MS. D'AGOSTINO: Hi. My name is Emma D'Agostino. I am a consumer representative. I'm a graduate student at Emory University and a patient advocate with the Cystic Fibrosis Foundation. And yes, I confirm that I have viewed the presentations in their entirety.

DR. BAUTISTA: Dr. Evans?

DR. EVANS: This is Scott Evans. I am a pulmonologist at MD Anderson Cancer Center in Houston, and I confirm that I have viewed all of the prerecorded presentations in preparation for today's meeting.

DR. BAUTISTA: Dr. Kelso?

DR. KELSO: My name is John Kelso. I'm an allergist at Scripps Clinic in San Diego, and I have viewed all of the pre-meeting presentations from both the FDA and the applicant.

DR. BAUTISTA: Dr. Marshall?

DR. MARSHALL: Good morning. Gailen Marshall. I'm an allergist-immunologist at the University of Mississippi Medical Center in Jackson, and I confirm that I have viewed all eight of the presentations in preparation for the meeting.

DR. BAUTISTA: Dr. May?

DR. MAY: I'm Suzanne May, professor of biostatistics at the University of Washington in Seattle, and I have also reviewed all the presentations in their entirety.

DR. BAUTISTA: Dr. Redlich?

(No response.)

DR. BAUTISTA: Dr. Redlich, can you please unmute yourself and state your name and affiliation?

(No response.)

DR. BAUTISTA: Dr. Redlich, can you please unmute yourself?

(No response.)

DR. BAUTISTA: Alright. We will come back around for Dr. Redlich.

Dr. Tracy?

DR. REDLICH: This is Dr. Redlich. Can you hear me now? I have been unmuted.

DR. BAUTISTA: Yes, we can hear you now.

DR. REDLICH: Okay. This is Dr. Carrie Redlich. I'm professor of medicine at Yale School of Medicine, and also professor of epidemiology and a pulmonologist, and I confirm that I have reviewed the presentations.

DR. BAUTISTA: Dr. Tracy?

DR. TRACY: Good morning, everybody. I'm Dr. Jim Tracy. I'm an allergist both in private practice and in academic practice in Omaha, Nebraska and University of Nebraska, and I, too, have viewed all of the preliminary presentations. Thank you.

DR. BAUTISTA: Dr. Dawn Carlson?

DR. CARLSON: Hi. I'm Dawn Carlson, the industry representative, and I'm currently [inaudible - audio fades].

DR. BAUTISTA: Hi, Dr. Dawn Carlson. Can you repeat yourself?

DR. CARLSON: Can you hear me?

DR. BAUTISTA: Yes, I can hear you clearly now.

DR. CARLSON: I'm Dawn Carlson. I'm the industry representative. I work at Abbvie in clinical pharmacology and pharmacometrics, and I have reviewed the materials.

DR. BAUTISTA: Thank you.

Dr. Carvalho?

DR. CARVALHO: Good morning. I'm Paula Carvalho, and I'm a pulmonologist and intensivist with the University of Washington and the Boise VA Medical Center, and I confirm that I viewed all eight recorded presentations. Thank you.

DR. BAUTISTA: Dr. Dodd?

DR. DODD: Hello. I'm Lori Dodd. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases. I confirm that I have read the prerecorded presentations from the FDA and GSK prior to this meeting. Thank you.

DR. BAUTISTA: Dr. Ellenberg?

DR. ELLENBERG: Good morning. I'm Susan

Ellenberg. I'm a professor of biostatistics at the Perelman School of Medicine at the University of Pennsylvania, and I confirm that I have listened to all of the presentations.

DR. BAUTISTA: Ms. Lupole?

MS. LUPOLE: Hello. My name is Patricia Lupole. I am the patient representative and advocate. I confirm that I read the FDA and GSK prerecorded presentations in their entirety. Thank you.

DR. BAUTISTA: Dr. McCormack?

DR. McCORMACK: My name is Frank McCormack. I'm a pulmonologist and professor of medicine at the University of Cincinnati, and I confirm that I've reviewed the GSK and FDA videos. Thank you.

DR. BAUTISTA: Dr. Medoff?

DR. MEDOFF: Yes. My name is Ben Medoff. I'm a pulmonologist and intensivist at Mass General Hospital in Boston, and I confirm that I've viewed all the pre-meeting material.

DR. BAUTISTA: Dr. Shapiro?

(No response.)

DR. BAUTISTA: Dr. Shapiro, will actually be joining us a little later. At the next opportune time, we'll ask him to introduce himself for the record.

Dr. Stoller?

DR. STOLLER: Yes. Good morning. This is Dr. Jamie Stoller. I'm a pulmonary critical care doc at the Cleveland Clinic, and I confirm that I've reviewed all the materials.

DR. BAUTISTA: On to the FDA participants, starting with Dr. Seymour?

DR. SEYMOUR: Good morning. My name is Dr. Sally Seymour. I'm the director of the Division of Pulmonology, Allergy, and Critical Care at the FDA.

DR. BAUTISTA: Dr. Karimi-Shah?

DR. KARIMI-SHAH: Good morning, everyone. My name is Banu Karimi-Shah, and I'm the deputy director of the Division of Pulmonology, Allergy, and Critical Care.

DR. BAUTISTA: Dr. Busch?

DR. BUSCH: Good morning. My name is Robert

Busch, and I'm the medical officer in DPACC and the FDA clinical reviewer for this application.

DR. BAUTISTA: Dr. Kim?

DR. KIM: Good morning, everyone. My name is Yongman Kim. I'm a statistical team leader, Division of Biometrics III in the Office of Biostatistics at FDA.

DR. BAUTISTA: Ms. Susan Duke?

MS. DUKE: Good morning. My name is Susan Duke. I am in the Division of Biostatistics at FDA and the reviewing statistician for this application.

DR. STOLLER: Great.

Welcome, everyone. This is Jamie Stoller, and welcome.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder,

individuals will be allowed to speak into the record only if recognized by the chairperson. We will look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you very much.

DR. BAUTISTA: Hi, all. I was informed that Dr. Shapiro has joined the meeting.

Dr. Shapiro, can you state your name and affiliation, and whether you have reviewed all prerecorded presentations in preparation for the

meeting? Thank you.

DR. SHAPIRO: Hi. Steve Shapiro, UPMC, University of Pittsburgh, and yes I have reviewed all the materials. Thank you.

Conflict of Interest Statement

DR. BAUTISTA: Thank you, Dr. Shapiro.

I will now read the Conflict of Interest Statement for the meeting.

The FDA is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found under 18 U.S.C. Section 208, is being provided to the participants in today's

meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves supplemental new drug application 209482/S-008 for Trelegy Ellipta, a fixed-dose combination submitted by GlaxoSmithKline for the following proposed labeling claim: reduction in all-cause mortality in patients with chronic obstructive pulmonary disease. The focus of this discussion will be on the efficacy data submitted to support the proposed labeling claim, including the results from the Informing the Pathway of COPD Treatment trial and the influence of inhaled corticosteroids withdrawal on the results.

This is a particular matters meeting during which specific matters related to GlaxoSmithKline sNDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers

have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they may have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Dawn Carlson is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Carlson's role at this meeting is to represent industry in general and not any particular company. Dr. Carlson is employed by Abbvie.

We would like to remind members and temporary voting members that if the discussions involve any other drugs or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they

may have with the firm at issue. Thank you.

DR. STOLLER: Thank you, Dr. Bautista.

We will now proceed with the FDA introductory remarks from Dr. Banu Karimi-Shah.

FDA Introductory Remarks – Banu Karimi-Shah

DR. KARIMI-SHAH: Thank you very much.

Good morning, Dr. Stoller, esteemed advisory committee members, GSK team, my FDA colleagues, and members of the audience, my name is Dr. Banu Karimi-Shah, and I'm a pulmonary and critical care physician and deputy director in the Division of Pulmonology, Allergy, and Critical Care.

On behalf of the agency, I'd like to welcome you all to this virtual advisory committee, where we will be discussing the supplemental new drug application for Trelegy Ellipta, for the proposed labeling claim for the reduction in all-cause mortality in patients with COPD.

While we would prefer to be sitting in a room with all of you today, we are thankful that we can utilize this virtual setting to proceed with this very important discussion. In an effort to

focus the meeting and accommodate different time zones, we have adopted a unique format for today's meeting. Rather than take the time to give our comprehensive presentations this morning, we have provided prerecorded presentations from both the applicant and the agency ahead of the meeting, in addition to the written briefing document. These prerecorded presentations from the applicant, Dr. Robert Busch, Ms. Susan Duke, and myself, as well as their transcripts, have also been posted to our website. We thank you for taking the time to review these materials prior to today's meeting.

The agenda for today's meeting will be as follows. After my brief introductory and welcome remarks, I will turn the meeting over to Dr. Stoller and then GSK to give a summary presentation, after which you will have the opportunity to ask clarifying questions of the applicant. I will then return to similarly give a summary presentation from the agency, followed by clarifying questions to FDA.

The scope of the clarifying questions to

either the applicant or FDA can cover the entirety of their prerecorded and live presentations. The advisory committee panel members may refer to any of the slides that have either been shown in the applicant and FDA's summary presentations, or those that have been provided to you from the comprehensive prerecorded presentation. We will be able to pull up these slides to facilitate the discussion. We ask that you provide the name of the presenter, title of the presentation, and the slide number to facilitate the process.

From the agency side, Dr. Robert Busch, Ms. Susan Duke, Dr. Yongman Kim, Dr. Greg Levin, Dr. Sally Seymour, and I will be available to respond to questions. After clarifying questions to the agency, we will take a break for lunch and return for the open public hearing. We will then turn to the discussion points and voting questions, which I will review this morning and that were provided to you in my prerecorded presentation entitled, Charge to the Committee.

As we navigate this virtual meeting format

together, we thank you for your patience should we experience any technological issues or problems. Thanks again for your participation today. We look forward to a robust discussion. I will now turn the meeting back to Dr. Stoller.

DR. STOLLER: Thank you, Dr. Karimi-Shah.

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

For this reason, FDA encourages all participants, including the GSK non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interests in the applicant, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the

beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the GSK summary presentation, please.

Applicant Presentation - Elaine Jones

DR. JONES: Good morning to the chair, members of the advisory committee, and the FDA. I'm Elaine Jones, the medicine development leader for Trelegy Ellipta at GlaxoSmithKline. I would like to thank the advisory committee and the agency for this opportunity to present data on all-cause mortality from the IMPACT study. I will provide a high-level summary of the data that you have previously received from the video presentation and the briefing document. No new data are being presented in this summary.

Trelegy is a triple-inhaled therapy taken once daily and approved in September 2017 for the

maintenance treatment of patients with chronic obstructive pulmonary disease or COPD. The exacerbation data from the IMPACT study were included in the label for Trelegy in April 2018.

During the pre-sNDA discussions for the exacerbation supplement, GSK and FDA agreed that submission of the all-cause mortality data from IMPACT would be submitted in a future supplement after GSK had completed its efforts to obtain the missing vital status data.

GSK submitted the supplement in June 2019. The safety profile of Trelegy is consistent with the data submitted in the exacerbation supplement. Consequently, only the efficacy data pertinent to the all-cause mortality endpoint will be discussed today.

COPD is a progressive disease, and patients with more advanced COPD have an increased risk of exacerbations and hospitalization. The risk of readmission and death remain elevated for an extended period of time following hospitalization for a COPD exacerbation.

Data from a natural history study by Rothnie in nearly 100,000 patients, in a primary care COPD population, demonstrates the relationship between exacerbation frequency and death. Shown here on the X-axis is the time to death in years and on the Y-axis is the proportion of patients who died.

As the frequency and severity of exacerbations increases, so does the proportion of patients who died. In fact, the greatest risk of death was in patients with one or more hospitalized exacerbations shown here as severe and represented by the red line. Therefore, a therapy that reduces exacerbations and, more importantly, COPD hospitalizations would be expected to reduce mortality.

I would now like to discuss the IMPACT trial. Firstly, a brief description of the IMPACT study design. IMPACT was a year-long, randomized, double-blind, parallel group, multicenter, phase 3 exacerbation study in 10,355 patients designed to demonstrate superiority of Trelegy over effective dual inhaler therapies, fluticasone furoate

vilanterol combination or FF/VI and umeclidinium vilanterol combination or UMEC/VI, for the reduction in the reduction in the rate of moderate and severe COPD exacerbations.

This study was conducted. Because of the time, controversy existed regarding the use of inhaled glucocorticoids in COPD and the relative benefits of triple therapy compared with dual therapy in patients with a history of exacerbations. At the time, regulators and ethics committees reviewed and raised no objection to the study design.

The IMPACT trial included clinically-relevant, prespecified endpoints to assess multiple aspects of COPD, including lung function, quality of life, and exacerbation reduction. All-cause mortality was included as a predefined other endpoint with a prespecified analysis plan and was not an exploratory endpoint.

Firstly, I will show you the exacerbation data followed by the mortality data. Trelegy, shown in blue, demonstrated a significant

15 percent reduction in the rate of moderate and severe exacerbations compared with FF/VI, shown in red, and a 25 percent reduction compared with UMEC/VI, shown in green, both with a p-value of less than 0.001.

Trelegy, shown in blue, reduced the rate of on-treatment severe exacerbations, those requiring hospitalization, by 13 percent compared with FF/VI, shown in red, although this did not achieve statistical significance.

Trelegy reduced the rate of severe COPD exacerbations by 34 percent compared to UMEC/VI, shown in green, which was highly statistically significant. Both the moderate-severe and severe exacerbation data are presently in the label. This reduction in hospitalized exacerbations is clinically relevant for patients and could translate into a reduction in the risk of dying.

In fact, that is what we do see. In this Kaplan-Meier plot showing time to death on the X-axis and probability of dying on the Y-axis, there is a 28 percent reduction in the risk of

dying for patients randomized to Trelegy compared with those randomized to UMEC/VI. There was also a numerical reduction in the risk of dying of 11 percent for Trelegy compared with FF/VI, illustrating the contribution of the LAMA, UMEC to the overall treatment effect. That's the greatest benefit on all-cause mortality, as seen with a triple combination of Trelegy.

The FDA has asked in the division memorandum that you consider five key clinical and statistical points for discussion, and I would like to GSK's perspective. I would like to acknowledge that while there are areas of agreement between the FDA and GSK, there are some differences, which we will highlight.

The first point relates to the statistical persuasiveness of the mortality results. We believe that the all-cause mortality result is persuasive because IMPACT was a well-designed, well-conducted, large global multicenter trial. All-cause mortality was a predefined endpoint with a prespecified analysis plan.

We did not discuss or agree with the agency the level of statistical significance required for all-cause mortality in the context of IMPACT meeting its primary endpoint. The data are reliable and have high quality with independent adjudication of death, and there was minimal missing data. We have demonstrated clinical plausibility between all-cause mortality and reduction of severe COPD exacerbations. The data from the exacerbating population in SUMMIT provides directly relevant supportive data.

We acknowledge that we did not adjust for multiplicity, however, it is important to note that multiplicity adjustments are performed to avoid a study being declared successful when only a few endpoints achieve a p-value of less than 0.05 without the context of how many endpoints were tested.

This slide shows all of the 34 predefined efficacy endpoints, which compared Trelegy with UMEC/VI in the overall IMPACT population. All but one directionally favored Trelegy; 29 had a p-value

less than 0.05 in favor of Trelegy, including 23 that had a p-value less than 0.001. Thus, we are not singling out all-cause mortality, and we believe in the statistical persuasiveness of the all-cause mortality findings.

The next point I would like to address is the data from TORCH and SUMMIT and their relevance to this discussion. TORCH was the first mortality study conducted in 6,112 patients with COPD, however, it was initiated over 20 years ago. TORCH showed a 17.5 percent reduction in mortality for Advair, the combination of fluticasone propionate and salmeterol compared with placebo with a p-value of 0.052.

The ICS and LABA studied in TORCH are not the same as those in Trelegy. In particular, fluticasone proprionate and fluticasone furoate are different molecules and are not metabolized to fluticasone. As TORCH studied, different molecules and the standard of care and treatment guidelines have changed. In particular, there were no long-acting muscarinic antagonists approved at the

start of the study. We do not consider that the TORCH data are pivotal to the discussion of the IMPACT mortality data.

SUMMIT, however, was conducted more recently than TORCH, and thus the treatment paradigm for patients with COPD was similar to that of IMPACT. It also evaluated FF/VI, the same ICS and LABA components contained in Trelegy, and thus we consider the SUMMIT data directly relevant to this discussion.

SUMMIT was a randomized, double-blind, event-driven, placebo-controlled parallel group study that evaluated the efficacy and safety of the combination of FF/VI and the individual components in more than 16,000 patients compared to placebo. The primary endpoint of SUMMIT was all-cause mortality and the median study duration was 1.8 years. Patients in SUMMIT were required to have moderate airflow limitation and a heightened cardiovascular risk, however, they were not required to have a history of COPD exacerbations.

Shown here is a Kaplan-Meier plot from the

SUMMIT study for the primary endpoint of all-cause mortality. I am going to focus on the comparison of FF/VI, shown in red with placebo in black, as this was the predefined primary comparison. SUMMIT showed a 12 percent reduction in the risk of all-cause mortality, which did not reach statistical significance. However, when we look at the nearly 3,500 patients in SUMMIT, who would have met the entry criteria for IMPACT with regard to their exacerbation history, we actually see a much larger reduction in the risk of dying.

In this post hoc analysis, we see a clinically meaningful 34 percent reduction in the risk of all-cause mortality for FF/VI compared with placebo with a p-value of 0.013. These data provide evidence, in this frequently exacerbating population, of the treatment benefit of FF/VI on all-cause mortality.

The FDA suggests that since the SUMMIT study had more events, it had greater power to show a treatment effect on mortality, however, power also depends on the true treatment effect. Fewer events

will be required to power for a larger true treatment effect. This is illustrated in the SUMMIT exacerbating population where we see a 34 percent reduction with 59 events on FF/VI and 89 events on placebo.

We believe that the data from the exacerbating population from SUMMIT provides supportive data, demonstrating the beneficial treatment effect on all-cause mortality and is directly relevant and highly informative to this discussion.

The next point I'm going to discuss is the time frame of the mortality events observed in IMPACT. The agency in that briefing document present post hoc exploratory analysis, excluding data from the first 90 days of treatment to explore the time course of mortality.

We agree with the agency that these analyses are limited, as they could represent a healthy survivor effect and should be interpreted with caution. The agency notes that these analyses suggest a potential trend of early mortality events

in the UMEC/VI arm. GSK disagrees.

This graph shows the cumulative number of deaths on UMEC/VI in the overall population. There is not a sudden bolus of deaths for the start of the study in the UMEC/VI arm. The events occur gradually over the course of the study; in fact, 89 percent of the deaths occurred after the first 30 days.

Furthermore, the agency suggests that an ACM effect within 90 days has not been seen in other studies. Here is the Kaplan-Meier plot from the exacerbating population in SUMMIT, and we do start to see a separation within 90 days.

The next point I'm going to address is the effect of ICS removal in IMPACT. That is to say that patients who came into the study on an ICS and were randomized to UMEC/VI, not surprisingly, given that IMPACT enrolled a population of frequently exacerbating COPD patients, 71 percent were on an ICS-containing medication at screening either as a triple, dual, or monotherapy, while 29 percent of patients came into the trial on an non-ICS regimen.

Because of the 2:2:1 randomization scheme, only approximately 14 percent of patients would have actually undergone ICS withdrawal.

The FDA questions whether abrupt ICS withdrawal would make these patients less stable, and we show you data on FEV1 and SGRQ that demonstrate this is not the case. These graphs present change from baseline in trough FEV1 over the course of the study. The panel on the left presents the results of those on an ICS screening, and the one on the right, those who were not on an ICS screening.

As anticipated in a progressive disease, FEV1 declines over time in all treatment groups, with a treatment difference remaining consistent. If abrupt removal of ICS was making patients COPD unstable as suggested by the FDA, you would expect the UMEC/VI green line on the left to go below zero. In fact, an improvement in FEV1 was seen. There was no abrupt deterioration in lung function because of ICS withdrawal.

These graphs present change from baseline in

SGRQ. As a reminder, a decrease in SGRQ score corresponds to an improvement in health status. The panel on the left presents the results of those on an ICS screening, and the one on the right, those who were not on an ICS screening. If abrupt removal of ICS was making patients COPD unstable as suggested by the FDA, you would expect the UMEC/VI green line on the left to go above zero. In fact, an improvement in SGRQ was seen. There was no abrupt deterioration in health status because of ICS withdrawal.

We agree with the FDA that the mortality benefit is seen in those patients taking an ICS-containing medication at screening with a 39 percent reduction in risk of dying. This is not surprising, as this is a sicker COPD population with a higher rate of severe exacerbations experienced before and during the study; and as we saw from the Rothnie data, those patients with higher numbers of exacerbations and more severe exacerbations are at greater risk of death.

We see no evidence of the mortality benefits

in the non-ICS users, potentially due to the small sample size and low number of events, and it is not surprising that there is a lower number of deaths in this group, as these patients have less severe disease.

The final point that the FDA raises regards the clinical generalizability of the IMPACT ACM results. The FDA has questioned whether the trial design of IMPACT can answer the clinically relevant question of whether Trelegy per se reduces all-cause mortality.

The overall population demonstrated a statistically significant 28 percent reduction in risk of dying with a p-value equal to 0.042. Thus, we believe the all-cause mortality data generated in IMPACT are generalizable to a symptomatic exacerbating COPD population and are reflected in our proposed labeling.

It should be of little controversy that a reduction in the risk of dying is clinically important. The absolute annual all-cause mortality risk reduction with Trelegy versus UMEC/VI was

0.83 percent in the IMPACT study. The magnitude of the benefit is greater than that achieved with smoking cessation, which has been widely accepted to affect mortality in patients with COPD. This is the first pharmacologic therapy to prospectively demonstrate a survival benefit in patients with COPD.

Shown here are the data that we are proposing to include in the Trelegy label. The data is proposed to be included as text only, and it's in a similar format to the other endpoint data already included in the Trelegy label. Specifically, there was a 28 percent reduction in all-cause mortality for Trelegy compared with UMEC/VI in the on and off treatment data set.

There was a 39 percent reduction in all-cause mortality for Trelegy compared with UMEC/VI in the on and off treatment data set for those patients who were on an ICS prior to the study. There was no evidence of a reduction in all-cause mortality observed for Trelegy compared with UMEC/VI in the on and off treatment data set

in patients who were not on an ICS prior to the study.

We believe these results and the context regarding the specific patient population are of the utmost importance for physicians to know and to be included in the clinical study section of the Trelegy label given the medical importance of a mortality endpoint.

Here with me today to respond to your questions are Dr. David Lipson and Dr. Robert Wise, whose presentations you reviewed in advance of this meeting. It is worth noting that Dr. Wise was a member of the IMPACT independent data monitoring committee.

In addition from GSK, we have Dr. Sally Lettis, who is the statistical lead for the project, and Dr. Courtney Crim, the physician lead for TORCH and SUMMIT. We also have Dr. Robert Makuch, who is our statistical consultant.

I thank the advisory committee and the agency for the opportunity to present this important data.

Clarifying Questions to the Applicant

DR. STOLLER: Thank you, Dr. Jones.

We will now take clarifying questions to GSK. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you've asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That's all for my questions," so we can move on to the next panel member. Thank you very much.

I see Dr. Kelso has his hand raised. Dr. Kelso?

DR. KELSO: Yes. There seems to be quite a bit of disagreement about this issue about whether or not the difference in mortality was noted in the first 90 days. My eyeball test tells me that, in

fact, the curve separated primarily during the first 90 days and then were parallel for the rest of the study.

One of the slides that was shown that kind of addresses this was CR-19 in the presentation that we just had. I think it was CO-34 in the original presentation.

Do you have this same -- where are the other arms on this slide? This is the UMEC/VI group. Where are the other two curves?

DR. JONES: Thank you, Dr. Kelso. Yes, we do have that slide. Slide up.

DR. KELSO: Here again, this looks like what I just stated, that when it's presented this way in terms of number of deaths or the mortality rate, as time marches on through the study, it looks to me like there's a clear separation starting at the beginning of the study that happens through roughly 90 days, and then the curves are roughly parallel after that. So I don't know how we get around that.

DR. JONES: Thanks, Dr. Kelso. You can see

the slide here. UMEC/VI is in green, Trelegy is in blue, and FF/VI is in red. We're presenting here -- because of the 2:2:1 randomization, deaths per 1,000 subjects here is on the Y-axis and deaths in the all-treatment arm do accumulate over the entire course of the study. But I'm going to ask Dr. Lettis, our statistician, to address the question you have regarding parallel lines. Thank you.

DR. LETTIS: Hello. Sally Lettis, statistics, GSK.

I think, yes, we agree that the lines do appear to become parallel around 90 days in the analysis of the most complete data set, which includes vital status both on and off randomized treatment. However, it is impacted by patients who discontinue randomized therapy within 90 days, and in fact twice as many patients stopped UMEC/VI within the first 90 days compared with Trelegy.

When patients stop their randomized treatment, they actually get switched to any COPD medication at the discretion of their physician,

and 70 percent of those who stopped UMEC/VI during the study went on to an ICS-containing medication.

I'd like to share with you an analysis of the on-treatment data just to try and explain what might be happening. So despite the caveats of an analysis excluding post-randomization data, I'd like to show you the Kaplan-Meier plot repeating the FDA exploratory analysis, excluding the first 90 days for the on-treatment data only.

Can I have QR-33, please? So in this analysis -- oh, it's not up yet. Sorry, I'm waiting for the slide. Thank you.

In this analysis, the lines do appear to become parallel after around 90 days -- sorry. In this analysis, you see a clear separation in the lines beyond 90 days, i.e., the treatment benefit of Trelegy is not entirely within the first 90 days.

I also want to point out that the death rate off randomized therapy is higher than that whilst on randomized therapy, which does suggest it is the more severe patients who are discontinuing from

their randomized therapy, and the majority of those patients are prescribed an ICS.

So it is true that the patients who are remaining on the therapy could represent a healthy survivor population, as the FDA has suggested. It's therefore not surprising that the separation in the curve that you see on treatment is reduced once you include the off-treatment data.

I'd actually like to ask Bob Wise to actually give you his clinical perspective on this.

DR. WISE: Thank you, Dr. Lettis.

I'm Bob Wise. I'm a pulmonary physician from Johns Hopkins University School of Medicine. I'm here today as a paid consultant to GSK, but I have no financial interest in the outcome of this committee.

I think the tendency toward the null that was exhibited in the FDA briefing document, Figure 5, showing the after 90-day mortality overlaying each other is not too surprising given the fact that there was both dropout and drop-in amongst the two treatment groups.

When you look at patients who were on UMEC/VI, as Dr. Lettis said, there was an excessive drop-out rate compared to the other arms, and 70 percent of those patients who dropped out went on an inhaled corticosteroid, which would tend to nullify any difference. So in order to test that hypothesis, the slide you see here takes patients who only remained on their assigned treatment. As you can see, there's a good amount of daylight between the two curves and not the overlapping curves that occur in the ITT population, which was in Figure 5.

Thank you. That's the end of my response.

DR. KELSO: Well, I appreciate that thought, but obviously there are many important reasons that we use intention-to-treat analyses, and I still think that requires some manipulation after the fact to get around that issue.

Can I see CR-17? I don't agree that the SUMMIT trial really is providing supporting information. It doesn't seem like a fair comparison to compare something to placebo when our

other comparisons in the current trials are to active treatment. But nonetheless, this is what a gradual separation seems to look like over time, as was the IMPACT trial. This just doesn't look like the IMPACT trial.

I have another question, but I will conclude for now and come back later, and let others speak.

DR. STOLLER: Very good. Thank you, Dr. Tracy.

(Dr. Kelso previously spoke.)

DR. STOLLER: Dr. May has a question.

DR. MAY: Yes. Suzanne May. You can stay on that slide that you just had up. That was CR-17. I had a question regarding that.

Going back to the previous comment, this seems not a fair comparison because we are particularly concerned with withdrawal of the ICS, and here it's the combination of FF/VI versus placebo. And I was wondering whether there is a similar slide having the two comparisons that single out FF, meaning the comparison of FF versus placebo and the comparison of FF/VI versus VI, to

show what the difference was for those two comparisons that single out the FF.

DR. JONES: Thank you, Dr. May. Yes, we do have that slide, and I'm going to ask Dr. Courtney Crim to address your question. Thank you.

DR. CRIM: Yes, this is Courtney Crim, pulmonary critical care physician in clinical development at GSK. Before I address that, based on the discussion we've been having, I think it's important to just go back to the point that had been raised previously in that the agency had analyzed the ITT population from SUMMIT to ask this committee to address whether it supported or refuted the conclusions from IMPACT but, again, as we all have mentioned, acknowledge the limitations of those analyses.

It was for that particular reason that it's important that if you're going to use any study for comparison, when you consider the limitations of such cross-study comparisons, the populations should be as similar as possible, and likewise the standard of care.

It is in this regard, as Dr. Jones mentioned, it is important to recall that SUMMIT only enrolled subjects with moderate airflow limitation in contrast with IMPACT, which allowed subjects with moderate to severe obstruction, and SUMMIT did not require that exacerbation history, where as that was a prerequisite in IMPACT. And it is for those reasons that we feel it's more appropriate to compare the subgroup in SUMMIT with those who met the IMPACT inclusion criteria based on exacerbation history.

So what I would like to do first is to bring up the slides to show you the demographics of this exacerbating population in IMPACT and SUMMIT so that you can see how it compares with the IMPACT inclusion criteria.

What I've highlighted in the boxes in green is the lung function, which, as you would expect, would be greater in the SUMMIT exacerbating population because they were restricted to moderate airflow limitation. But when you look at the exacerbation data, also in green, the green box

above, again, you can see that we can deselect in an exacerbating population.

So now go back to the slide that you had requested. We will bring up, again, the slide that includes the additional arms. What you can see, again, which takes into account the slide that was initially presented, is you have now all 4 arms on the figure, so you can see the difference between the FF/VI and placebo with the 34 percent reduction. Also, getting to the committee member's request while you also have this slide up, because of the concern that the agency raised about the effect of the steroid, you also see this direct comparison between FF and placebo.

We believe that having this direct comparison will provide more information than an indirect comparison between FF/VI and VI. So now you see this direct effect of the steroid, and again you see a 35.7 percent reduction in mortality in this exacerbating subgroup with a p-value of 0.010, and also an effect with the VI versus placebo.

I would like to turn this back over to Dr. Jones to see if she would like Dr. Wise to comment.

DR. JONES: Thank you, Dr. Crim.

Yes, Dr. Wise, if you could add some clinical perspective as well, that would be terrific. Thank you.

DR. WISE: Yes. If you could bring up 2R-93 again, I can address that. In this study, in this analysis, the exacerbating patients from SUMMIT, the striking thing is that both the combination, ICS/LABA, the ICS and the LABA, all independently had about the same effect on improving mortality.

The way I would interpret this is that there is basically a floor effect on mortality such that in this more mild population, once you achieve a certain benefit in terms of exacerbations, which is translated into mortality, you can't do much better. And this floor effect that you see in SUMMIT probably represents what you might call the natural mortality rate in these patients who also had coronary disease and coronary risk factors.

But I do think that this does provide evidence that the inhaled corticosteroid not only reduced exacerbations but also improved mortality in these exacerbating moderate patients.

DR. JONES: Thank you, Dr. Wise.

DR. MAY: Is it ok for me to speak? Suzanne.

DR. STOLLER: Dr. May, yes.

DR. MAY: This is Suzanne May again. Would you mind going back to that slide 93 that you just had?

In the SUMMIT trial, I can see the differences of each individual component as is represented here. The one other question that I had asked, that was not addressed as part of this slide, was the comparison of FF/VI versus VI only. That is more similar to comparisons that we're looking at in IMPACT because in IMPACT we're looking at dual and triple therapies.

So the comparison of FF/VI versus VI doesn't seem to be a substantial addition, maybe due to the fact that what you have mentioned is that there is

a floor effect. But just to point out, I believe that the FF in addition to the VI does not seem to have a substantial mortality benefit. Thank you very much.

DR. STOLLER: Thank you, Dr. May.

Dr. Evans has a question.

DR. EVANS: Thank you. This is Scott Evans at MD Anderson. I would like to understand from the applicant whether they have a perceived biologically plausible hypothesis for why we see the early separation. I understand that there's a suggestion that -- I'm sorry. And I'm referring to the difference in mortality that appears to be occurring at least by around day 40 when they split out the ICS use at screening population.

I'm currently looking, on my computer, at the slide that was labeled CO-45, which is similar to what was presented in Dr. Lipson's Blue Journal paper this year. I'm not sure -- yes, that's it that you have on the screen now. As was raised by Dr. Kelso earlier and was raised by the agency, there seems to be a steep curve in those early

days, which to my eye seems to appear much earlier than day 90. It sounds as if the applicant is arguing that the subsequently parallel curves are due to a healthy survivor effect perhaps.

To what does the applicant ascribe that early benefit in terms of a biologically plausible mechanism? That's my question. Thank you.

DR. JONES: Thank you, Dr. Evans. We have discussed this and presented some information in the presentations regarding the biological plausibility and relating that to exacerbations; in particular, severe exacerbations, hospitalizations. In IMPACT, over the course of the study, there was a 40-fold increase in the risk of dying during the severe exacerbation, and in fact 41 percent of the on-treatment deaths in IMPACT occurred during or within 90 days of an exacerbation.

I'd like to ask Dr. Wise to give some of his perspective around severe exacerbations and mortality, and then I'll follow up with Dr. Lipson for some of his perspective as well, including the plausibility of an early effect on ACM.

DR. WISE: Yes. Well, I think that there's no reason to think that a delayed benefit, in terms of severe exacerbation, should not have an early effect in reducing mortality. I don't think this is a disease-modifying effect. I think this is mediated through the reduction in severe exacerbations, which is seen early in the study.

But I also want to address on this slide the striking difference between the two groups; that is to say those who were on ICS use at screening and those who were not on ICS use at screening. The striking thing when you look at the slides, of course, is that there's separation of the curves in terms of those who were using ICS, but not on those who had not been using ICS at screening.

When you look a little more closely, though, you'll notice that all three of the curves in the patients who were not using ICS show a distinctly lower mortality than the UMEC/VI group in the ones using ICS.

This along with the reduced frequency of exacerbations and severe exacerbations, the better

lung function, the fewer symptoms, and the reduced beta agonists use all suggest that the patients who were not on ICS were a distinctly healthier subgroup; and therefore I don't think we can say that we're doing the same experiment, either withdrawal or addition of inhaled steroids, in the same population, but rather this non-ICS population represents a distinctly healthy subgroup where they're going to be benefited regardless of the treatment, very much like the floor effect that we saw in the moderate patients in the SUMMIT trial. Thank you.

DR. JONES: Thank you, Dr. Wise.

I'll move over to David for your perspective, Dr. Lipson.

DR. LIPSON: Yes, thank you. David Lipson, pulmonary critical care physician at GSK. I think it's important that you're asking about the biologic plausibility. Dr. Jones earlier presented data from the Rothnie study showing the relationship of exacerbation and risk for mortality. In fact, the greatest risk of mortality

were those who had a hospitalized or severe exacerbation.

So I'd like just to present some data from the IMPACT study showing the effect of a severe exacerbation during the trial on the risk of death. What we've shown is that the hazard ratio for a patient having a severe COPD exacerbation within the trial was 41.2, representing a 40-fold increase in the risk of death during or within certainly 90 days of a COPD exacerbation.

Therefore, a therapy that can reduce moderate-severe exacerbations, and most importantly severe exacerbations, by 34 percent in the trial, we would expect to see a reduction in the risk of death. Thank you.

DR. STOLLER: Thank you.

Dr. Ellenberg was next. I'm mindful that we're trying to conclude this section by 11:15. We'll have an opportunity to come back for clarifying questions for the committee, but the FDA will be asked to present at 11:15.

Dr. Ellenberg?

DR. ELLENBERG: Yes, Thank you.

Dr. Jones made a distinction between other endpoints as described in their protocol and exploratory endpoints, and noted that these other endpoints were all prespecified. I've seen many protocols list exploratory endpoints along with primary and secondary, and I would like to know what is the difference between an other endpoint and an exploratory endpoint, and what was the particular reason that they called these "other endpoints" rather than "exploratory endpoints." Thank you.

DR. JONES: Dr. Ellenberg, thank you for your question. All-cause mortality was an other endpoint. It was not an exploratory endpoint in the IMPACT study. It was a predefined endpoint with a predefined analysis plan and also a committee to adjudicate the mortality events. So this all-cause mortality here was an other endpoint but was not an exploratory endpoint.

DR. ELLENBERG: So did you have any exploratory endpoints in this study? You had a

number of other endpoints. The point is I do not typically see the phrase "other endpoints." So did you distinguish between other endpoints and exploratory endpoints? I'm just exploring the semantics here.

DR. JONES: Okay. I'm going to hand over to Dr. Lipson who ran the study. We have primary endpoints and few secondary endpoints, and then the other endpoints were other, and they were all related to the management of COPD.

Dr. Lipson?

DR. LIPSON: Thanks. David Lipson, GSK.

That's correct. What Dr. Jones said was correct. We had our primary endpoints, secondary endpoints, and other endpoints, and we did not have any exploratory endpoints within the trial. But all of the endpoints were designed to try to better understand the patient's experience, efficacy, and safety of Trelegy compared to dual therapies within the trial. Thank you.

DR. JONES: Thank you, Dr. Lipson.

I think to clarify some things on

exploratory endpoints, there were none in the IMPACT study, but generally exploratory endpoints, when we do include them in studies, are there to kind of inform us on future studies that we may do.

DR. STOLLER: Does that answer your question, Dr. Ellenberg?

DR. ELLENBERG: It answers that question. I have one other quick statistical question, if I might.

DR. STOLLER: Please.

DR. ELLENBERG: And that is, I'm wondering why there was no consideration of a multiplicity adjustment for the comparison of the Trelegy arm to the two dual therapy arms.

DR. JONES: Thank you, Dr. Ellenberg, for that question. I'm going to ask Dr. Makuch, our statistical consultant, to address the issue of multiplicity. Thank you.

DR. MAKUCH: Thank you for the question. Robert Makuch, biostatistics, director of the regulatory affairs program and past special government employee, FDA. Thank you for the

question.

It was not part of the prespecified analysis to account for that comparison that you alluded to, and I think, in general, it relates to the remark that for overall mortality, it is the ultimate stand-alone clinical endpoint of medical and regulatory interest. So there was no adjustment as you correctly pointed out. Thank you.

DR. ELLENBERG: Thank you.

DR. STOLLER: Very good. Dr. Tracy --

DR. JONES: Thank you very much -- oh, I was going to say, do we want to move back -- Dr. Lettis also has some comments that she'd like to make around that question as well, if that's ok.

DR. STOLLER: We'll ask you to be brief, but yes.

DR. JONES: Okay. Actually, it wasn't on that question. It was on the SUMMIT curve that people alluded to earlier, where they talked about -- I think it was Dr. May who was talking about the fact that it looked like FF/VI versus VI, that there was no difference.

I do just want to point out that SUMMIT is an event-driven trial and that you have very few subjects still in the study after two years. If you actually look -- and if we could maybe at some point get the slide up later -- at the period of around two years, there is still some separation between FF/VI and VI. So I think you should be very careful in interpreting those estimates out to three years in the SUMMIT trial.

Thank you, Dr. Lettis.

DR. STOLLER: Good.

Dr. Tracy, you have a question.

DR. TRACY: Yes, it's actually fairly simple. Can we go back to slide 93 just for a second? I think it's OR-93.

If you look at placebo versus all the treatment groups, it looks like pretty much everything helps, whether you're doing FF/VI, VI, or FF. If you look at this basic slide, it says if you do something, you do good; you don't do anything, you don't do good, which is definitely given.

Then I want to circle back to slide 23. I think that was with Dr. Jones. Let's circle back to 23. It deals with the issue about the separation with removal of ICS. I really want to hear what she says about that again, because this is a big deal with the agency, and I want to make sure I understand her perspective on this. Let's talk about the separation from the withdrawal of ICS in that run-in period versus nothing. Help me out here.

DR. JONES: Dr. Tracy, I just want to clarify. So the question that you're asking -- I just want to make sure -- is it around ICS withdrawal in the first 30 days or the stabilized COPD during the course of the study? I just want to confirm that I've got the right question.

DR. TRACY: It's the former.

DR. WISE: I think it's QR-53.

DR. JONES: Oh, it's 53, not 23.

Okay, so ICS withdrawal. In the first 30 days -- again, I'm clarifying again. I want to make sure it's ICS withdrawal.

DR. TRACY: Yes.

DR. JONES: Thank you. In the first 30 days, there were deaths in both the UMEC/VI and FF/VI arms. There were no deaths in the Trelegy arm. These patients were all taking an ICS prior to randomization, and while there were fewer deaths on the FF/VI arm compared to the UMEC/VI arm, we do see deaths on those patients who were on and continue to take an ICS through the study.

The patients who went through the trial of an ICS had more severe disease, and that was evidenced by more severe lung function and a higher proportion of patients with hospitalized COPD exacerbations prior to entering the study, and also a higher rate of COPD exacerbations during the study.

I think it is noteworthy that of the 7 patients who died on the UMEC/VI arm, only two were related to COPD, one of which was a pneumonia, suggesting that these patients did not have uncontrolled COPD, which was then exacerbated by the ICS withdrawal.

I would like to ask Dr. Wise as a member of the IDMC to comment as well.

DR. WISE: Thank you, Dr. Jones.

This is Bob Wise. Could you put up QR-53? Because I think that's what Dr. Tracy was looking for.

Is this the slide you were looking at?

DR. TRACY: Yes.

DR. WISE: The way the agency has interpreted this is that these were two different experiments done in the same population. The slide on the left were people who were using inhaled corticosteroids and had withdrawal in the dual bronchodilator arm, whereas in the experiment on the right, these were patients who were not using inhaled corticosteroids, and therefore had inhaled corticosteroids added.

So these are like, in the agency's and Suissa's paradigm, two separate experiments that were done in the same population. But when you look closely at the data, this population who were not using ICS at baseline were a different

population. As Dr. Jones said, they had better lung function, they had fewer exacerbations, they had fewer symptoms, and there was less beta agonist use.

So I would interpret this finding to mean not that we were doing two experiments in the same population, but really there was a subgroup that was taken out in whom the benefits of inhaled steroids were not apparent because they didn't need them and their physicians were not treating them with it, and they had a very good outlook in terms of mortality.

But I certainly want to point out that the fact that you can find a subgroup in a clinical trial that does not respond to the therapy in no way should be interpreted to mean that the entire population does not respond overall to that therapy. That's a bedrock principle of interpreting clinical trials since the days of the ISIS-2 study. Thank you.

DR. TRACY: I just thought I needed to clarify that. It's a big piece of the agency's

perspective, and I wanted to make sure I had that properly addressed. Thank you.

DR. STOLLER: Thank you.

This is Jamie Stoller. I'm aware there are still some questions, but in the interest of maintaining schedule, I will remind all of us on the committee that have questions, that includes me, we'll have an opportunity, hopefully, to ask these questions after clarifying questions to the FDA, time permitting, and perhaps in the afternoon should that be necessary.

So let's turn now to the FDA presentation, please.

FDA Presentation - Banu Karimi-Shah

DR. KARIMI-SHAH: Good morning once again. This is Banu Karimi-Shah, and I will now provide FDA summary remarks. The comprehensive prerecorded presentations have been provided to the panel members to view prior to today's meeting and also have been posted to our website.

In this summary, I plan to give you the highlights of the agency's presentation. These

slides will be familiar to the panel, as they have been taken from the prerecorded slide deck. Therefore, my presentation of these slides will be abbreviated and focus on the salient points and uncertainties in the application.

As has been previously reviewed by Dr. Jones, this slide shows the proposed all-cause mortality labeling claim for Trelegy Ellipta. With this comparison, the applicant is asserting that the efficacy on all-cause mortality is attributable to fluticasone furoate, the ICS component. Currently, there are no FDA-approved drug products which improve all-cause mortality in COPD.

Let's begin with a high-level look at the agency's presentation entitled, Overview of the Clinical Program. This is a schematic of the pivotal IMPACT trial. The typical design features have been reviewed by the applicant. I would like to highlight one key design issue here.

Subjects in IMPACT entered the study on their prestudy medication regimen, continued these medications during a 2-week run-in period, and then

were randomized to study drug. The change from prestudy medication to the study drug occurred directly at randomization. There was no washout period of prestudy medication to assess for clinical stability.

Given the clinical and statistical uncertainties that arose during our review of IMPACT, the agency looked to SUMMIT and TORCH for confirmatory evidence to increase our ability to rely on the evidence from this single trial. The study design and enrolled patient populations are summarized in this table across IMPACT, SUMMIT, and TORCH.

IMPACT evaluated all-cause mortality over one year, while SUMMIT and TORCH evaluated over longer periods. Based on enrollment criteria, IMPACT recruited a sicker COPD population who had uncontrolled COPD despite maintenance medication. TORCH and SUMMIT's inclusion criteria did not require the same markers of disease severity and did not require prestudy medication. IMPACT's run-in continued prestudy medications until the day

of randomization. In contrast, SUMMIT and TORCH required changes to any existing prestudy medication regimen prior to randomization through run-ins and other design elements.

Seventy-one percent of IMPACT's randomized population had a prestudy medication regimen that included ICS, and 38 percent were on prestudy triple therapy. SUMMIT and TORCH had lower proportions of prestudy ICS users. Seventy percent of subjects in IMPACT were frequent exacerbators at trial entry despite the use of these prestudy medications. SUMMIT and TORCH had lower proportions of frequent exacerbators.

I will now summarize the statistical review of efficacy. The primary objective of IMPACT was to understand the contribution of FF and UMEC to FF/UMEC/VI on exacerbation endpoints. It was not designed to assess all-cause mortality as a primary or secondary objective. Because the study was designed for exacerbation, it was not powered for mortality. The study duration was one year, which is typical for exacerbation studies. Historically,

however, studies evaluating mortality in COPD have been of longer duration.

As already noted, IMPACT met its primary exacerbation endpoint; furthermore, all key secondary analyses were statistically significant. I would like to use this slide to highlight the first bullet.

All-cause mortality was one of many other endpoints, most of which had two pairwise comparisons and none of which were under strict type 1 error control. This makes interpretation of the results challenging, as every such additional exploratory analysis conducted increases the probability of observing p-values less than 0.05 purely due to chance.

This slide shows the overall all-cause mortality results for IMPACT. The comparison of FF/UMEC/VI versus UMEC/VI, assessing the contribution of FF, revealed an estimated hazard ratio of 0.72 with a 95 percent confidence interval as shown and a nominal p-value of 0.042. While this p-value is less than the commonly used

threshold of 0.05, this was an exploratory analysis that was not under strict type 1 error control, so the statistical and clinical significance of the results are difficult to interpret.

This Kaplan-Meier plot uses the same data as the previous slide and shows the probability of death over the 52-week study, with the Y-axis ranging from 0 to 3.5 percent. The blue line represents the FF/UMEC/VI treatment arm, the red line represents FF/VI, and the uppermost green line, which has separated from the other two treatment arms, is the UMEC/VI treatment arm. These colors and the Y-axis will remain consistent throughout my presentation of IMPACT.

We note the separation of the UMEC/VI and the FF/UMEC/VI mortality curves over 52 weeks, but notably there is an early separation as denoted by the red arrow and bracket. This early separation of the mortality curves was unexpected and is inconsistent with previous trials that evaluated inhaled corticosteroids in COPD over longer periods of time, including SUMMIT and TORCH. I'll come

back to this early time frame later, but first let's look at the overall results across trials.

SUMMIT and TORCH were both designed with a primary objective of evaluating mortality through primary analyses that were powered to detect differences in mortality events between ICS/LABA and placebo.

Both trials were of longer duration than IMPACT. Neither of the two studies achieved statistical significance in the primary analysis of ICS/LABA versus placebo with respect to all-cause mortality, but to look for supportive evidence for a defective fluticasone on mortality that could help us evaluate the signal in IMPACT, we turned our focus to the comparisons that isolated the ICS effect.

This slide shows all the treatment comparisons from IMPACT, SUMMIT, and TORCH that isolate the effect of fluticasone products. As shown here, SUMMIT and TORCH had between 398 and 526 mortality events for each of the relevant fluticasone comparison. In contrast, IMPACT

yielded only 164 mortality events. So SUMMIT and TORCH provided roughly three times the amount of statistical information as IMPACT, and therefore had greater statistical power to detect an all-cause mortality difference attributable to fluticasone if it existed.

As illustrated by the hazard ratios and confidence intervals for the ICS comparisons shown here, SUMMIT and TORCH did not provide evidence of an effect of the fluticasone product on mortality.

Next, given the early separation of mortality curves, I discussed some exploratory analyses of impact to examine this early time frame of efficacy. The KM curve on the left shows the same analysis of the all-cause mortality data at 52 weeks shown previously.

The right panel shows an exploratory analysis where we eliminate the first 90 days and look only at mortality occurring after day 90. Notably, in the right panel, there is no separation between the curves, suggesting that the observed difference at trial completion may have been driven

by early events.

We acknowledge that these exploratory analyses are subject to bias and hypothesis-generating and that there are many potential explanations for the observed early separation of curves, including a real benefit, a chance finding, or some other factor in the UMEC/VI arm that may have influenced the early mortality signal in this group.

Given the design of IMPACT, this other factor could have been the effect of ICS removal in the UMEC/VI arm. I will use this idea to segue into the next portion of this summary presentation, which summarizes the agency's clinical considerations.

This is a useful schematic of how ICS removal may affect trial comparison in a trial that combines ICS naive and prestudy ICS subjects. This figure shows that ICS-naive subjects entering the trial could be randomized to either the addition of ICS, which serves as the intervention, or placebo, which serves as the control. This design is

typical of traditional add-on designs.

In contrast, subjects already on prestudy ICS could either be randomized to ICS removal or ICS continuation. Since their ICS status has not changed, the arm that continues ICS could be considered the control arm, while the arm that has ICS removed would be the interventional arm.

These two interventions, ICS addition for ICS-naive subjects and ICS removal for prestudy ICS subjects, are fundamentally different for the subjects going through a clinical trial. However, many COPD trials, including IMPACT, SUMMIT, and TORCH, have reported a result which combines the subgroups.

This concept has been discussed by multiple authors in the COPD literature, including Suissa, et al., and some of these authors suggested that effect estimates combining data from these two subgroups were uninterpretable in the setting of exacerbation data.

To apply these concepts to the IMPACT trial, I will jump to the prestudy ICS subgroup. In this

schematic of the IMPACT trial, we can see that subjects with prestudy ICS entered the trial and continued their ICS through the run-in period, but upon randomization, subjects randomized to UMEC/VI, the LABA/LAMA arm, underwent an intervention of ICS removal. In contrast, subjects randomized to Trelegy Ellipta, the ICS/LABA/LAMA arm, continued their ICS. This highlighted comparison isolates the contribution of the ICS, and in the case of this subgroup, of the removal of ICS.

This prestudy ICS subgroup comprises 71 percent of the subjects in IMPACT, meaning this subgroup contained over 7,000 subjects and nearly 1500 were randomized to ICS removal in the UMEC/VI arm. In the proposed claim, the effect on all-cause mortality is being attributed to FF, the ICS component of Trelegy Ellipta.

However, given the protocol mandated ICS removal for those subjects on prestudy ICS randomized to the UMEC/VI arm, an existing published literature describing the effects of ICS treatment and removal in COPD, we explored the

effect of prestudy therapy and ICS removal in IMPACT.

To do this, we examined the probability of all-cause mortality by prestudy medication subgroup. The Kaplan-Meier curve displaying the all-cause mortality results for the prestudy ICS subgroup is pictured here. In this left panel, we can see that the separation between the UMEC/VI Trelegy Ellipta arm suggests a difference in mortality that develops in approximately the first 90 days as denoted by the black arrow.

Since all subjects in this analysis entered the study on ICS, those randomized to UMEC/VI had ICS removed. Those randomized to Trelegy continued ICS. These data raise the possibility that ICS removal may have led to increased mortality events among these COPD subjects in the UMEC/VI arm, rather than fluticasone improving mortality in the Trelegy arm.

In the right panel, among ICS-naive subjects in which randomization to Trelegy meant the addition of ICS, we see no separation. We

acknowledge the exploratory nature of this analysis and that the ICS-naive subgroup is underpowered to show a difference in mortality. However, even a trend in this subgroup would help support the idea that the overall analysis result was not driven primarily by effects of ICS removal.

Given the different behavior of the subgroups, we tested for the presence of a statistical interaction between prestudy ICS and treatment for the FF/UMEC/VI versus UMEC/VI pairwise comparison, which resulted in a p-value of 0.08. These results, again while exploratory in nature, suggest that the overall population mortality results may be difficult to interpret and that it may be more appropriate to analyze the prestudy ICS subgroups separately.

In this table, we attempted to quantify the effect of ICS removal and addition across IMPACT, SUMMIT, and TORCH by focusing on the ICS comparison. Here, we look at ICS removal data from the prestudy ICS subgroups at the day 90 time point, but the hazard ratio is inverted to describe

ICS removal as the intervention and ICS continuation as the control.

We acknowledge once again that these exploratory analyses are subject to the bias. Despite the limitations of potential underpowering, differences in trial design, enrolled population, and fluticasone products between these trials, in each of these trials, we observed an increased risk of all-cause mortality after ICS-removal events at 90 days in comparisons that isolate the effect of the ICS.

In contrast, with respect to ICS addition, we see that the effect estimates for nearly all of these fluticasone addition comparisons hover around 1. These ICS-naive subgroup data from SUMMIT and TORCH reinforce the ICS-naive subgroup data seen in IMPACT; and despite these ICS-naive subgroups including over 1700 subjects in IMPACT, almost 11,000 subjects in SUMMIT, and almost 3,000 subjects in TORCH, we see that the data from all three trials is consistent, suggesting that the addition of fluticasone product did not improve

mortality.

With these data discussed, we can move to a summary of my charge to the committee. In my charge to the committee, I reviewed the regulation which requires substantial evidence to support a labeling claim or new indication. The regulations governing determinations of effectiveness are further described in guidance documents from the agency.

The GOLD standard is evidence from at least two adequate and well-controlled studies; otherwise in some specific setting, a finding of substantial evidence of effectiveness can be made based on one adequate and well-controlled clinical investigation, plus confirmatory evidence.

Key factors to allow for such a determination include the persuasiveness of evidence from a single study and the robustness of confirmatory evidence. The guidance indicates that reliance on a single study should be limited to situations in which the trial has demonstrated a clinically meaningful and statistically very

persuasive effect. In that light, there is often an expectation of evidence of an effect at a statistical significance level considerably lower than 0.05 when a proposed effectiveness claim relies on results from a single study.

There are a number of issues that raised concern about the ability of the results from the IMPACT trial to support an all-cause mortality claim for Trelegy Ellipta. Here is a bulleted list of the efficacy considerations, which I have summarized in this presentation:

The statistical uncertainty of the ACM results in IMPACT, given that it was a single trial without strict type 1 error control; the inability of the evidence from SUMMIT and TORCH, two trials of longer duration designed to evaluate all-cause mortality, to provide confirmatory evidence despite their greater statistical power; the early time frame of efficacy in IMPACT, which would be unexpected for ICS given what is known but not inconsistent with ICS removal;

The effect of ICS removal across studies.

The data from IMPACT, as well as SUMMIT and TORCH, suggest that subjects with prestudy ICS therapy, who had ICS removed by randomization, had a clinically significant increased risk of death by day 90. Addition of fluticasone in ICS-naive subjects did not suggest a mortality benefit for ICS addition;

And finally, the generalizability to clinical practice in which healthcare providers are considering the benefit of adding a therapy. Seventy percent of patients in IMPACT entered this study on prestudy ICS and could be randomized only to ICS removal or ICS continuation, but not ICS addition.

Because of this, it is uncertain whether the IMPACT trial is able to answer the clinically relevant question of whether the addition of fluticasone furoate to UMEC/VI, in a subject without previous ICS therapy, will decrease all-cause mortality in COPD.

To focus your deliberations on each of these points, we present each of these issues in the

following discussion questions followed by a single voting question. I will briefly review these now, and these will be displayed again to facilitate your discussion this afternoon.

The first question asks the committee to discuss the persuasiveness of the data in the IMPACT trial to support the claim that fluticasone furoate as a component of Trelegy Ellipta improves all-cause mortality in COPD. In order to facilitate your discussion, we have included a number of elements that we would like you to include in your discussion.

The second question asks the committee to discuss the implications of prestudy ICS use and ICS removal on the interpretation of the all-cause mortality data in the IMPACT trial. Once again we have provided certain elements that we would like you to include in your discussion.

The third discussion question asks the committee to consider the generalizability of the IMPACT data to relevant clinical practice decisions about fluticasone furoate as add-on therapy in

COPD. Again, there are several elements that we would like for you to include in your discussion listed.

Finally, a single voting question of whether the data from the IMPACT trial provides substantial evidence of efficacy to support the claim that Trelegy Ellipta improves all-cause mortality in patients with COPD. If you vote no, we ask you what further data would be needed.

Thank you for your attention. We can now move on to the clarifying questions to the agency. You may refer to any slides that were either presented here this morning or that were provided to you as part of the prerecorded presentation.

Please remember to refer to the name of the presenter, the title of the presentation, and the slide number when making your request. From the agency, Dr. Robert Busch; Ms. Susan Duke; Dr. Gregory Levin; Dr. Yongman Kim; and Dr. Sally Seymour, and I will be responding to your questions.

Dr. Stoller, I turn the meeting back to you.

Clarifying Questions to the FDA

DR. STOLLER: Thank you very much, Dr. Karimi-Shah.

We will of course, as said, now take clarifying questions. Again, please use the raised-hand icon to indicate you have a question. Remember to put your hand down after you've asked your question. Please remember to state your name for the record and direct your question to a specific presenter if you can.

If there is a specific slide you wish to be displayed, as said, please specify the presentation, presenter, and slide number. And again, it would be helpful to acknowledge the end of your question with a thank you or end of any follow-up question with, "That's all for my questions," so we can move on to the next presenter.

So with that as a background, the first hand raised is I believe Dr. Marshall.

DR. MARSHALL: Thank you, sir. I'd like to ask two hopefully very specific clarifying

questions.

Dr. Karimi-Shah, if you would respond, I would be grateful. The first question is, in listening to the response and looking up the issues in the change in mortality risk for IMPACT versus SUMMIT and TORCH, is it the contention or position of the agency that a one-year duration reduced mortality is less clinically significant than a multiyear?

In the argument that while there may be statistics, I think most clinicians would be very interested in a therapy that could reduce, substantially reduce, mortality even for one year, if not for multiyears.

DR. KARIMI-SHAH: This is Dr. Karimi-Shah. Thank you for your question, Dr. Marshall. It isn't so much a contention that a one-year trial is less clinically significant than a multiyear trial for a mortality claim. The point that I was trying to make in that slide, and that we've made in our briefing document and in our other presentations, was more of the plausibility of seeing a difference

over a one-year trial than rather these multiyear trials, which have been done in the past.

So that was really the point that that slide was trying to make. Obviously, if there was clinical certainty in the effect over a one-year trial, I think that would of course be clinically significant, but it's more about the plausibility of seeing the effect over one year, given the uncertainties that we have with the application.

DR. MARSHALL: Thank you. The second question I hope is well focused. If it's generally agreed, in the sense that I heard in both the original presentations that we reviewed and your comments this morning, that the FDA as well as the sponsor would agree that ICS removal in these more severe patients was associated with increased all-cause mortality -- the argument being that the ICS is typically not added until the disease progresses further and multiple presentations and comments about the old risk for pneumonia that has been back and forth for many years -- the question is, is there a difference in the thinking of the

agency if, say, something as straightforward as the claim severe COPD was used as opposed to just COPD across the board?

I'm an allergist-immunologist, but we are starting to take care of COPD earlier in the course of the illness. Our pulmonary colleagues take care of them later in the period we typically don't take care of people. We don't go to the ICU, et cetera, but we certainly are interested in therapies that would slow down the progression of this ultimately fatal disease.

The question is, with these more severe individuals, that when ICS is withdrawn, the events start to increase, and by extension, their mortality risk starts to increase, is it the term "COPD inclusive" or is it a subgroup that you would refer to as severe COPD that would make the difference? I'm just trying to clarify the agency position on this.

DR. KARIMI-SHAH: Yes, Dr. Marshall. Thanks for that question. In order to answer your question about this, I'm going to turn it over to

Dr. Robert Busch.

DR. BUSCH: Hi. This is Rob Busch, FDA. I'm going to try and answer your question because my understanding of your question is, is the severity argument presented by the sponsor compelling, and then how could we incorporate that perhaps into how we describe the data. I'm going to ask for the backup slide deck, slide 5, and then 6, but we'll start with backup slide deck, slide 5 to come up.

The severity issue is an interesting question. We've had a lot of discussions about it internally because the applicant presented the same explanation for the disparate results in the subgroups of IMPACT early in our review cycle; and the use of prestudy ICS and severity are somewhat correlated, as has been mentioned. But I think there are some issues with this explanation that might limit how we would apply this, for example, in a labeling setting, which is not the proposed labeling that is being asked for now.

First, when we presented these subgroup

data, we asked you to look at each subgroup on its own and draw conclusions from the prestudy ICS and ICS-naive subgroup separately, almost like looking at two separate trials because each subgroup had different functional interventions.

We heard Dr. Wise say that we were asking you to see this as two separate trials in the same population, but I don't think that's what we're asking you to do. While we are asking you to look within subgroup comparisons where severity across the arm should be equal or comparable, we're not asking you to make any sort of formal across subgroup comparisons; not only because they had some differences in severity, but more importantly because subjects in each subgroup had very different interventions imposed upon them at randomization.

In my opinion, the only time an across-subgroup comparison is being made is the implicit comparison of accepting the combined data into an overall analysis, because when we do this, we're assuming that the patient groups and

interventions are similar enough to throw together and give a single point estimate of effect. Also, the severity argument completely sidesteps the fundamental point that ICS was removed from some patients and not from others.

If you could bring up the backup slide deck, slide 7 -- oh, excuse me. Could you bring up slide 6 from this backup slide deck? It should just be the next one. This is the "within" subgroups. The ones in the red boxes, you can see that across the arms -- excuse me. Within each subgroup, the arms are somewhat similar in severity, so the comparison should be somewhat valid for lack of a better term.

Could you bring up slide 17 from the backup slide there? Again, the severity argument I think sidesteps on the fundamental point, is that we're talking about ICS removal as an intervention. As we've talked about, the prestudy triple therapy subgroup could not have had any drug class added at randomization, only drug classes taken away or continued.

So it's hard to see how we can interpret the difference in the subgroup as a benefit from addition rather than harm after drug removal. As you mentioned, it seems inconsistent with current practice to say that we see a patient on triple therapy who still has uncontrolled symptoms and frequent exacerbations, and then we decide or jump to a decision about ICS removal.

The same concerns apply to that prestudy ICS subgroup because attributing the observed effects in the prestudy ICS subgroup to severity difference still avoids the fundamental point that mortality events observed in the UMEC/VI arm compared to FF/UMEC/VI are from a comparison where the only difference between arms is that the subject in the UMEC/VI arm had ICS removed.

Finally, one last point. You asked a direct question; I apologize. The data argument that I think, again, takes away from this issue of severity and how we would potentially interpret that in labeling is the sponsors proposed -- excuse me. The subgroups we see in IMPACT and how we

presented those data, we see these early risks of death due to ICS removal across the prestudy ICS subgroups of all three trials, IMPACT, SUMMIT, and TORCH, and we see no effect or sort of a flat effect of ICS addition over all three trials, IMPACT, SUMMIT, and TORCH.

So each of the prestudy subgroups in these trials has a different severity, and each of the ICS-naive subgroups in each of these trials has a different severity, and both other trials, even at ICS-removal run-in scenarios, that may have eliminated the most vulnerable patient.

So if were just a severity difference in the prestudy ICS subgroup of IMPACT, which admittedly has the highest severity, then why are we seeing that similar pattern across all three trials, and especially in SUMMIT?

So I think the severity argument is difficult to justify in the face of the data from those other trials and again avoids the fundamental point of ICS removal occurred and how do we judge that. So I think it would be very difficult to

incorporate that and craft labeling around that without dealing with that generalizability issue and the ICS removal directly. Sorry for the long-winded reply.

DR. MARSHALL: Oh, no. Thank you both very much.

DR. STOLLER: Thank you.

I think Dr. Tracy is next, please.

DR. TRACY: No, I'm good. Thank you.

DR. STOLLER: Dr. Ellenberg?

DR. ELLENBERG: Yes, thank you.

I'm not sure who wants to answer this. My question is about, actually, the GSK slide 23 and 24 that purport to show no difference in worsening in lung function, according to whether or not people were on an ICS beforehand. Dr. Jones made the argument that this undercuts any concern that those who had ICS withdrawn were at greater risk because the lung function was about the same, and I wanted to know what the FDA's perspective was on that argument. Thank you.

DR. BUSCH: I can try and take that one as

well. This is Robert Busch from FDA. In COPD, I think that FEV1 and exacerbations are somewhat different measures, and this is recognized by international guidelines such as the GOLD guidelines which have separate severity scales for FEV1 and exacerbation history. Looking at FEV1 does not necessarily refute the premise that we brought up if you maybe buy into the idea that severe exacerbations lead to death, which I think that association is certainly present in the literature. FEV1 is a factor, but I'm not sure that the FEV1 data refute what we're saying.

Also, the graphs that Dr. Jones presented show you the mean numbers for FEV1 and SGRQ. This is a fair comparison of everyone, but it doesn't capture the decline that could be seen in individual patients, and especially in those who died. So something like a responder analysis of the proportion of patients who had significant decline in these parameters might be more appropriate in this case, but we didn't ask for that, and it might be unfair to look at only the

subjects who died since we know that these subjects could represent the greatest decline in the study.

So that's I guess the main points of why we acknowledge these results, but I'm not sure that it refutes what we're talking about.

DR. ELLENBERG: What about the other measure on slide 24?

DR. BUSCH: I believe that's the SGRQ, but I'll wait for it to appear. My screen is spinning, but if somebody could confirm to me whether that slide represents the St. George's Respiratory Questionnaire results.

DR. JONES: This is Dr. Jones from GSK. Yes, it does.

DR. BUSCH: Thank you, Dr. Jones. I appreciate that.

SGRQ, the St. George's Respiratory Questionnaire, incorporates a lot of different measures on some level in a patient-reported outcome. So I think that that one, we could interpret some of those data differently, and they may have more bearing on exacerbation certainly

than FEV1 perhaps, but also potentially on how the patient is feeling from a holistic perspective. But even in that situation, what I was mentioning earlier about mean numbers across the entirety of the trial versus individual patients that did much worse, I think would still be worth thinking about. So it's hard to say exactly what to make of those.

DR. ELLENBERG: Thank you.

DR. STOLLER: Great. This is Dr. Stoller. I have a question that follows up on Dr. Ellenberg's point. It strikes me that the primacy of the issue here, if we're looking at the consequences of ICS withdrawal, relate to the consequences of ICS withdrawal. The confusion that I have is about a couple of things. One is the data that we just addressed about FEV1, SGRQ, as well as I think in the sponsor's slide on UMEC mortality, the continuous accumulation of mortality over time.

So perhaps, Dr. Busch, can you again try to help me understand if the mortality effect were related to ICS withdrawal, I would expect clinical

metrics to be in the direction of deterioration, and I would have expected the mortality events to occur relatively acutely given the temporal relationship between hospitalization for severe exacerbation and mortality, which is generally clinically observed. So I'm struggling with that discordance between the functional physiologic and accumulated mortality data compared to the 90-day window on ICS withdrawal.

Is my question clear?

DR. BUSCH: I think so, although -- this is Rob Busch. I think it's definitely clear. It is certainly a difficult one to answer, so let me give it a shot, though. I'm going to pick it apart into perhaps two separate points.

First, can we bring up backup slide deck, slide 14? The sponsor presented data for cause of death in the first 30 days, and while the sponsor's statement about the first 30 days is correct, it's not clear that 30 days should be the absolute cutoff for this analysis, nor the 90 days should be necessarily.

In the Kaplan-Meier curve, we saw different behavior of the UMEC/VI curve up until approximately day 90, and that's what you're mentioning, Dr. Stoller. If we look at the death narratives and adjudication among subjects who had ICS removed during that time frame, we would get the results on this slide.

I want to mention here, though, that drawing important conclusions from cause of death and death narratives in clinical trials should be approached with caution. Again, we have to be careful since the actual cause of death can be difficult to ascertain, especially if the event is unwitnessed or happens outside of a healthcare facility. We can talk about that more. This is definitely not a criticism of GSK data collection on the subject, but a comment that applies broadly across all clinical trials.

But as we can see on this slide, within the first 90 days, 5 subjects in the prestudy ICS subgroup who were randomized to ICS removal in the UMEC/VI arm had a cause of death attribution that

explicitly lists COPD or COPD exacerbation compared to zero in the FF/UMEC/VI arm, where ICS was continued. If we expand these terms a little more to be a little more inclusive, to include terms like "respiratory failure" and then again to include terms like "cardiopulmonary arrest," we see a similar trend.

So again, I want to advise caution about this and about taking these cause of death narratives as gospel, but these data may still suggest that COPD exacerbations may have played a role in at least 5 death events by day 90 in the ICS-removal arm.

That's one part. Another part is despite our uncertainties surrounding the ICS removal in IMPACT, and the way these data may or may not support the idea, it's also important to note that GSK is seeking a claim for all-cause mortality, not respiratory-related mortality. So FEV1 did go up, did not go up, did go down, did not go down. If we focus more on the mortality data, the exact cause of those I think is very difficult to discern.

There was another part of your question that I think I've gotten away from. I believe I answered one part about why didn't these events -- or why don't we see some of these effects of these events in the data and in the time frame, but there was another part to your question.

Could you repeat it, please?

DR. STOLLER: Sure. I think you're suggesting that in fact there was a consequence of ICS withdrawal here. The other dimension was the continuity of mortality over time in the UMEC/VI population that we showed in the sponsor's slide. It's not as though there was a bolus of deaths in the first 90 days, but deaths accrue over time. And I wonder if you have a response to that in the context of the hypothesis that ICS withdrawal was the causal event to the mortality.

DR. BUSCH: Okay. Thank you. I understand.

This is part of the reason why we asked for the after day 90 data, understanding that there are plenty of limitations as we've discussed a few times. In this case, we have to think about how

the difference develops. If you look at the data after day 90, they're pretty flat. So it is not that these few events were the only events in the data -- oh, actually, could we bring up Clinical Considerations, slide 15?

Again, we had discussions about how these early events might affect the mortality interpretation, and it's true that they represent a minority of the mortality events in the trial, so sorry, I'm on track now. But the reason we find the data within the first 90 days compelling are sort of twofold.

First, the signal for that early mortality after ICS removal is present in all three trials. It's a few mortality events, but we keep seeing that sort of signal, which raises doubt about the idea that this is just a chance finding.

Then second, and perhaps more importantly, even though these early events are few in number, it's the only period where a difference between the study arms is clearly established, as we can see on the slide that we talked about just a moment ago,

which is after 90 days. So that is summary slide deck slide 16; if you could pull that up? And we've seen that previously.

This does not appear to be the -- the first slide was Clinical Considerations, slide 15, and if that's this, I apologize, and we'll figure it out. This is Clinical Considerations. It appears that this is the overview of the clinical program slide deck, I believe, if I remember my own slides.

Could you bring up the Clinical Considerations, slide 15?

DR. BAUTISTA: Hi, Dr. Busch. This is Phil Bautista, the DFO. Give us one second, and we'll bring it up for you.

DR. BUSCH: Sorry. No problem.

Well, I'll keep talking about the other point briefly just to make sure that we get through stuff. I know we're on a time crunch.

Again, the data after that first 90 days, while it contains the bulk of the mortality events, those mortality events then don't differ across the arms. And again, ICS removal and severity are

somewhat linked, but if we don't see any effect after day 90, it's difficult, given that we have these ICS-removal events, and we see this effect within the first 90 days.

So we felt that we needed to discuss these early mortality events among the ICS-removal subjects and the analyses of those subjects in such detail because they drive the mortality difference observed at trial end, so they're a big part of the difference the applicant is relying upon for the claim.

DR. STOLLER: Fair enough. That answers my question.

I'm aware we have one minute left, and Ms. D'Agostino has the last clarifying question for the FDA, please?

MS. D'AGOSTINO: Thank you. My question is quick, so that's perfect. This is Emma D'Agostino. Given that one of the main concerns is about the lack of type 1 error control, have you done multiplicity corrections for all-cause mortality just to see what would happen to the p-value, maybe

using the same strategy that was used for the primary endpoint?

DR. LEVIN: This is Greg Levin. I didn't introduce myself earlier. I'm the deputy director for the Division of Biometrics III. I'm a statistician at FDA.

If you did any sort of multiplicity adjustments to handle the long list of exploratory endpoints, and if you were comparing it to a threshold of 0.05, it would not meet that threshold quite quickly. We did not do that. We think there are additional factors here beyond that, such as the level of evidence that one needs to support a claim based on the single study and some of the other uncertainties.

But to directly answer your question, any sort of multiplicity adjustment, when you have a p-value of 0.042 and you have the number of comparisons that were looked at here, would quite quickly send the p-value above a 0.05 threshold if that's the threshold you were utilizing.

MS. D'AGOSTINO: Okay. Thank you.

DR. STOLLER: So I'm aware we're at 12:05. I'm also aware that there were many questions, both to the sponsor and to the FDA, that have not yet been addressed, and my hope is that those who've asked, and we've recorded who you are, can frame those questions perhaps in the discussion of the clarifying questions after the open public hearing. So as we are now at 12:05, we will break for lunch. We will reconvene in 45 minutes, at 12:50 p.m. Eastern Standard Time.

Panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should please plan to rejoin at about 12:35 p.m. to assure that you are connected before we reconvene at 12:50 p.m.

Thank you. We're on break. We'll reconvene at 12:50 with the open public hearing. Thank you very much.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)

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

(12:52 p.m.)

Open Public Hearing

DR. STOLLER: Well, let me welcome everyone back. We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the

meeting.

FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and the committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce

yourself, please? Please state your name and any organization you are representing for the record.

DR. HAN: Hello. My name is MeiLan Han, and I'm representing myself today. I am a professor of pulmonary -- [inaudible - audio gap] -- at the University of Michigan in Ann Arbor, and in full disclosure, I have also consulted for GlaxoSmithKline, as well as multiple other pharmaceutical companies, including AstraZeneca that also makes a triple therapy product for COPD, and the ETHOS study, which is also of relevance. I have also participated in the external steering committees for the IMPACT study program, but I'm also, therefore, quite familiar with the Trelegy data.

The question at hand today is whether Trelegy demonstrates clear mortality benefit in COPD as compared to LAMA/LABA in the particular patient population that was studied in IMPACT. These are highly symptomatic individuals that were at high risk for exacerbation.

Since submitting my original comments, I've

had the chance to review the FDA briefing document for this meeting, and the FDA is to be commended for the meticulous review and reanalysis of the existing data. I would like to point out, however, that significant emphasis in this report is placed on the number of deaths occurring directly after inhaled corticosteroid removal.

I am intimately familiar with the data, as I have mentioned, and what we've found is that patients who had received ICS before entering the trial do seem to be a unique patient population and really did need inhaled corticosteroids. This was the group that saw, for instance, the greatest exacerbation benefit during the study.

I would like to point out when we're looking at mortality, however, that in some ways it becomes a bit of a circular argument; whether patients die or experience exacerbations because the medication was removed or they experience benefit because the medication was added. To me, the resulting interpretation is the same, and that is that in select patients, triple therapy improves

exacerbations, as well as improves survival.

Now, I know there's a lot of data that you're wading through today and interpreting data in isolation such as this I think is quite difficult. And while I'm not on the panel today, I know that if I were, I would ultimately want to be on the right side of history.

So while I realize it's not being discussed today, I would like to emphasize to the panel that the ETHOS program sponsored by AstraZeneca -- this data is also fully publicly available, which has a different study design and does not have inhaled corticosteroid withdrawal as an issue to contend with -- shows the exact same mortality benefit for triple therapy in a very similar COPD patient population as compared to LABA/LAMA.

So for me, taking both sides into account, the data is actually highly convincing. In weighing the decisions today, I think it is also important to remember that we're not really looking at the safety or efficacy of a new medication, but rather the question at hand is whether something

that's already approved is beneficial among highly symptomatic individuals at high risk for exacerbations with respect to mortality.

The final thought that I wanted to leave the panel with is what a decision here today could mean for the entire COPD patient community. Having a therapy that improves COPD mortality, even in a subset of patients with COPD, I believe has the potential to improve care for all patients with COPD in the U.S.

As a pulmonologist, I've witnessed significant nihilism on the part of the medical community at large with respect to diagnosing and treating COPD. Many primary care health providers are not compelled to appropriately diagnose any COPD with spirometry simply because they have a sense that they can't get it wrong, because whatever treatment is chosen, it's good enough. There are really no consequences to their actions.

However, if there is a therapy that changes disease course in this profound way, than to me it behooves all healthcare providers to appropriately

diagnose and treat all patients with COPD, because by not appropriately assessing and treating all patients, providers may potentially miss patients that could experience mortality benefit.

This is the first time we've had evidence that correct treatment with respect to pharmacotherapy can save lives, and I really urge the panel to think about the potential impact that recognizing mortality benefit in appropriate patients could have, not just on the select subset, but on the entire population of COPD patients.

The decision being weighed today could improve the lives of millions of Americans by transforming the landscape of how COPD care is approached, particularly in primary care. I strongly believe this data will be a game changer in compelling primary care providers to appropriately diagnose, assess, and treat all patients with COPD, as there would now be real consequences to not doing so. Thank you.

DR. STOLLER: Thank you.

Will speaker number 2 begin and introduce

yourself? Please state your name and any organization you're representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I'm Dr. Meg Seymour, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Today, the committee is asked to discuss whether data from the IMPACT trial provides substantial evidence supporting the claim that Trelegy improves all-cause mortality for patients with COPD. The design of the IMPACT trial limits its ability to address this claim. We share the concerns of the FDA scientists that trends shown by the data do not support the claim that Trelegy improves all-cause mortality.

In the IMPACT trial, the difference in all-cause mortality between ICS and non-ICS trial

arms was limited to the first 90 days of the trial and disappeared after that. This clearly suggests that the difference could have been due to how some patients assigned to the non-ICS arm were being treated with ICS prior to the study.

As FDA scientists pointed out, 71 percent of patients were treated with ICS prior to the study, however, if they were assigned to the non-ICS arm, they had their ICS removed as part of the study design. Of the 29 percent of patients who were ICS-naive, there was no apparent difference in all-cause mortality between those in the ICS and non-ICS arms.

Although this analysis was underpowered, the data suggest there is no meaningful difference. Thus, the difference in all-cause mortality between the ICS and non-ICS arms appears to be due to this removal of ICS. It's essential to note that when FDA scientists analyzed the data as if ICS treatment was a control and ICS removal was an active condition, they found a potentially clinically significant fivefold increased risk of

mortality attributable to ICS removal from baseline to 90 days into the trial.

This analysis clearly suggests that Trelegy does not actually reduce all-cause mortality. Instead, removing ICS for some patients appears to have led to the difference in all-cause mortality between the ICS and non-ICS arms. In other words, the all-cause mortality result of the IMPACT trial is due to the design of the trial rather than the drug itself reducing all-cause mortality.

In addition to this apparent effect of the study design, we're also concerned about the limited diversity of the trial samples, which was mostly older white males. In addition to this apparent effect of the study design, we're also concerned about -- it's unclear whether women, people of color, or other age groups would or would not benefit.

The design of the IMPACT trial is not consistent with how patients will be treated in the real-world clinical setting. In a typical clinical setting, patients would be generally prescribed

Trelegy because they're moving from double to triple therapy. A Trelegy prescription would mean adding treatment with ICS to those who are ICS-naive.

Since the IMPACT study design terminated ICS use in the control arm, the data from IMPACT cannot address whether adding ICS to those who are ICS-naive reduces all-cause mortality. We therefore urge the committee to keep this in mind when discussing the proposed labeling claim and to reject it as not adequately supported by the data. Thank you.

Clarifying Questions (continued)

DR. STOLLER: Thank you very much.

The open public hearing portion of the meeting is now concluded and we will no longer take comments from the audience. I'll remind the committee that we're at 1:02, and recognizing that there were questions both to the sponsor and the FDA that were clarifying questions that were not addressed earlier because of time, we now have approximately 48 minutes to do so. We've kept

track of those questioners.

We'll begin with questions to the sponsor that were unasked, and then questions to the FDA. So let's keep them in that order, please. I'm aware that the order of questioners to the sponsor were, first, me; then Dr. Dodd; Dr. Kelso; Ms. D'Agostino; and Dr. Carvalho, and then to the FDA, Drs. McCormack; Carvalho; and Kelso.

So I will begin and pose my question to the sponsor, and that is this. It regards CR-17, the analysis of SUMMIT and in what is in the presentations, the same slide CO-11. The predicate is that given the importance of convincing replicate data in the FDA guidance of the condition for approval of a labeling change, my question is this.

You've posed here the subset analysis of the exacerbating population. We acknowledge the fact that in SUMMIT, as with the other trials, there were patients, albeit before the washout, that were on ICS and even triple therapy. As I recall, it was 9 percent in SUMMIT on triple therapy and

33 percent on ICS.

So my question to the sponsor is whether you've done this analysis of placebo versus FF/VI in the prior ICS subgroup of SUMMIT. I understand the numbers get progressively small, but the trends would be important.

Is my question clear? I have a follow-up question, but I want to make sure that questions clear.

DR. JONES: Thank you. Dr. Stoller. Yes, it is. I'm going to hand over to Dr. Crim to address it.

DR. CRIM: Thank you. Dr. Jones.

Before I address that, I just wanted to go back to a previous question raised by one of the committee members from the standpoint of the comparison between FF/VI and VI in this exacerbating population.

DR. STOLLER: Can you respond to my question and we'll come back to the other, please?

DR. CRIM: Yes. Okay. I'll respond to your question first. Slide up.

Here's the data from, as you can see, both the IMPACT as well as the SUMMIT study in terms of those that were using ICS at screening and those that were not. As you can see, those that were using an ICS at screening, which was only 10 percent of the subjects in the exacerbating population, got randomized to placebo. So again, it's only 10 percent. And then you can see the non-ICS users.

In those that were using ICS -- again, 10 percent -- you can see that treatment effect with a p-value of 41 percent reduction favoring FF/VI versus placebo, and you can see the p-value. In those that were not using ICS, although it did not achieve statistical significance, you can see that the point estimate does in fact favor FF/VI.

Does that answer your question?

DR. STOLLER: No. Is this the exacerbating subset or is this just the ICS baseline subset? I'm asking about the exacerbating subset who were on ICS before.

DR. CRIM: This is the exacerbating subset,

yes.

DR. STOLLER: Oh, I see. Okay.

I have one follow-on question as well, again, regarding replicate studies. Now, you've contended, perhaps unlike the agency, that TORCH is irrelevant, given a different molecule and practice standards 20 years ago. Nonetheless, I would wonder whether you've done a similar analysis of this very analysis in TORCH, and if you have, I would like to see that; in other words, the exacerbating subset in TORCH that were on ICS at baseline.

DR. CRIM: I'll see if we have that slide, but in the interim, what I can say about the TORCH population from the standpoint of looking at those who were an exacerbating population, and again recognizing the points that you raised from the standpoint of the treatment paradigm at that time, looking at the exacerbating population and, again, the comparison of particular fluticasone proprionate and salmeterol, the treatment difference did not achieve statistical

significance, although the point estimate did favor the combination compared with placebo with about a 10 percent reduction in mortality, but did not have the p-value less than 0.05.

DR. STOLLER: Okay. Thank you. That answers my question.

Did you have a follow-up comment to a prior question? We'll ask you to be brief, but Dr. Dodd is next, if not.

DR. CRIM: It was just to make the point that -- I think a committee member had requested if we had a comparison in the exacerbating population of SUMMIT that looked at the comparison of FF/VI with VI. And again, since I've shown in the slide, and as Dr. Wise mentioned, you have a floor effect, therefore, just looking at those point estimates, you would not see a large difference between the FF/VI and the VI arm.

That's why I think it was more important to look at the FF versus placebo arm, where, again, you saw about a 34-35 percent reduction in mortality because of that floor effect. Looking at

the FF/VI versus placebo was probably the best way of getting a sense of the FF effect. Thank you.

DR. STOLLER: Thank you very much.

Dr. Dodd?

DR. DODD: Hello. This is Lori Dodd. I have a question for the statistician from the company. I want to address the multiplicity question. I noticed that in the primary publication, and as noted in the documents from the company, there were planned multiplicity adjustments for the co-primary hypothesis of the comparison of Trelegy versus FF/VI and Trelegy versus the UMEC/VI. This plan extended to the secondary endpoints with the closed testing procedures.

For example, just focusing on the co-primary, my understanding of the procedure was that they either both had to be statistically significant at p less than 0.05 or one of them had to be significant at some other or much lower threshold like p less than 0.01. Then there was a similar adjustment for multiplicity with a

secondary endpoint, but there was no plan for multiplicity adjustments for the other endpoints.

I think this is quite concerning. In general, there are two areas of concern with multiplicity that I see here. The first has to do with the multiple endpoints for a given treatment arm comparison, so this gives multiple chances for a drug combination to win on one of many endpoints. The applicant has commented on this by stating that 33 -- if that's the exact number -- of 34 endpoints meet statistical significance at the 0.05 level. I find this argument ad hoc, and I think it needs more statistical rigor behind it.

But most importantly, this argument misses the other key problem with multiplicity, which is that there are two armed comparisons that need consideration. So this gives Trelegy two chances to win on every endpoint considered, so it gives Trelegy two chances to win on the mortality endpoint, which is what we've seen.

So I would like to hear from the statistician what was the reason for the logic

about multiplicity for having multiplicity adjustments for the co-primaries and the co-secondaries but not for the other endpoint.

DR. LETTIS: This is Sally Lettis, statistician, GSK. I'm sorry. I got cut off, and I missed part of your question. So I'll start to answer it, and if I don't answer all of it, please could you just ask me to add further clarification?

Could I first have up slide SL-2? This study was primarily set up as an exacerbation study, so the primary endpoint was the weight of moderate-severe exacerbations for both comparisons of Trelegy versus each of the joules, and that was block 1 of the multiple comparison. Slide up. Sorry. I'm waiting for the slide.

If we actually met significance on those, then we would move to the secondary block, which was actually changed from baseline in trough FEV1 and changed from baseline in SGRQ at week 52, but those comparisons were only for Trelegy versus FF/VI, and that was because they're the endpoints that we felt assessed the bronchodilator benefit.

Then if we made it through that block, then we had time to first moderate-severe COPD exacerbation for Trelegy versus both joules. That was the hierarchy that was prespecified. We had a number of other endpoints.

Again, I want to stress that these were not exploratory. They were all endpoints related to COPD, both symptoms and to do with lung function. However, I also want to clarify that ACM we don't think is an exploratory endpoint. We had an adjudication committee and we also, by design, collected mortality off-study, even in the original protocol. The most complete data set, which you've seen today, actually collected additional post-study deaths, but the original intent was to collect deaths post-study.

I did also want to pick up on multiplicity more generally because I think the concern for multiple comparisons stems from the fear of finding falsely significant findings. As we've said, we've got 34 endpoints both for Trelegy versus FF/VI and Trelegy versus UMEC/VI. I think if those

34 endpoints were sets of random numbers, then it is quite reasonable to say that any finding you would have p less than 0.05 would be due to chance. However, these 34 endpoints all relate to physiological effects of a pharmaceutical agent, and actually for both Trelegy versus UMEC/VI and Trelegy versus FF/VI, we have statistically significant results in 29 of the 34 comparisons. If these were really due to chance, you'd only expect two to be significant by chance for each of those comparisons. We have more than 85 percent of endpoints, which are actually significant.

I would like to just actually hand over to our statistical consultant, Dr. Makuch, to see if he wanted to add anything further.

DR. DODD: Before you do that -- this is Lori again -- may I just ask then, given that that's the case, how do you explain that there is an observed potentially statistically significant mortality benefit for the UMEC/VI comparison with Trelegy but not one with the comparison with FF/VI, given what you've stated about the statistical

significance of the other secondary endpoint?

DR. LETTIS: Yes. I think we believe, and I think as Dr. Jones said in her presentation, as also Dr. Wise alluded to in terms of a clarifying question earlier, that it's really severe exacerbations which increases the risk of mortality in COPD patients. So the fact that actually Trelegy versus FF/VI was not actually significant for severe exacerbations, they were the only endpoints for Trelegy versus FF/VI that were not significant in addition to all-cause mortality. So actually, it's really the risk on severe exacerbations which is driving the mortality effect, is our belief.

Does that answer your question?

DR. DODD: Sort of, yes. Thank you.

DR. LETTIS: Could I ask Bob Wise -- I'm sorry. Bob Makuch, do you want to comment?

DR. MAKUCH: I'll just make a very brief remark -- Robert Makuch, Yale University -- that in this case, the need for multiplicity adjustment does begin, as Dr. Lettis indicated, with an

assessment of the reasonableness that the data are essentially random. The p-value must be interpreted within this broader context because p values are not strict decision rules, but rather one piece of evidence to be evaluated within the broader context of the study's quality; for example, the mortality ascertainment right here being 99.6 percent and the conduct and the consistency of the results.

As you heard, there were 29 of 34 for analyses which were significant and less than 0.05. So in this setting, the p-value multiplicity adjustment for the prespecified ACM endpoint did not seem warranted because the trial supports the tenability of the thesis that the outcomes provide real evidence of a positive biologic effect. Thank you.

DR. STOLLER: Thank you.

DR. JONES: Thank you. Sorry --

DR. STOLLER: I'm sorry?

DR. JONES: This is Elaine Jones from GSK. I was just going to ask Dr. Wise for his thoughts

on not seeing the benefit in the FF/VI arm, to complete that question.

DR. STOLLER: Okay. Dr. Wise?

DR. WISE: Thank you. This is Bob Wise. I think that although the FF/VI arm did not show statistical significance, if you look at the curves, it certainly looks like it's very close to the Trelegy effect on all-cause mortality, which is reasonable if we postulate, as I think the FDA also does, that this is an effect of the inhaled corticosteroids reducing exacerbation. So from a clinical perspective, I don't think that that's such an important distinction.

DR. STOLLER: Very good.

Ms. D'Agostino, I think you're next, then Dr. Kelso, and Dr. Carvalho.

Ms. D'Agostino, question, please?

MS. D'AGOSTINO: Thank you. My question is for -- I think it was Dr. Wise who was on the IDMC. We were given -- I don't know from the slide number, but it was page 109 on the FDA briefing document, how the IDMC expressed concerns about

their early best trend. I just wanted to clarify, that was in the comments that were sent over to GSK; is that correct?

DR. JONES: Ms. D'Agostino, if I can just clarify, you're referring to the conduct of the IDMC of which Dr. Wise was a member. You'd like to ask him about some operational and procedural aspects?

MS. D'AGOSTINO: Yes.

DR. JONES: Okay. Thank you.

Dr. Wise?

DR. WISE: Yes. What is the question?

DR. JONES: I think, actually, Dr. Wise, it's about how you got the information from GSK, and the decisions and the discussions that you had when you saw the data in the early portion of the study. I think that's what it is.

MS. D'AGOSTINO: Yes, that's correct.

DR. WISE: Okay.

MS. D'AGOSTINO: We were shown a comment that expressed concern about some of the early deaths that were occurring, specifically that could

potentially be attributed to patients being withdrawn from steroids, and I was wondering if you could elaborate on the conversations that you caught at that time.

DR. WISE: Yes. I think early on in the study, in November of 2015, was the first time that we noticed that there was an imbalance in deaths. That was when about half the participants were enrolled. There was no statistical evaluation. It was only presented to us as a proportion of patients or numbers in each group. This was obviously concerning to the Data Monitoring Committee.

We did ask that not only the proportions of deaths in each group be presented to us, but also the timing of the deaths. And by the next meeting, that was in April of 2016, we were presented with Kaplan-Meier curves that showed this difference between the two inhaled corticosteroid arms and the dual bronchodilator arm.

At that time, again, this was of some concern to us, and we discussed a variety of

explanations for it, one of which was that this was due to failure to prescribe the inhaled corticosteroids along with the dual bronchodilator, that this could be considered potentially a toxic effect, if you will, of the dual bronchodilator such as has been suggested to occur in asthma, where bronchodilator monotherapy is considered -- without an inhaled corticosteroid chaperone is considered improper. So that was one consideration.

From the point of view of the committee, we made no distinction between withdrawal of corticosteroids as a harmful effect and prescription of inhaled corticosteroids as a beneficial effect. To us, these were just two sides of the same coin, and you couldn't make a comment about one without making a comment about the other.

Ultimately, with that meeting and then a continuing meeting in November of 2016, we continued to see this effect and discuss it, and we decided that the trial should not be stopped.

There were several things that went into that consideration. Number one was the fact that the dual bronchodilator, Anoro, is already, or was already, at that time an approved medication and was widely used. It had a very clean record in the registration trials, and after being widely used, there was no implications of a toxic effect, if you will, in COPD.

But the more important issue was that we recognize that even though the dual bronchodilator arm had a higher mortality rate than the two inhaled corticosteroid arms, the overall mortality was very low compared to what we would expect in this population that would qualify as GOLD Group D at that time. So where we would have expected about a 10 percent annual mortality rate, we were saying an annual mortality rate of around 2 and a half percent, which subsequently turned out to be the case.

So our ultimate conclusion was that this was an important trial. It was key to trying to determine the effects of inhaled corticosteroids in

COPD, and we thought that the overall low mortality rate in all three groups reflected that there was a benefit in all three groups and, therefore, there was no reason to stop the trial.

Have I responded to your question?

MS. D'AGOSTINO: Yes. Thank you. That's helpful.

DR. WISE: Thank you.

MS. D'AGOSTINO: I have one other question that was raised I think very nicely by the second public speaker. I'm not sure who's best to address this question, but anyone who is involved in the trial design, explain what measures to typically recruit women and people of color.

I don't know if you have this slide that shows efficacy broken down by subgroups, race and gender, but given that this study ended up not being powered to detect efficacy, really, by gender or race, what measures were actually taken to physically recruit any group besides white men?

DR. JONES: Thank you, Ms. D'Agostino. I'm going to ask David Lipson, who designed the study,

to address that question.

DR. LIPSON: As a matter of principle, GSK intends and attempts to enroll a broad group of patients that are representative of patients with COPD. It is important to recognize, for example, that the IMPACT trial was performed in over a thousand sites in 37 countries around the world, so clearly demographics are different. But to take, for example, people of color, in the IMPACT study, although, overall, African Americans, for example, totaled about 3 percent in the trial, if you look at the U.S. population, the numbers of African Americans that were enrolled was 8 percent.

So it is important to recognize the demographics of the different countries, and, again, we attempt to enroll women, people of color, in order to ensure the generalizability of the data overall. Thank you.

DR. STOLLER: Does that respond to your question, Ms. D'Agostino?

MS. D'AGOSTINO: I suppose. Thank you.

DR. STOLLER: Okay. Dr. Kelso is next,

please.

DR. KELSO: Yes. Is it possible to bring up CO-45, slide CO-45 from our original slide set? Yes.

I think this just tells the whole story that the benefit is confined to those people who were on ICS at screening and that the intervention that has been done in those patients is to remove their ICS. On the one hand, I guess you could argue, well, if taking away an ICS is bad, why isn't adding an ICS good? But that means that these have to be, as has been stated, two different patient populations.

One of the letters to the editor about the IMPACT trial said that a history of asthma was not an exclusion criteria, so I'd like to find out if that's correct because, presumably, then some of these patients could have had asthma or what's sometimes called asthma COPD overlap syndrome, and withdrawing their ICS might have been particularly harmful.

But at any rate, I don't think there's any other way to look at the difference in these curves

on the left except that these are patients that -- the intervention that was done here is that their ICS was taken away, and that led to a higher mortality rate. So I guess I'd like to find out, again, if patients with asthma were excluded from the trial and why there's any other way to look at this other than a withdrawal trial.

DR. JONES: Thank you, Dr. Kelso. Just to confirm, this was not an asthmatic population. All patients within the study met the ATS-ERS criteria for COPD, and the current asthma diagnosis was an exclusion. Investigators were only allowed to enroll patients if their symptoms were due to COPD; the patients, either active or former smokers, with an almost a 47 pack-year of cigarette exposure.

So I've given you the information around the population with regards to asthma, but I'd like to ask Dr. Wise to address some of the other comments that you've made.

DR. WISE: Yes. This is Bob Wise. I think the issue really surrounds the question that you've raised, Dr. Kelso, of whether withdrawal of an

inhaled corticosteroid from a population whose been prescribed that by their physician is harmful, and I would say that these data certainly support that, and I don't think that it's just a chance finding.

The real question is how do you put that into clinical decision making. If you want to look at this as making a recommendation that people who are on triple therapy should not have their steroid removed, I think that's very reasonable. I think you can also look at this data and say that if you have a patient who's doing well on dual therapy without an inhaled corticosteroid, you should not remove the inhaled corticosteroid, and I think you can make that case.

I think it becomes problematic, and I think the agency and the sponsor are what I would call 360 degrees apart on the question of inhaled corticosteroids. The labeling, how the labeling goes, is of course subject to negotiation between the sponsor and the FDA; and whether that labeling wants to call Trelegy beneficial, or failure to prescribe Trelegy as harmful, in this population I

think is something to be negotiated.

Okay?

DR. KELSO: I guess my only other comment would be, then, the group on the right. There clearly is also a group of patients for whom being on this drug, those who were not on ICS at screening, does not decrease their mortality. So again, I realize that they're sort of circular arguments here, taking a drug, the inhaled corticosteroid, away versus adding it, et cetera, but I just find it very hard to conclude, from looking at these two graphs, that you can make a blanket statement that being on this medication decreases all-cause mortality. Thank you.

DR. STOLLER: Thank you, Dr. Kelso.

Dr. Carvalho is the last of the remaining clarifying questions to the sponsor, and then we'll turn in the remaining 20 minutes to remaining clarifying questions to the FDA, beginning with Dr. McCormack.

Dr. Carvalho, please?

DR. CARVALHO: Thank you, Dr. Stoller.

I just have a single question, which Dr. Kelso asked verbatim. But I did wonder if there's any pre-enrollment airflow reversibility data for the subjects included the IMPACT trial.

DR. JONES: Thank you, Dr. Carvalho. I don't know the answer to that question, so I'm going to ask Dr. Lipson, the study physician, to address it.

DR. LIPSON: Hi. David Lipson. The question, was there any free -- I just want to clarify the question, was there any requirement to have reversibility in the trial in order to get into the trial?

DR. CARVALHO: No. The question was just to see if there was any airflow reversibility data available so that we can compare what Dr. Kelso was alluding to with the asthma COPD overlap syndrome with those that would not have reversibility.

DR. LIPSON: Yes. Eighteen percent of patients would have met reversibility criteria as designated with 200 mL and 12 percent increase in FEV1 after albuterol, which would be expected and

seen very commonly in a population with COPD.

DR. CARVALHO: Then are there outcomes for those specific patients?

DR. LIPSON: We would have to pull them up.

DR. JONES: Actually, I'm looking at the slide, and I don't think we have that data.

DR. CARVALHO: Thank you.

DR. JONES: It's something that we can try and have a look at, but at the moment we don't.

DR. CARVALHO: Okay. Thank you so much.

DR. STOLLER: Alright. Well, that concludes the clarifying questions to the sponsor. There were some remaining questions to the FDA, three in fact, the first of which was posed by Dr. McCormack.

Dr. McCormack, your question to the FDA, please?

(No response.)

DR. STOLLER: You may be muted.

DR. McCORMACK: Can you hear me now?

DR. STOLLER: I can.

DR. McCORMACK: Okay, great. Sorry about

that.

This is Frank McCormack. My original question was about the multiplicity analysis and how the FDA viewed the logic that was listed in the briefing documents in GSK, but I think we had a good discussion of that.

There were two remaining questions that I had. One was about how the FDA views this discussion of exploratory versus other endpoints. We had the view of GSK expressed, but I wondered if the FDA makes a distinction between these two types of endpoints. And secondly, I wondered if there's any difference in the level of evidence that's required, or what the difference is, for changing a labeling indication versus a labeling claim.

DR. LEVIN: This is Greg Levin at FDA. Let me see if I can address both of those. For the first one, I don't see much of a distinction between "and other endpoints" classified as "in other endpoints" in the statistical analysis plan. That is not included in the multiple testing strategy and one that is labeled as exploratory.

Clearly, it would be a little bit better if the endpoint is included in the statistical analysis plan at all, as mortality was done here, as compared to other endpoints and analyses that were not even included in the statistical analysis plan to begin with, so I think that is a distinction that one could make. But this was an exploratory analysis in that it was not included in the multiple testing strategy, and most protocols in statistical analysis plans that I have seen would classify those as exploratory endpoints, so I don't really see much of a distinction, and I think it's kind of one in the same.

Can you remind me of what your second question? Oh, it was about -- sorry, go ahead. Yes. Can you remind me what the second question was?

DR. McCORMACK: Level of evidence required for labeling claim versus changing an indication or adding an indication.

DR. LEVIN: Okay. That's right, yes.

In terms of our guidance on the topic,

including the two guidances that were referenced in our presentations, there's no distinction made. Claims of effectiveness in labeling are expected to be supported by substantial evidence, and the criteria for what qualifies as substantial evidence, as were outlined in our slides, includes a high degree of persuasive evidence if it's relying on a single study.

DR. McCORMACK: Thank you. That concludes my question.

DR. STOLLER: Thank you, Dr. McCormack.

I believe Dr. Kelso -- sorry. Dr. Carvalho has a question for the FDA, please, and then Dr. Kelso.

DR. CARVALHO: My question has been actually answered by other speakers. Thank you.

DR. STOLLER: Thank you, Dr. Carvalho.

Dr. Kelso, a question to the FDA, please?

DR. KELSO: Yes. I know that we're not evaluating the ETHOS trial, but since it was brought up, I wondered if the FDA had any comment about the ETHOS trial as sort of potential

corroborating evidence and whether the difference in mortality seen in that trial could have also been due to this issue of ICS withdrawal.

DR. BUSCH: Hi, Dr. Kelso. This is Rob Busch. In general, we don't want to speculate about exactly why a phenomenon may or may not have happened in that particular trial since they were not a part of this review, and we haven't necessarily analyzed the patient level data in the same way we have done for IMPACT, SUMMIT, and TORCH.

Publicly available data -- well, let me say -- I'll stress again that the prestudy medication subgroup analyses were exploratory analyses here, despite raising these issues, and that we're asking for your opinion on how these concerns may influence the interpretation of the data from IMPACT in that claim. So with those caveats, you can still say a tiny bit to point out some differences.

Publicly available data from the ETHOS trial shows that subjects could enter the trial on

prestudy ICS among other drugs and subjects could be randomized to LAMA/LABA, so prestudy therapy concerns are worth considering in this trial. There are some differences in this trial in the population of IMPACT, though. Around 80 percent of subjects in ETHOS had prestudy ICS, although only 56 percent were frequent exacerbators in the prior year, and the exacerbation criteria were slightly different.

There was a 1 to 4-week run-in in this trial that required washout of LAMA and LABA, which could potentially have led to some attrition of vulnerable patients, but ICS was continued during the run-in. In addition, the publicly available data focuses on the on-treatment data and not all patients randomized. IMPACT did a lot of vital status follow-up to get us as much data as possible for this application. The publicly available data is that on-treatment data.

So prestudy ICS and ICS-naive subgroup analyses in the ICS LAMA versus LABA/LAMA orientation -- so not the same flipped orientation

that we've given -- are presented in their supplement for exacerbations, but there's not sufficient mortality data and analyses from the study in the public domain for the agency to discuss the potential effects of ICS removal on mortality in this context. But based on the publicly available data on the trial design issues, that prestudy medications might be considered when interpreting the trial results.

DR. KELSO: Thank you. So I guess at least there's a potential of the same issue with having ICS withdrawn because if you look at the mortality curves in ETHOS, it to my eye looks like there's the same issue of the kind of early separation of the curves. And, again, that's just an eyeball assessment, but thank you.

DR. STOLLER: So I'm aware that all of the clarifying questions have been posed to the sponsor and to the agency. We do have about 10 minutes on the schedule before we go to discussion questions, so I'll ask the committee as to whether there are any remaining clarifying questions that should be

addressed; otherwise, we'll turn to the discussion questions.

Please raise your hand if you have a remaining clarifying question.

(No response.)

Questions to the Committee and Discussion

DR. STOLLER: Okay. Seeing none, we'll now proceed with the questions to the committee and the committee discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, and then we will open the question to discussion.

As the committee knows, we have three discussion questions and one single voting question. Each of the discussion questions has multiple parts, a total of 11, A, B, C for question 1; A, B, C, D for question 2; and A, B, C, D for question 3. For the sake of clarity, I'd

like to propose that we discuss each lettered subset of the question first, so I'll begin with reading discussion question 1A, and then ask for the committee as to whether there are any questions about the wording.

Discussion question 1. Discuss the persuasiveness of the data in the IMPACT trial to support the claim that fluticasone furoate, as a component of Trelegy Ellipta, improves all-cause mortality in COPD. Include the following elements in your discussion. The first element is A) the exploratory nature of the all-cause mortality ACM analysis, the lack of type 1 error control, and the strength of evidence in IMPACT.

Let me ask if there are any clarifying questions about the wording of the discussion question to the committee, please. If you have a question, please raise your hand.

(No response.)

DR. STOLLER: I see no hands raised, so let me invite anyone who wants to comment on question 1A, please.

Dr. May?

DR. MAY: Suzanne May. With regard to the lack of type 1 error control and the strength of the evidence, I think it is a subset or it's not as important as the potential for this benefit to actually be removal of the ICS and harm. So even if there was, all of the issues were not issues with regard to that brought up. The exploratory nature, even if it wasn't exploratory, the p-value would have been much smaller. If they strengthened the effect, it would have been bigger. If it is truly due to the removal of the ICS, that would have trumped, or would trump for me, all of the other issues.

That said, it doesn't seem to me as if the all-cause mortality outcome meets the effectiveness standards that are otherwise required for this type of analysis type 1 error control and the strength of the evidence, and that was my comment.

DR. STOLLER: Thank you, Dr. May.

Dr. Ellenberg, I think your next, please.

DR. ELLENBERG: Yes. These analyses,

presented both by the sponsor and the FDA are rife with multiplicity We have multiple endpoints, we have multiple subsets, we have multiple time intervals. We have an endpoint that was clearly prespecified but it was one of a very large number.

I'm not persuaded by the argument that all of the, quote, "other" endpoints and secondary endpoints were positive. If you also had another endpoint that was something like which arm resulted in someone being able to sing better, or something that was completely unrelated, and that showed a difference, we would all roll our eyes and say that's a chance, even though it wouldn't make any difference that all the other 34 endpoints were significant.

So I don't think you can get away from the multiplicity issue with the endpoints, but we also have different subsets and different time frames. My bottom line on this is that I agree with Dr. May that the criteria for a definitive answer from a single study that has to provide very statistically persuasive evidence, in addition to supplementary

evidence from other sources, is not met here.

DR. STOLLER: Thank you, Dr. Ellenberg.

I believe my comment is next, and then Dr. Dodd. With regard to the very specific focus of this question, the multiplicity issue, I will say that I am actually not concerned about the multiplicity issue. I agree with Dr. May that the juggler issue in the interpretation of these data with regard to a label approval is not the statistics but the methodologic interpretation with regard to withdrawal, yes or no, and I'll reserve discussion of that for later questions.

But I am not concerned. Given the type 1 errors are around chance findings and many of the secondary other outcomes satisfied statistical significance, I think the chance that this is observed by chance alone is rather low.

Dr. Dodd had a question, and then Dr. Evans.

DR. DODD: Yes. I was just going to support the statements of Dr. Ellenberg, that I see the multiplicity issue as particularly problematic. I think there was a clear acknowledgment of the need

for multiplicity in the careful analysis that was applied to the co-primary and co-secondary endpoints, and that level of rigor was not applied here.

It's clear that we do not see a survival benefit in the Trelegy versus FF/VI, but there is one that's being claimed for the Trelegy versus the UMEC and VI combination; and to me that just speaks to the importance of having clear multiplicity adjustments. So this I think is particularly concerning. Over.

DR. STOLLER: Dr. Evans, please?

DR. EVANS: Yes. I actually have a question for the other members of the committee. My general take on this is very similar to Dr. Stoller's in terms of the meaning in portion A, but an interesting question was raised earlier by one of you, that in fact this is a three-arm trial. There were two chances to win per comparison, and I'm wondering if the statisticians in the group could point us to what they would consider to be a reasonable control for type 1 error in that

context.

DR. DODD: How do you want us to approach this? I'm sure that we could all give answers.

DR. EVANS: Perhaps whoever spoke earlier would be the right person to start with. I'm sorry that I don't remember who it was.

DR. DODD: Yes. I did bring up the point about the co-primaries and the two opportunities for Trelegy to win. One could use the approach that was protocol defined, which was the Hochberg method, which required that both comparisons -- this is for the primary -- be statistically significant. I believe it was either at 0.04 or you could require that they be significant, both of them, at 0.05.

Then if they both were not statistically significant, then the plan would be to test each one individually at some lower type 1 error threshold. I had read in their SAP that they were testing at a 0.01 threshold for the individual arm comparisons.

An alternative would be to use Dunnett's

test, which is pretty much similar to a Bonferroni adjustment with only comparisons which would require 0.025 for each of the comparisons. Those would be two suggestions that I would have proposed, but there are others.

I see that Dr. Ellenberg has her hand up, so I will let her comment as well.

DR. STOLLER: Yes, Dr. Ellenberg, please?

DR. ELLENBERG: Yes. I would just say, even forgetting about all of the co-primaries and other secondary endpoints, at the very least there should have been accounting for comparing between the two different comparative arms. The simplest way to do that would be to consider a Bonferroni comparison, testing each at 0.025. I just don't think you can get away from the multiplicity issues here. Thank you.

DR. STOLLER: Okay. Are there other questions, hands raised, with regard to question 1A, please? If not, I'll summarize what I think I heard, and then we'll go to 1B. Other questions, please raise your hand.

I see Dr. Evans and Dr. Ellenberg. Have you additional questions/comments on 1A? No.

I've been asked to just summarize the tone of the discussion. I heard a variety of opinions, one, with regard to the inescapable importance of multiplicity, and Bonferroni, or other corrections, and the other suggesting that because of the multiplicity of outcomes, the majority of which satisfied conventional p less than 0.5, that this was less material, purely on the statistical issues.

Let's turn then to question 1B, and let me read the question and, again, ask whether there are clarifications needed about the wording of the question, and then we'll go to the discussion. 1B is whether the all-cause mortality ACM results from IMPACT are persuasive in light of the additional all-cause mortality data from fluticasone comparisons provided by both SUMMIT and TORCH.

Any questions about the wording of the question, please?

(No response.)

DR. STOLLER: Seeing no hands raised, let me open that question for discussion by the committee, please.

I see Dr. May's hand raised, please, and then Dr. Kelso.

DR. MAY: This is Suzanne May. I think this goes back to the question that I had for the GlaxoSmithKline people with regard to the comparison of the FF/VI versus VI, and that we are here in IMPACT talking about double and triple therapies, and that for me, still, that comparison is more important than the FF versus placebo comparison because we're in the multiple therapy options.

So I think what they presented as supposedly supportive for the mortality claim for me is not convincing because the one that would have been more similar or most comparable to the IMPACT study was actually not as supportive as they would have hoped. That was the end of my comments on this.

DR. STOLLER: Thank you. Dr. May.

Dr. Kelso, please?

DR. KELSO: Yes. I would just point out, again, in the SUMMIT trial, the findings say, quote, "All-cause mortality was unaffected by combination therapy," close quote. So the SUMMIT trial I don't think is a positive trial. What was presented was to pull out some subgroup of patients who were more exacerbating to be more like the patients in the IMPACT trial, and what was presented was comparing that active treatment to placebo, showing that it had an advantage. But again, I don't think that's a fair comparison to the other active treatment arms, so I don't think that SUMMIT provides us with supporting data.

DR. STOLLER: Thank you, Dr. Kelso.

This is Jamie Stoller. I'm mindful, again, in the FDA's guidance about approval, it requires convincing data ideally from replicate studies. My comments are, acknowledging what was said about the overall effects of SUMMIT, on the one hand recognizing it as a post hoc subset analysis, I was on the one hand struck by the findings in SUMMIT on a baseline ICS exacerbating population, recognizing

the differences in the SUMMIT study design, and similarly by the lack of effect in TORCH.

So recognizing, again, different molecules, different standards of care, I think most pulmonologists regard the use of ICS as a class effect, I have to say. So as I look at the replicate data, there are, even in the subset analyses, discordant views from the two replicate studies. That concludes my remark.

Dr. Ellenberg has her hand raised, please.

DR. ELLENBERG: Yes. I think those other data from those other studies are suggestive, and I think that if the data from IMPACT had been unquestionably positive and of the very statistically persuasive nature in the criteria, I would be comfortable considering those as supportive. But without that kind of very statistically persuasive data, I think what you have are several items that are suggestive but not definitive. Thank you.

DR. STOLLER: Thank you, Dr. Ellenberg.

Are there any other comments about question

1B, before we turn to 1C?

(No response.)

DR. STOLLER: I see no new hands raised, so let's turn to discussion question 1C. I'll read the question and then ask for any clarification comments from the committee about the language of the question. Question 1C is, the observed time frame of the IMPACT results; that is to say the early separation in survival.

Any questions about the wording of 1C, please?

(No response.)

DR. STOLLER: Seeing none, let me open the question for discussion by the committee, please. Please raise your hand if you have a comment.

Dr. Kelso, and then Dr. Carvalho, please.

DR. KELSO: It seems very clear to me, from our discussion and the slides that have been shown, that this early separation is a very real thing. Virtually all of the supposed advantage occurs in that first 90 days, and while you can argue that people continue to die in the study, that's true of

all of the arms, as was pointed out.

So people with this disease, no matter what treatment they're on, will continue to die over time. What we're looking for is, is there an advantage. Are fewer people dying over a longer period of time? And I just can't think why it would be plausible that all of that advantage would occur in the first 90 days, and from my interpretation of the data, that early separation is what we're seeing here.

DR. STOLLER: Thank you, Dr. Kelso.

Dr. Carvalho, I believe is next, then Dr. D'Agostino, and Dr. Ellenberg.

DR. CARVALHO: Yes. My concern is we know that there's many phenotypes of COPD at this point, and I just wonder if we're having effects on different populations in the very beginning, where some will not mind being off the ICS, and some physiologically are going to be different and perhaps are more reactive, and perhaps have more of an asthma component. So I would be interested in seeing additional data on this. Thank you.

DR. STOLLER: Thank you, Dr. Carvalho.

Dr. D'Agostino? Sorry. Ms. D'Agostino, please?

MS. D'AGOSTINO: Yes, thank you. My comment really piggybacks off of Dr. Carvalho's. I think this early separation really gets into the design of the trial from the beginning. I don't really understand why there wasn't a withdrawal period or a run-in period if there was that much of a concern about pulling patients off of their existing therapy.

I don't particularly understand why there would be a trial design that then involves pulling patients off the therapy, and that's a real sticking point for me. Then, as Dr. Kelso said, we certainly see that early separation. It's concerning to me that the DMC not only saw that separation but didn't choose to act on it. That's my comment. Thank you.

DR. STOLLER: Thank you, Ms. D'Agostino.

Dr. Ellenberg, and then Dr. Medoff.

DR. ELLENBERG: I think that early

difference looks pretty clear. I wouldn't make very much out of looking at the analyses, forgetting about everybody in the first 90 days and just looking past that. You've lost the benefits of randomization there, and the people remaining in the three arms therefore may well have different prognoses.

If there had been more deaths early on in the arm without the ICS, the remaining people may be somewhat a better prognosis than the remaining patients in the other two arms, and that could account for a certain parallelism of the curves. I think it's very hard when you start cutting off and taking out people like that to make something of what's left. You have major selection factors there. But there certainly does seem to be something real in the first 90 days. Thank you.

DR. STOLLER: Thank you.

Dr. Medoff, please?

DR. MEDOFF: Yes, I'll echo the feelings from others in saying that that difference is real. I've been struggling with trying to think of a

mechanism by which steroid withdrawal would be not equivalent to adding a steroid. As brought up by one of the commenters, how is that different for survival?

You just wonder if there is some accommodation to a steroid inhaler, whether it's upregulation of beta receptors or something else, that with the withdrawal, there is this increased risk that's seen early in that period. So I think, as stated earlier, that that is something significant and certainly makes me worry about the effects of steroid withdrawal in this population.

DR. STOLLER: Thank you, Dr. Medoff.

Any other comments on 1C? Then I'm reminded I'm remiss in not having summarized 1B and 1C, which I will do once all questions have been posed -- comments have been posed around 1C, please.

Any other? Dr. Shapiro has his hand raised, please.

DR. SHAPIRO: Yes, I agree with the conversation. I'd like to commend the FDA for

really pulling out the first 90 days and second 90 days to make it very clear. I think people are on the right track trying to think about why withdrawal might be harmful in looking at subgroups. But I think that's going to be our only way forward to really get a clear answer to this question. But I agree with the conversation, and congratulations to the data presentation.

DR. STOLLER: Thank you, Dr. Shapiro.

Any other hands raised about 1C before I summarize 1B and 1C, and then turn to question 2?

(No response.)

DR. STOLLER: I'll ask those of you who have your hands raised to lower them so we're sure that you don't have an additional question, please. Thank you very much.

Let me summarize what I believe I heard. On 1B, whether the all-cause mortality results for IMPACT are persuasive in light of the additional -- while there was a comment I made about the SUMMIT data and a post hoc subset analysis, I think the weight of the opinion, as I

heard it from the committee, was that the replicate data were not terribly persuasive.

On 1C, I think it was a fair degree of concordance about the concern of the impact of the data in the first 90 days on the outcome, whatever explanation may exist for those first 90 days, based on the analysis we saw of 90 days and then post 90-day survival. So hopefully that's a fair-minded summary for the agency of what we heard on questions 1B and 1C.

We might then turn to question 2, and again, this has four components. We'll take each separately, and let me read the question, again asking the committee for clarification on wording if there's any uncertainty.

Discussion question 2 is discuss the implications of prestudy inhaled corticosteroid, ICS use, and ICS removal on the interpretation of the all-cause mortality data in the IMPACT trial. Include the following elements in your discussion. We'll consider A first; A) the clinical understanding of the contribution of inhaled

corticosteroids to COPD therapy and the effects of ICS removal in patients with uncontrolled COPD and frequent exacerbations.

Any questions on the wording of question 2A for the committee, please?

(No response.)

DR. STOLLER: Seeing no hands raised, let me ask for comments. Please raise your hand if you have a discussion point for the committee, please. Dr. Kelso, please?

DR. KELSO: I think that there's consensus that there are some group of patients who are on triple therapy, or at least double therapy, with an ICS, for whom removing the ICS increases their mortality, and that we would all like to know who those people are. But I don't think that in clinical practice, somebody who had a patient who was already on double or triple therapy, including an ICS, who was still having exacerbations would start removing parts of their therapy. We'd be looking for something else to add to their therapy, or some alternative diagnosis, or something else.

But I don't think too many people would be withdrawing one of those elements, including the ICS, clinically in somebody who was already on it and not doing well.

So it's clearly not a good idea, in some subset of these patients, to take away their ICS, but I don't think too many people would do that.

DR. STOLLER: Thank you.

Dr. Tracy has a comment, please.

DR. TRACY: Yes. It kind of goes right along with Dr. Kelso. As far as the high-risk group goes, one of the things about the IMPACT study is they definitely looked at a sicker group. I think it's fair to say that one can assume that when you're looking at a group of individuals who are particularly ill or are particularly at risk, changing a therapy is probably not in your best interest.

So to Dr. Kelso's point as to who would remove that from a clinical practice standpoint, I believe that the answer is not many people. Most of us are looking for opportunities to make things

better, so it's a little bit of discordance here. But I would say to the point of what makes this different is the fact that the IMPACT study really does look -- when you compare it against TORCH, especially when you compare it against TORCH and SUMMIT, we are looking at a different population. Thank you.

DR. STOLLER: Thank you, Dr. Tracy.

Any other comments about question 2A from the committee, please?

(No response.)

DR. STOLLER: Again, what I heard in summary is that most clinicians would be loathe to withdraw ICS therapy from patients who were deemed to have severe COPD, group D, GOLD D, and so on. I think that was the concordance of the two comments made.

Let's turn then to question 2B. Again, I'll read the text of 2B, and ask if there's any clarification required from the committee about the wording. Question 2B is, the implications of randomization to study drugs that do not contain ICS among patients with uncontrolled COPD despite

prestudy ICS therapy.

Any questions about the wording of the question?

I'm seeing no new hands raised. Dr. Tracy's hand is presumably raised from his prior question. These are clarifications on the text, I assume.

Dr. Marshall?

DR. MARSHALL: No. I'm sorry. I don't have any trouble with the clarification.

DR. STOLLER: Okay. I'm sorry. It sounds like the text of the question is clear, then let's take comments.

Dr. Marshall, please?

(No response.)

DR. STOLLER: You may be muted.

DR. MARSHALL: I'm sorry; that's correct. I'm guessing that all of us, certainly including the sponsor, would love to have the advantage of a retrospectoscope. I think there's little idea that one would, in any sort of design like this, want to withdraw inhaled corticosteroids from the group that would be at highest risk for a negative

outcome, particularly related to mortality.

Having said that, again, as was introduced not only by the sponsor but by the FDA in the presentations that we all watched prior to this meeting, the role of inhaled corticosteroids has been very much controversial in the overall management of patients with COPD, and to the best of my knowledge that's still the case today. Not everyone agrees that all COPD patients would benefit from inhaled corticosteroids.

I think that that is changing steadily. I think that there's more and more acceptance of the idea of the role of inhaled corticosteroids, but in the context of this specific component, I still struggle with the idea of the relationship between withdrawing and seeing an exacerbation as opposed to adding on and seeing an improvement. The ideal would be to see patients that were on it, they were withdrawn, and then had a deterioration in their condition, and then a design where it was added back to see improvement.

I think that probably was not the nature of

the design of the data that we've been allowed to see. I understand the difficulty in the design of such a trial, but I think most people now are getting to the point to recognize and agree that the more severe COPD patient is likely to benefit from inhaled corticosteroids on a regular maintenance basis and that the severity of that illness is this is not disease-modifying. It slows down the progress of the disease, but the presence of the inhaled corticosteroid allows the individual to stay better controlled and have less serious or severe exacerbations. That statistic has been tied with mortality risk.

The sponsor acknowledges that there is a logic progression, and they make what seems to me to be a fairly compelling case of logic progression in the use of inhaled corticosteroids affecting exacerbation rate and the exacerbation rate affecting mortality risk. That was not directly examined in the studies that were presented, specifically the IMPACT study, but it does bring up an idea for us, with the implications -- this 2B

here -- to successfully pull someone off an inhaled corticosteroid to show the inferiority of management on non-ICS containing therapy. That's the end of my comment.

DR. STOLLER: Thank you, Dr. Marshall.

This is Jamie Stoller. I have to say I struggled with this issue, and I think the best adjudication I can come to is that hindsight is 20/20. At the time that this trial was launched, perhaps it wasn't deemed as imprudent to withdraw an ICS from the severely exacerbating population, a GOLD D or, if you will, certainly a severely affected population, as perhaps might be the case today.

I think most of us would regard a patient who is severely affected with significant airflow obstruction, certainly substantial if not satisfying the traditional criterion for frequent exacerbators, that it would be imprudent to withdraw the drug. Whether this is tantamount, as has been stated, to the advisability of adding the drug for mortality benefit is the subject of this

discussion. I'm not sure those two questions are conflated in my mind.

So I think through the current lens, it would be imprudent to withdraw an ICS from a patient on ICS who is deemed to have severe and exacerbating COPD. That's the end of my comment.

Ms. D'Agostino has a comment, please.

MS. D'AGOSTINO: Yes, thank you. I agree that I think it was more difficult to know at the time of the study design that it potentially could have been dangerous to withdraw these patients. I think that we have to use the knowledge that we have now, which is there is this increasing evidence that it seems imprudent to withdraw patients.

I know we'll get to clinical practice later, but I think the question that we're really being asked is, practically speaking, if we have a patient in front of us, we're not really asked to stop a patient's therapy to start the same thing; you'd be looking to add a therapy on. So the more practical question is, is there a benefit of adding

ICS, not is there a detriment to removing it and restarting it on.

So given that it doesn't appear to be this benefit to actually adding ICS to the ICS-naive patients, that's really the sticking point for me, and that's the end of my comment.

DR. STOLLER: Thank you, Ms. D'Agostino.

Dr. McCormack has a question, and then Dr. Dodd.

DR. McCORMACK: I just wanted to bring up something Dr. Wise alluded to, which was should this be added to the label in another form. And perhaps we're not talking about the same thing, but as an adverse reaction, and I wondered if that's a possible outcome of the decisions today.

DR. STOLLER: Thank you, Dr. McCormack.

Dr. Dodd?

DR. DODD: Hello. This is Lori Dodd. I just want to bring up one comment I have heard us sort of skate around or skirt around, and that is this discussion about exacerbations and whether it's a surrogate for mortality. I think when we're

talking about exacerbations predicting mortality, I think we need to be very careful because, as we've seen from the evidence of this trial, we have two comparisons where we have proven effect on exacerbations. In the one case, we're debating whether there's an impact on mortality, and then in the other case, we're not even debating it because the evidence isn't there.

So the idea that exacerbations is a surrogate endpoint for mortality I think just needs to be considered carefully. If we move from this question into thinking about exacerbations, and because there was an effect on exacerbations, therefore there is an effect on mortality, I think that there's a lot of leaps in the logic there that don't line up. Thank you.

DR. STOLLER: Thank you, Dr. Dodd.

Any other comments on this question 2B, before I summarize and we go to C?

(No response.)

DR. STOLLER: Actually, prior to doing that, I guess Dr. McCormack's question was posed to the

FDA, and we might invite the FDA to comment. He asked a labeling question, so might we invite a comment from the FDA to respond to Dr. McCormack's question, please?

DR. BUSCH: Sure. This is Rob Busch. Your question was about whether the issue of ICS removal and some of the results we saw after that was something that could be added in a different way to the labeling, presumably safety.

This is a very important question, and we've thought about these kinds of issues a lot during the review cycle. In the context of today's meeting, we're asking you primarily about whether these concerns affect the interpretation of the proposed efficacy claim on all-cause mortality for this current application.

So while your discussions regarding the safety concerns raised by this are something that the agency definitely will consider, the particulars of any potential safety labeling or anything of that nature are somewhat outside of the scope of the current discussion. I realize that's

somewhat unsatisfying as an answer, but we want to make sure that we get the ideas about the efficacy claim first, and then we have some leeway to discuss how that could or should otherwise be included in labeling.

DR. STOLLER: Thank you.

Dr. Medoff has a question, I believe, or a comment.

DR. MEDOFF: Well, I was going to agree with Dr. Dodd that I think making a leap from exacerbations to mortality, although seemingly logical, is problematic, as the point raised that in the group that was naive to inhaled corticosteroids, there was a reduction in exacerbations but not an effect on mortality. So I think although it does make sense, I think we really can't make that leap necessarily, based on these data.

DR. STOLLER: Thank you, Dr. Medoff.

Dr. McCormack, do you have another question or might you lower your hand?

DR. McCORMACK: I do not have another

question. Sorry.

DR. STOLLER: Okay. Thank you.

So let me summarize what I believe I heard with regard to 1B. There are really several themes here, one with regard to the labeling, and the FDA responded that our focus today is on the text as proposed to us when we do come to a voting question.

With regard to the clinical advisability of withdrawing inhaled steroids from patients who are severely affected with exacerbations and severe flow obstruction, I think I heard relative concordance that based on 20/20, both in terms of visual acuity as well as chronology, 20/20 vision, that most of us would not withdraw inhaled steroids from such a patient, but that may not be tantamount to the effect of adding steroids.

Then finally, several commented and reminded us that while there's a plausible explanation based on the Roheen [ph] data and others, and many others certainly have clinical experience that exacerbations are drivers of mortality, I think

there's little question about that. It's difficult to conflate the impact on exacerbations and mortality as we see it in this data set.

I think that's a reasonable summary of what we heard on question 2B. Let's turn to then question 2C. I will read, as before, the text of the question and ask for questions about the wording, and then we'll go to comments. Question 2C is, the observed time frame of the IMPACT results; that is to say the early separation in survival.

Any questions on the wording of the question to 2C to the committee, please?

(No response.)

DR. STOLLER: I see no hands raised, so let me put that question in play for comments from the committee, please. Please raise your hand if you have a comment.

(No response.)

DR. STOLLER: I'm seeing no hands raised.

Dr. May has her hand raised. Thank you, Dr. May.

DR. MAY: This is the same question as was under point 1, number C, and I'm wondering whether everybody thinks that we had already answered it under discussion point 1.

DR. STOLLER: Fair enough. I'm aware there is some redundancy in the questions and that may certainly account for it. I think in the interest of full discussion, we do want to go through every question, and if there are no comments, then so be it.

Any other comments on 2C?

(No response.)

DR. STOLLER: Again, I will just make a personal comment and then the summary, that I think everyone's identified this early separation as being an important consideration. The juggler issue from my point of view is what's the explanation for the early separation and what is its relationship to mortality.

My experience with Dr. Busch's response to my question is that the early separation mortality is what tends to drive the ultimate differences in

mortality, as there were no differences in mortality after 90 days, recognizing that those are subgroup analyses. But I think that the crucial question is regarding the early separation, whether it's ascribable or attributable to withdrawal or whether it somehow relates to the prescription of the triple drug given the runoff and baseline ICS utilization patterns in IMPACT, and I think that's a reasonable summary of what we heard from the entire group.

So if there are no other comments on 1C, we'll turn to 1D. 1D is -- and I'll again read the question and ask for clarification on the wording -- the prestudy inhaled corticosteroid subgroup data from SUMMIT and TORCH, in light of the differences from IMPACT in study design and patient population.

Any questions about the wording of question 2D, please?

(No response.)

DR. STOLLER: I see no hands raised, so let me invite you to raise your hand for a comment on

question 2D, please.

(No response.)

DR. STOLLER: I'm seeing no hands raised. I'm imagining that may, again, relate to Dr May's comment on perhaps the redundancy of the question. This in some ways replicates question 1B, the replicate studies.

Dr. McCormack has a comment.

DR. McCORMACK: I just wanted to point out that in the TORCH study where the drug was different, there's at least a twofold difference in potency of that drug versus fluticasone furoate. Relative to beclomethasone, for instance, there's a many-fold difference; 30, 30-fold difference or some.

So I do think that perhaps that comparison with TORCH was a little bit flawed, but I do agree with you, Jamie, that we often as pulmonologists consider inhaled steroids as a class effect and don't really think much about potency. But perhaps given the results of this trial, we should be thinking about potency because furoate is at the

top of the potency chain, as far as I understand, based on receptor affinity.

DR. STOLLER: Thank you, Dr. McCormack.

Dr. Ellenberg has a comment, then Dr. Carvalho, and Dr. Busch has his hand raised.

Dr. Ellenberg, please?

DR. ELLENBERG: I think all these analyses have been interesting. I think they're all somewhat suggestive, some more so than others. But again, to me that's really all they are. They might suggest ways we might answer this question definitively, but on their own, they certainly don't do that or even in combination with the IMPACT results.

DR. STOLLER: Thank you, Dr. Ellenberg.

Dr. Carvalho?

DR. CARVALHO: Yes, thank you. I'm wondering whether using SUMMIT and TORCH as head-to-head comparisons with the current study is a valid point because both of those studies had significantly less severity in their patients. In all fairness, the IMPACT patients were much sicker.

That's one comment.

The second comment is we generally would not remove an inhaled corticosteroid, but in some of our COPD patients who develop repetitive pneumonias, we would, but we would be loathe to do that if we have a situation where the patient had a high degree of reactivity or evidence of eosinophilic bronchial inflammation or suspicion of the overlap syndrome. So clinically we would go either way, depending on the patient's baseline function.

So I'm very curious to know about the patients in the IMPACT study who diverged. What were they like before. Did they have any myocardial underlying disease? Because COPD exacerbations can cause mortality with underlying heart disease; so a few questions to think about. Thank you.

DR. STOLLER: Thank you, Dr. Carvalho.

I believe we have a clarifying comment from Dr. Busch from the FDA, please.

DR. BUSCH: Hi, Dr. Stoller. Thank you.

I just wanted to highlight that the pertinent points that we're trying to get from question 1 and question 2, question 1 focused on the overall analyses, and this question 2 focuses primarily on the prestudy ICS subgroup and whether those subgroup analyses change how you think and whether that affects the specific idea of ICS removal or in the ICS-naive group. I think some have gotten there, but I just want to make sure that there's clarity on that issue.

DR. STOLLER: Thank you, Dr. Busch. That's very helpful.

Dr. May has a comment.

DR. MAY: I was just looking at the slides from the FDA, and I think this is slide 22, where it was specifically addressed, the ICS removal and addition across the trials in IMPACT, SUMMIT, and TORCH. To support this labeling claim, I would have wanted to see some evidence, even though it's a different population, of benefit, particularly in the group where the ICS was added, and truly added, but that was not the case.

So I do think that the evidence from SUMMIT and TORCH, just like Dr. Ellenberg said, is potentially suggesting in some way, but it's not suggesting in the way that is strong enough to change any conclusions that we have seen from the IMPACT study. Thank you.

DR. STOLLER: Thank you, Dr. May.

Any other comments about question 2D in the context of Dr. Busch's reminder that question 2, unlike question 1, is about the subset analyses of ICS-naive versus ICS baseline recipients? Any other comments about question 2D, please? Again, I'll ask you to lower your hand if you don't have additional comments, so I'm not conflating that with new comments, please.

(No response.)

DR. STOLLER: Let me summarize what I think I heard. First, Dr. McCormack reminds us that with regard to the applicability of TORCH, the replicate study, and as I recall, the sponsor's discussion that the effects on those subset analyses in TORCH was not concordant with that in SUMMIT, that these

are different drugs, and that's fair. The potency of FF is quite a bit higher than that FP.

I think I heard, in general, about question 2D and question 2, in general, that the subset analyses were deemed very material to the interpretation of the results. I also heard that in acknowledgement of the fact that, if you will, there are two different interventions embedded within IMPACT -- one, the addition of a new ICS, albeit to a different patient population as Dr. Wise pointed out, that's separate from the, if you will, restoration of triple therapy to a group that was on ICS, some 71 percent as I remember, at baseline in IMPACT -- that they're really two different interventions.

The question before the committee is can one conflate the addition of an ICS to the withdrawal of an ICS as was discussed? I think that's what we've heard in summary on question 2D in general.

Unless there are any other comments on 2D, having heard none, let's turn to discussion 3. There are four components. I will read the text.

We'll deal with 3A first. Discussion question 3 is discuss the generalizability of the IMPACT all-cause mortality data to relevant clinical practice decisions about fluticasone furoate as add-on therapy in COPD. Include the following elements in your discussion. We're talking about question 3A, the clinical relevance and persuasiveness of the all-cause mortality results from fluticasone comparisons among ICS-naive populations -- subgroups of IMPACT, SUMMIT, and TORCH.

Any questions about the wording of question 3A?

(No response.)

DR. STOLLER: Seeing no hands raised, let me invite comment from the committee on question 3A, please.

I see Dr. Kelso's hand is raised, please.

DR. KELSO: Yes. As the patients were coming into the study, which of course the study investigators didn't have any control over that, it appears that the clinicians that were taking care

of these patients may have done a good job already deciding who needed to be on an ICS and who did not, because in the group who were already on and ICS as part of their therapy, removing it appeared to be harmful; but in patients who were not already on an ICS, adding it did not seem beneficial

So whatever went into the multitude of individual clinical decisions that were made by individual clinicians about these patients coming into the study suggests to me that they were already doing a good job deciding who needed to be on ICS and who did not. Now, whether that's because they think the patient also has a little bit of asthma or whatever other they were exacerbating more, whatever went into that decision, it appeared to be that that decision had been made correctly for the vast majority of patients prior to coming into the study. Thank you.

DR. STOLLER: Thank you, Dr. Kelso.

Ms. D'Agostino has a comment, please.

MS. D'AGOSTINO: Yes. I would add, I think

the evidence that I would really want to see as far as deciding whether to add a therapy would be if I had a patient who was not previously taking ICS and wasn't controlled versus that these patients were, although I recognize that the ICS-naive subgroup was relatively better controlled than the not ICS-naive subgroup, I would really want to see that the ICS-naive subgroups who had a step-up therapy received benefit.

I think that's really the relevant clinical question, and those patients, there's really no evidence that they received benefit. I think that's the question that I really would want to see answered in a trial, and the answer is there was no benefit received. Thank you.

DR. STOLLER: Thank you.

Any other comments from the committee on question 3A, please?

Dr. Dodd?

DR. DODD: Yes. I just want to support D'Agostino's comment that we didn't see evidence of benefit in this group. That's my only comment.

Thank you.

DR. STOLLER: Any other comments?

(No response.)

DR. STOLLER: So let me summarize then what I think we heard about 3A. There was an affirmation of the wisdom of the managing docs in terms of ascertaining, prior to randomization, who needed inhaled corticosteroids versus those who didn't and a recognition that the addition population -- that is to say the baseline ICS-naive group -- was different, as we've seen, than the ICS at-baseline group; again, an affirmation that the managing docs seemed to recognize those differences by virtue of their pretrial randomization management, if I understood the comment correctly.

That then concludes the discussion of 3A. Let's turn to 3B. I will again read the question and invite comments or questions about the wording of the question before we comment on the question. Question 3B is the clinical relevance of data from the prestudy ICS subgroup to inform decisions regarding the addition of fluticasone furoate.

Any questions about the text of the question 3B?

(No response.)

DR. STOLLER: I see no hands raised, so let me invite comments on question 3B, please.

Dr. May's hand is raised, please.

DR. MAY: Suzanne May. I have to preface this, that I'm not a clinician; I'm a biostatistician. But it seems to me as if information with regard to the ICS subgroup that had the ICS before and the withdrawal of it cannot give good information with regard to the addition of the FF for people who have been ICS-naive. Thank you.

DR. STOLLER: Thank you, Dr. May.

Ms. D'Agostino?

MS. D'AGOSTINO: Yes. I would agree with Dr. May. I think as the FDA pointed out very well in their briefing document, unless your trial is really asking the question of what happens if you remove a therapy versus continue it, which is not what this trial purported to be asking, I don't

think it's set up well to ask a question of what happens when you add an ICS to someone who already takes an ICS.

I don't think that makes a lot of sense as a question to actually ask, as Dr. May just pointed out very well. It's not really set up very well to answer the question of what happens when we add a steroid to a group who is already on the therapy. Thanks.

DR. STOLLER: Thank you.

I'll make a comment as, again, a clinician who manages these patients, as many of you do, that of course recognizing the desire of a study that looks exclusively at the addition of an inhaled steroid in a severe population, the practical realities of that are quite daunting in the sense, a was pointed out, the managing physicians in this study were doing a good job of making that ascertainment at baseline.

The practical realities of conducting a trial of group D or severely exacerbating, severely obstructed patients -- given current

understandings, GOLD, et cetera, of ICS -- are difficult to do from a practical point of view. To accrue a population of 10,000 such patients with severe exacerbating COPD who are naive to ICS would be, I think we need to acknowledge, difficult to do. So that would be my comment.

Dr. Tracy has a comment, please.

DR. TRACY: Yes. Jim Tracy. You kind of chimed in right about when I was going to key in here. The question really is about the clinical relevance of the data, and to Dr. May's point, I understand the study issues. But from a practical standpoint, as I reflected both on the presentations, the pre-meeting stuff, and what we discussed here, the basic thing is how does the addition of FF come into play, and I think it does good stuff. We clearly can't discern about the addition, but what we clearly can discern is what happens when it goes away.

So when we look at this thing from a clinical relevance standpoint, I think the presence of FF in this whole process, in this drug, or

whatever regimen that the guy who's sitting in the clinic room and makes their decision, it's a good thing. We also recognize from this is that taking it away is probably not a good thing. So as we reflect on that, there are a lot of statistical issues we have to bounce back and forth in questions, but in the end, FF is a good thing in this particular group. Thank you.

DR. STOLLER: Thank you, Dr. Tracy.

Any other comments on 3B, question 3B?

Dr. Ellenberg? Sorry. Thank you.

DR. ELLENBERG: Yes. I was just thinking about FDA's interest in recent years on enrichment designs, a randomized withdrawal design, where you start everybody on a certain treatment, and then you randomize some of them to stop it and some of them to keep on taking it, and determine whether the treatment is really effective by seeing whether people who keep taking it are doing better than those who stopped.

That has some similarity to this, although I think the issue here is whether -- it's not just

that people stop benefiting from their treatment or whether they're actually harmed by stopping it, but I wonder if the FDA would want to comment on the difference in this situation from the idea of a randomized withdrawal design, where they would use that kind of a design to establish efficacy with regard to a particular outcome.

DR. STOLLER: Comment from the FDA, please?

DR. BUSCH: Sure. Thank you for that question. This is Robert Busch. If we can still bring up slides, then I would bring up the clinical program slide deck by me, Dr. Busch, slide 31.

This is a great question about randomized withdrawal or removal of design, and we definitely had some back and forth about this internally as well. You heard Dr. Han mention it and Dr. Wise mention it.

I'm going to try and focus on how randomized withdrawal applies to IMPACT. First, I think it's been mentioned back and forth, we usually perform randomized removal trials among patient groups where this decision might be considered in clinical

practice, like patients in remission from inflammatory diseases or where signs and symptoms are perhaps best controlled. As we've mentioned, it seems inconsistent with current practice to say that we see a patient on triple therapy who still has uncontrolled symptoms and frequent exacerbations, and then we jump to a decision about ICS removal.

DR. BAUTISTA: Dr. Busch, can you repeat what slide number that you want?

DR. BUSCH: It was clinical programs slide deck, Overview of the Clinical Program, slide 31. I can quickly summarize.

Yes, this is the baseline disease characteristics and, again, I'm just highlighting that there's a lot of frequent exacerbators, a high St. George's Respiratory Questionnaire and an FEV1 that's quite low, all implying that these folks are uncontrolled and pretty sick. Again, it was commented that clinicians that are taking care of them might have had some sense of what they needed.

If you could bring up the summary

presentation slide deck, slide 25 by Dr. Karimi-Shah. The second point is that randomized removable data are probably most useful when there isn't an acute or subacute effect associated with drug removal. This is a challenging topic for ICS, and I think a few of you -- I think Dr. Medoff sort of hinted at this as well.

If this trial recruited patients on chronic oral corticosteroids for over 3 months, we wouldn't really be debating that the systemic effects of acute steroid withdrawal could be harmful, and we wouldn't use data from that subacute removal time period to say that adding oral steroids was efficacious, or potentially wouldn't.

But the problem with inhaled corticosteroids is that the degree and duration of pharmacodynamic removal effects are less well quantified, to my mind, in clinical trials, and then how long that pharmacodynamic effect could have an impact on clinical outcomes is also unclear because ICS-removal trials over the years have shown

different clinical results on different endpoints, in different patient groups, as all of you have alluded to at different points.

But I looked through this as best I could. If you look back at studies like this from Liesker and colleagues in 2011, among a few others, there's data that suggests an association between exacerbation after ICS removal and an increase in sputum inflammatory cells, serum myeloperoxidase, and a trend towards higher serum CRP. Data from Koon and colleagues in 2017 from the GLUCOLD trial also suggest an increase in bronchial CD3 cells, CD8 cells, mast cells, higher sputum total cellularity; macrophages, neutrophils, and lymphocytes.

The issue for me is that neither of these studies detail the evolution and time course of these changes completely, so these relationships with inflammatory factors after ICS removal could suggest a withdrawal, though we can't say that there are longer term effects that represent just reversion to the patient's inflammatory state if

they had never taken ICS, or a mixture of these short-term and long-term effects, so it's difficult.

If we already had convincing data that proved that the addition of ICS improved mortality, then the interpretation might also be slightly different, but we don't have that from IMPACT, SUMMIT, and TORCH. So because of both that generalizability issue and the potential influence of an acute withdrawal effect, I think we have to look more critically at randomized ICS removal in IMPACT and not necessarily -- or it is up to you to tell us, hopefully, whether you feel that ICS removal equates to ICS addition. Thank you.

DR. STOLLER: Thank you.

We have a comment from Dr. Ellenberg, and then Dr. Tracy, please.

DR. ELLENBERG: No, that was my question, so thank you.

DR. STOLLER: Okay. Dr. Tracy, please?

DR. TRACY: Yes. Jim Tracy. As I've kind of wrestled with this stuff for a while, if we

start with at least a limited perspective that exacerbation is a surrogate for mortality, and I realize that that's not exactly a one-to-one here, the whole idea of step-down therapy is certainly a reasonable direction clinically.

From a study standpoint, when I first read this, I kind of wrestled with the -- well, first of all, if we recognize that exacerbations may be a surrogate of mortality, why would we want to place somebody in this position? And I realize there are statistical questions that need to be answered, but I really wrestled with that. And I kind of wonder what -- I'd really like to hear -- I'm blocking on his name here -- Dr. Busch's statement on that.

I mean, how do you wrestle with at least the potential ethical considerations of a withdrawal of a therapy, where we're trying to answer the question, at least from a surrogate standpoint, exacerbations as a surrogate of mortality? I'd love to hear the FDA's response on that.

DR. STOLLER: Dr. Busch?

DR. BUSCH: The ethical questions are

challenging, and this is a very important question, obviously. I guess I can say it this way. I think review teams at FDA do our best to protect the safety of subjects in clinical trials and that we have to accept responsibility here for not potentially predicting the scenario. There are plenty of small factors that could go into this, but the bottom line is that sometimes we don't recognize an issue until we review the final data. I've certainly been concerned with this issue.

But with this trial, once we found this ICS-removal issue and performed these analyses, we understood that it was something that required public and transparent discussion to understand because decisions about this could affect, most importantly, COPD patients in practice and in future trials, as well as this all-cause mortality claim.

So that is why, or partially why, we've brought it to the meeting today. What we do about it in the context of other trials I think partially depends on the discussion. We wanted to understand

the broader discussion in the community from y'all about whether this interpretation was something that was agreed with, frankly.

I hope that answers your question to some degree. I don't think we're in a position, within the scope of this meeting, to say what we're going to do going forward yet. I think we are asking y'all about these issues, and then we will make determinations about that going forward.

DR. TRACY: And I appreciate that. I really wrestled with this issue ever since I read the briefing documents, and I think that, really, again, for those who are not clinicians out there, the concept of a step-down treatment process is certainly not novel, but I think that how we look at that from an investigational and regulatory standpoint is really critical, and I felt it was necessary to bring that to our attention. Thank you.

DR. STOLLER: This is Jamie Stoller. I'll make a comment with regard to this issue and then try to summarize, unless there are other comments

from the committee.

I think we're all wrestling with the issues embedded here, which is the withdrawal versus the addition in a severe patient population. I think we can all acknowledge that prior withdrawal studies, WISDOM, SUNSET, and others, have addressed a much more mildly, well-controlled population for ICS withdrawal than is the case in IMPACT, which was a severe patient population, CAT score above 10, frequent exacerbations, pretty severe airflow obstruction, et cetera.

While I think certainly I and, I suspect from our comments, many on the committee would love to have a trial that focuses on the addition of ICS to a severely baseline exacerbating population, I think I mentioned before that the practical realities of that, given, as was pointed out before, the wisdom of the managing group of physicians here, would be very difficult to accrue a population of 10,355 patients who were severely affected just on the verge of their physician or being randomized to add an ICS.

So the strange paradox of this scenario, in my view, is that on the one hand, we have a trial what in 20/20 vision might be ethically suspect to withdraw steroids from a severe population, which was probably not the case when this trial was initiated; hence, the question wasn't asked early on by either the agency or the sponsor.

I think it probably would be asked today, and almost makes the question of isolating the addition of an ICS to a severely exacerbating population regrettably -- I'm sure smarter people than I can figure out adaptive designs and so on, but relatively difficult to answer. So that's my personal comment with regard to this.

I see Dr. Dodd has a comment before I summarize on 1B.

Please, Dr. Dodd?

DR. DODD: Yes. Can you hear me?

DR. STOLLER: Yes.

DR. DODD: This is Lori Dodd. I think this question may go to the agency. In terms of approvals for drugs, clearly this approval was

given based on the primary endpoint of exacerbation. So this discussion about all-cause mortality and this dilemma that we're talking about, is it really necessary for evaluating new drugs or is an endpoint of exacerbation an appropriate endpoint for the population that we're talking about right now?

DR. STOLLER: This is for the FDA. Let me make --

DR. DODD: Yes.

DR. STOLLER: Let me just make one clarifying question, as I think I misspoke. This is question 3B, not 1B, as I may have misstated. So we're responding to question 3B. Please, this is a question for the agency.

DR. DODD: Yes, I guess Dr. Busch perhaps.

DR. BUSCH: I can give it a shot. This is Dr. Busch.

My understanding of your question is, is all-cause mortality an appropriate endpoint for COPD patients of this severity? Is that correct?

DR. DODD: Actually, I think we would

probably agree it is an important endpoint, but is it a necessary endpoint for approval? Would an exacerbation endpoint be sufficient?

DR. BUSCH: Thanks for the clarification.

I think in one of my earlier presentations, I mentioned the context of this application. Trelegy Ellipta is not a new medication. It is on the market. A decision on this today will not add or subtract a drug from the market. This is purely trying to get to the issue of whether there is substantial evidence here.

Of course, I agree with you that both exacerbations and especially all-cause mortality are very important, severe exacerbations, all of these things are very important endpoints in COPD for patients, for their providers who are trying to help them, and for everybody involved. But again, in this context, it's not a new drug. We have approved drugs on exacerbations alone.

I hope that answers your question. Is that reasonable?

DR. DODD: Yes. Thank you.

DR. BUSCH: Thanks so much.

DR. STOLLER: Any other comments on 3B from the committee, please? And I'll ask those of you have your hands raised to lower them, if you would, so I can distinguish between new questions and recurrent questions.

(No response.)

DR. STOLLER: No hands raised. Thank you.

So let me summarize what I think I heard on 3B. There was a general discussion about, on the one hand, the desirability of isolating the impact of adding inhaled steroids to a severely exacerbating, severely affected COPD population, but the recognition that this is a daunting challenge given the current understanding, and in some ways is validated by the comment that the managing docs in IMPACT seemed to do a pretty good job of
discriminating those patients who needed an ICS at baseline versus those who didn't, recognizing that those two subsets analyses represent different patient populations.

We're also reminded by the agency that the discussion here, the voting question, is really about a labeling indication, not about the availability of the drug, which is already approved and has been approved, as I understand, on the basis of the exacerbation data that were shown here and published in the New England Journal by Dr. Lipson and others.

So I think that summarizes our discussion of 3B. Let's turn to question 3C. I will, again, read the question, ask for comments or questions about clarifying the text, and then we'll open the question for the committee's comment. 3C is the clinical relevance of the IMPACT trial design and its ability to assess the benefit of adding fluticasone furoate.

Any questions on the wording of the question?

(No response.)

DR. STOLLER: Seeing no hands raised, let me invite comment on question 3C, please.

(No response.)

DR. STOLLER: I'm not seeing any hands raised.

Ms. D'Agostino has a comment, please.

MS. D'AGOSTINO: Yes. This is Emma D'Agostino. Another issue that I've been thinking about -- which I realize that we're being asked to directly assess the benefit of adding steroid. But as we're talking about the study design and as Dr. Busch mentioned, our comments here may impact future trial design, something that I've been thinking a lot about is how this trial could have been designed better and how future trials really could be designed.

But one question I had is, really, is the question that this trial needs to answer just whether step-up therapy is beneficial. That's certainly one question that would be great.

But to your great point, Dr. Stoller, that in an exacerbating population, most patients are going to be on ICS already, I think another relevant question is, is there benefit to moving from two or three inhalers to a single combination

inhaler? Because there would potentially or likely be a benefit in adherence. If it's easier to take, we know that people will take it more.

While, this trial wasn't particularly set up to address that, that's another thing that I've been thinking about, is why not compare three single inhalers or a dual plus whatever -- I guess it would be the ICS that would be part of the dual inhaler. I can't remember now what is included in the dual inhalers. Why not compare the three single inhalers versus a combination inhaler and judge for noninferiority or see if there's any improvement? Thank you.

DR. STOLLER: Thank you, Dr. D'Agostino.

Other comments from the committee? Dr. Dodd?

DR. DODD: Hello. Lori Dodd. I was going to say that I think we've addressed this question in previous discussion and the limitations of this study design being that so many patients enrolled with the FF are already on board, so it really limits the generalizability of this study to make

comments about the benefit of adding product. So it's something we've already discussed pretty extensively.

DR. STOLLER: Fair enough. I guess I'll take the chair's prerogative and ask the committee whether there are other thoughts on the practical realities of conducting a trial. This is a hard question. I certainly don't have the answer myself; hence, my asking; whether it's possible to imagine a trial design that would address specifically the question of adding an inhaled steroid to a severely exacerbating, severely affected COPD population, a GOLD D, for example.

(No response.)

DR. STOLLER: Well, we have asked a hard question. I can't answer it myself, so -- Dr. Shapiro has a comment. Please?

DR. SHAPIRO: Yes, I don't have the answer, but I do think it's a tough one. You're going to have to start earlier with a lot of patients, and no one's going to have the patients to do that. That's why you're going to need adaptive trials.

You're going to need biomarkers and precision medicine to limit the population because the cat's sort of out of the bag.

We probably have something that's disease modifying, mortality modifying, but it's difficult to prove because of the confounding factors and where we're at clinically already.

DR. STOLLER: Thanks, Dr. Shapiro.

Dr. McCormack? I'm sure you have the answer.

DR. McCORMACK: I don't have the answer, but I wanted to bring up the idea again that maybe a trial that randomized people to inhaled steroids of different potency and look at the effectiveness, and also the safety of inhaled steroids of two different potencies might provide some information about the benefit of adding corticosteroids and also the risk, inhaled corticosteroids.

DR. STOLLER: Fair enough, although, again, outside of the scope of this discussion, I'll just make the comment, as I struggle with that, that ETHOS, of course, did compare, although a different

inhaled steroid, two different doses and showed no benefit of the higher versus the lower dose in that particular trial; but of course that's outside of the domain of this particular discussion.

Dr. Ellenberg has a comment.

DR. ELLENBERG: Yes. The IMPACT trial demonstrated that you reduced the severe exacerbations, so in a disease like this, that's clearly enough for the FDA to approve this drug. I guess I'm not sure how critical it is to show that there's a survival benefit. In a disease like this, if you are improving people's quality of life, in some cases perhaps even with a slight reduction in survival, which certainly doesn't seem to be the case here, that's worthwhile.

So I'm not sure how critical it would be to try and think of how we could actually prove, once and for all, whether there was a survival benefit. It may be that a survival benefit may not be shown unless there's some new therapy, some new class of therapy, that's added to what we already have that can do it.

DR. STOLLER: Thank you.

Dr. Ellenberg has a comment, and then Dr. McCormack.

DR. ELLENBERG: Dr. Ellenberg just gave her comment.

DR. STOLLER: Oh, sorry. Forgive me.

Dr. McCormack, you have another comment, please?

DR. McCORMACK: I just wanted to raise the issue that a scenario that does come up in practice is in a patient with severe COPD who's had multiple admissions for pneumonia over a short period of time, we do consider withdrawal of inhaled steroid in those patients. And I agree with Jamie, it would be hard to find a population big enough to do a randomized trial, but it is a clinically relevant question of whether we should be withdrawing inhaled corticosteroids in some of our severe COPD patients.

DR. STOLLER: Right. Again, for clarification, I think I understand, Frank, that you're saying that such a trial would require, as a

baseline, inclusion criteria and the occurrence of multiple pneumonias, or at least one pneumonia, which would of course be the clinical indication to think about discontinuing an inhaled steroid given the data about inhaled steroids and pneumonia.

Is that correct? Am I hearing you right?

DR. McCORMACK: Yes.

DR. STOLLER: Okay. Other comments on question 3C before we turn to question 3D?

(No response.)

DR. STOLLER: So seeing no new hands, let me summarize what I think I heard. Again, this has been sort of discussed indirectly before, but I think there's a general sense that IMPACT is challenged in its ability to isolate the impact of the benefit of adding inhaled steroid, FF in this case, to a severely impaired population, given what is the practical realities of conducting such a trial.

The point remains that if one were designing such a trial, which goes to comments that the FDA will ask in the voting question, that the

withdrawal of an ICS from the severely affected population -- Dr. McCormack's comment -- perhaps to replicate the clinical question that arises, would require a baseline population of severely affected COPD with exacerbations who had previously experienced pneumonia, which would be the clinical driver of consideration of withdrawal of an inhaled steroid.

I think we all recognize that that Venn diagram of those overlapping subsets may be sufficiently small, that it would be perhaps difficult to mount such a trial certainly of the magnitude of 10,355, which is so impressive about IMPACT.

So I think that's a reasonable summary of what we heard on 3C. Let's now turn to question 3D. And again, I'll read the question and ask for clarifying questions about the text, and then we'll ask for comments. 3D is the clinical implications of the proposed labeling claim in light of the submitted data. I wonder if it would be helpful to put the slide up with the labeling

text when we address this question.

Let me first ask if there are any comments on the text of the question from the committee, please?

(No response.)

DR. STOLLER: So again, it's the clinical implications of the proposed labeling claim in light of the submitted data.

Could I ask for the slide to be shown of the actual labeling text, proposed labeling text, please, so that everyone could be reminded about this?

DR. BUSCH: Hi. This is Dr. Busch. For clarity to our AV staff, this comes from the Charge to the Committee slide deck by Dr. Karimi-Shah. It's slide 2.

We're pulling this up for your view, and we are asking you to comment about it in this question. I do think it's important to emphasize that the voting question does not ask you to make a determination on the exact wording of the claim; instead, we'll be asking you if you know whether

the submitted data from IMPACT provides substantial evidence of efficacy for an all-cause mortality claim. But this question asks about the wording and things like that. So I just wanted to clarify that as well. Thanks.

DR. STOLLER: Thank you, Dr. Busch. Yes, agreed.

I think there's another bullet point, perhaps, on the proposed labeling claim.

DR. BUSCH: Yes. Could you advance the slide, please?

Thank you.

DR. STOLLER: Yes, thank you. That's it.

So again, I'll read the question; the clinical implications of the proposed labeling claim in light of the submitted data.

Dr. Dodd has a comment.

DR. DODD: Actually, I have a clarifying question. This asks about the clinical implications of this new claim, but doesn't it make sense to juxtapose that against the existing claim? I understand the existing label refers to the

Trelegy Ellipta effect on exacerbation reduction; is that correct? I don't know if the FDA could clarify.

DR. STOLLER: Sure. Dr. Busch?

DR. BUSCH: Yes, no problem. You're correct in saying that there are a few different claims for Trelegy Ellipta in Section 14 of the labeling, including a section on exacerbations. So the proposed labeling claim here would be in addition to the other things that are there. Sorry if that wasn't clear before.

So the question is whether we add this to the labeling, not changing the previous label, or whether we do not add it to the labeling.

DR. DODD: Thank you.

DR. STOLLER: Does that answer your question, Dr. Dodd?

DR. DODD: Yes, thank you.

DR. STOLLER: Okay. Any other questions about the text?

Dr. Kelso has his hand raised. Is this a question about the text?

DR. KELSO: No, actually. It's about the discussion itself.

DR. STOLLER: Okay, great; then, please. I gather there are no other questions about the text.

Dr. Kelso, comment, please.

DR. KELSO: This labeling claim, the insertion or addition to the label, in the first bullet it says that there's a reduction in all-cause mortality by 27.7 percent, which through our discussion we have suggested may not be a reduction because of being on the triple therapy, but rather the removal of the ICS component.

The second bullet just further makes that point by then isolating the ICS-naive group from those already on ICS therapy, which shows an even larger difference in all-cause mortality in those who are already on ICS to start with, meaning now you're pulling out the people who had their ICS withdrawn.

So I think the clinical implication of this label is that a clinician would look at this and say, "Gosh. Being on this medication will decrease

my patients with COPD their chance of dying by 27.7 percent, or maybe even nearly 40 percent," and from our discussion, we just don't think that's the case.

You could look at this as a clinician and say, "Well, there's some subgroup of people who really are going to benefit from being on this treatment, and I can't identify those people ahead of time, so I'll just put everybody on it, thinking that I'm reducing everybody's mortality."

But as we've said, it may not be benign. Being on the ICS, there is an increased risk of pneumonia. Maybe the reason that it was bad to remove it is because you did something to the patient by putting them on it in the first place that changed their inflammatory milieu or something else, that only made it bad to withdraw it because they got put on it in the first place.

So there's enough unanswered questions here that I just don't think having this in the label -- the implication of this for most clinicians of wanting to put a patient on this

medicine to reduce their patient's chance of dying, I don't think we have the information to support that conclusion.

DR. STOLLER: Thank you, Dr. Kelso.

I'll make a comment as a member of the committee. I want to echo the comments that were made in public hearing and others that we all are desperate for evidence of a drug that changes the mortality curve in COPD. This would be of course highly desirable. I think everyone would acknowledge that.

The question that's being posed in 3D is regarding the clinical implications of management, recognizing that, again, the drug is available and the clinicians have access to the paper published by Dr. Lipson and colleagues in the New England Journal. So the data are available in the public domain.

But the question in my view is what are the implications -- and Dr. Kelso has alluded to this -- of putting this labeling in the package insert and creating the impression that, in fact,

there is a survival benefit by the addition of Trelegy, given the challenges that we've understood in ascertaining whether this is a withdrawal effect or an addition effect, and the complexity of that issue? So I struggle with the clinical implications of labeling in terms of the implications for clinical management.

My other comment on the label would be regarding the last sentence, actually what follows the semicolon, "the clinical relevance of these results is unknown." The last sentence, "in the non-ICS subgroup, the evaluation of all-cause mortality was limited by the small sample size." I would say that if the label were to go forward, it should say, with regard to all-cause mortality in the non-ICS subgroup, that there was no demonstrable difference; not that the data are necessarily limited by small sample size, which is of course a problem with all of the subsets. So that would be my comment on 3D.

Dr. McCormack has a comment.

DR. McCORMACK: I had a comment very similar

to both yours and Dr. Kelso's. But I would just add another therapy that has survival benefit in COPD that we all grew up with. Considering it as having a mortality benefit, it's been very hard to change practice with the prescription of oxygen in our patients, despite the evidence from the LOTT trial. So once this gets into the public domain and people start to think about mortality benefit, I think this drug will be prescribed in a way that may not be safe, given the pneumonia risk.

DR. STOLLER: Okay. Other questions about 3D, please?

Dr. May, please?

DR. MAY: On face value, it seems as if the one sentence could be really misleading when it says, "Post hoc subgroup analysis of all-cause mortality were conducted for subjects on ICS therapy at screening, and those not on screening in the ICS subgroup, Trelegy reduced the risk of all-cause mortality," one could think the way that this is worded that staying on a triple therapy reduces mortality compared to -- and then the

question is compared to who? It might be implied that it's those that are only on ICS therapy before or that the components that are not relating to ICS create that difference.

So I think this would raise, from my perspective -- again, I'm not a clinician -- more questions than it would answer and have the implication that we've discussed at length before with regard to withdrawal that is not clarified here. Thank you.

DR. STOLLER: Thank you, Dr. May.

Any final comments on 3D?

(No response.)

DR. STOLLER: Hearing none, let me summarize. I believe what I heard, there were some questions raised about the clinical implications of the label. Dr. McCormack raised the question extrapolated from LOTT, where those non-clinicians showed that the non-prescription of supplemental oxygen in patients with COPD, in a particular subset not quite as severe as before, has, in general, not resulted in the withdrawal of

supplemental oxygen, and worried about the implications of the genie is out of the bottle, if you will. I think I heard several concerns about the labeling text, which the agency has heard. I won't repeat those.

So at this point, I think we've now completed our discussion of the discussion questions 1 through 3, and if there are no further questions on these discussions, we'll now move on to the final question, which of course is a voting question. Dr. Phil Bautista will provide the instructions on the voting, please.

DR. BAUTISTA: Hi. This is Phil Bautista. For voting members, we'll be using email to submit their vote for this meeting. All voting members should have received their voting email. Please remember to reply "all" when submitting your vote. Again, please reply "all."

If we do not receive your vote within five minutes from the time Dr. Stoller opens the vote, we'll contact you directly. After everyone has submitted their vote, the vote will be compiled

while we take a brief break. When we return from break, the vote will be closed and all votes are final.

The vote results will then be displayed on the screen. I'll read the vote results from the screen into the record. Dr. Stoller will go down the roster and each panel member who voted will state their name and how they voted into the record. You can also state the reason why you voted as you did if you want to. We'll continue down in the same manner until the question has been answered or discussed for everybody.

Are there any questions about the voting process before we begin; with raised hands?

(No response.)

DR. STOLLER: I see no hands raised.

Okay. So at this point, as we have before, I will read question 4, and I will ask for any clarification on the text of the question before we actually vote. Question 4 is a voting question. Do the data from the IMPACT trial provide substantial evidence of efficacy to support the

claim that Trelegy Ellipta improves all-cause mortality in patients with COPD? The lettered subset question, if the answer is no, what further data are needed?

Are there any questions about the text of the question, question 4?

Dr. Tracy has his hand raised, or not?

Dr. Tracy?

DR. TRACY: Just for clarity here, in our email, do you want us to answer the "no" part or the "A" part, what data is needed, or do you want that as part of the discussion?

DR. BAUTISTA: Hi. This is Phil Bautista, DFO. When you do email your vote, please reply "all" to the FDA employees that are on the email, but you only have to answer yes, no, or other. You can save that section sub-A for your discussion when you do fit your vote into the record. Thank you.

DR. TRACY: Alright, perfect. Thank you.

DR. STOLLER: So the committee is asked yes or no on the reply all.

Any other questions about the text of question 4, the voting question?

(No response.)

DR. STOLLER: Seeing none, if there are no questions or comments concerning the wording of the question, we'll now begin the voting. Voting committee members, please email your vote now to the FDA advisory committee staff as instructed by Dr. Bautista. We'll now take a 15-minute break to compile the votes, and we'll resume after those votes have been accumulated.

Again, everyone will be asked to comment on their vote, and any comments made appropriate to that. So, please vote now.

(Voting.)

DR. STOLLER: We'll resume at 3:37, four minutes from now, please.

DR. BAUTISTA: Returning from break, everyone is voted and the vote is now closed. I will now read the vote results from the screen into the record.

We have 1 yes; 14 no's; and zero

abstentions.

DR. STOLLER: This is Jamie Stoller. Now that the vote is complete, we will go down the list and have everyone who voted state their name, their vote, and if you would like to, you can state the reason why you voted as you did into the record, and we'll start with Dr. Carvalho.

DR. CARVALHO: Thank you. I voted no because of many of the factors that we discussed today. I still have concerns about the makeup of the patients that contributed to the data in the first 90 days. I would like to have additional information before I could make a conclusion as to whether there are patient subsets that may have responded versus those that didn't. Thank you.

DR. STOLLER: Thank you, Dr. Carvalho.

Ms. D'Agostino?

MS. D'AGOSTINO: Thank you. I voted no. I, like I think most of us, was concerned about the early separation in all-cause mortality and that it seemed fee-driven, more of an ICS removal.

I was particularly really alarmed that it

seemed that the Data Monitoring Committee saw that separation and didn't seem to investigate it further. I just wanted to really note that for any of us that serve on DMCs.

I also was concerned about the lack of statistical control, given that the primary and secondary endpoints, one of our statisticians noted so well, had excellent control and the other endpoints did not. Also, the demographics of the trial, it's frustrating to see another trial that is largely comprised of white males as the largest demographic because it limits interpretations for other groups.

It appears particularly that women and people of color have a much smaller benefit or perhaps no benefit at all, and while we think of COPD as largely a disease in males, that's really not true. The prevalence, especially in the United States, for women is not less than in men. So I would really encourage for future studies to think about the demographics of the actual clinical population.

As far as future studies that I would want to see to answer this question better, as we discussed, a step-up therapy rather than one that involved removal therapy would really be ideal, although we discussed that, of course, that would be challenging in a severely exacerbating population, to find people who were not already on triple therapy. But I do think there also could be benefit in a noninferiority trial, comparing single-triple inhalers to the combined inhaler. Thank you.

DR. STOLLER: Thank you, Dr. D'Agostino.

Dr. Dodd?

DR. DODD: Hello. This is Lori Dodd. I voted no. The FDA label requires a high evidentiary standard, and this was not met. I think the FDA did a really nice job summarizing the issues clearly, including the focus on multiplicity and the issues related to whether the study design addressed the question of removal of ICS or the addition. So in terms of the study design, I think that the step-up design would be appropriate,

however, I wonder if this is needed given the value of exacerbations as a clinically meaningful endpoint. Thank you.

DR. STOLLER: Thank you, Dr. Dodd.

Dr. Ellenberg?

DR. ELLENBERG: I voted no. I think the reasons have been adequately conveyed in all of the discussions. I did not think it met the evidentiary standard. There were too many questions. The data I thought were suggestive, but far enough from definitive that I couldn't agree that a survival benefit should be added to the label.

DR. STOLLER: Thank you.

Dr. Evans?

DR. EVANS: Yes. This is Scott Evans. I voted no. My reasoning in brief is that, in my view, the presentation failed to adequately demonstrate the difference in survival in the triple therapy group versus the UMEC/VI group and isn't largely or importantly caused by harm from withdrawal of ICS to patients in the dual therapy

group. This concern is amplified by the questionable statistical methods to determine significance in the setting of multiple comparisons. Thank you.

DR. STOLLER: Thank you, Dr. Evans.

Dr. Kelso?

DR. KELSO: I voted no for the reason having to do with the apparent benefit likely being due to a harm from removal of the ICS. I would note that this drug is already on the market, and as I said in my comments earlier, it is apparently being used appropriately in terms of decisions about who needs to be on triple therapy, and I'm afraid that this label change, rather than leading to more appropriate use might lead, in fact, to more inappropriate use of the drug. Then just lastly, I'd like to thank our chair for running a thoughtful and well-organized meeting.

DR. STOLLER: Thank you.

Ms. Lupole?

MS. LUPOLE: Yes, sir. I voted yes. It was a difficult decision, but what persuaded me were

the complications to establish a ICS-naive mortality factor. I don't see how that can be done given the data that was presented. Another factor for me to consider this was the risk of compliance within patients. I think this is much more benefit to a patient. In most cases, patients proceed to a steroid type therapy to start with. If I get the gist of the meeting here, it's let's wait. Well, you're only going to wait for so long, so that's why I voted yes. Thank you, sir.

DR. STOLLER: Thank you, Ms. Lupole.

Dr. Marshall?

DR. MARSHALL: Yes, sir. This is Gailen Marshall. I voted no, and I voted no primarily because of two reasons. Number one, I felt like they did not achieve the bar that was described by the FDA for the appropriate labeling; and number two, I agree with previous comments about the concern about the relative indiscriminate use of triple therapy in those COPD individuals who do not need triple therapy.

What I would suggest is for the sponsor to

consider doing a registry type study, given the fact that most clinicians who use this for their COPD patients do it with the thought of affecting exacerbation. The questions that have been raised about whether severe exacerbations really do translate to increased mortality risk, many of us have grown up thinking that.

Perhaps the data could be stronger, and if the sponsor felt that it was important to come back to revisit this indication, more substantial data and a large database, that over time could show that these severe exacerbations and more severe patients do translate to increased mortality, might change at least my thinking in a future submission opportunity.

DR. STOLLER: Thank you, Dr. Marshall.

Dr. May?

DR. MAY: Suzanne May. I voted no primarily because the all-cause mortality outcome did not meet the effectiveness standard, and even if it did, it may be mostly due to worsening after ICS removal. Thank you.

DR. STOLLER: Thank you, Dr. May.

Dr. McCormack?

DR. McCORMACK: I voted no, and the reason was that this trial wasn't designed to answer the question of whether additional Trelegy could provide a mortality benefit, and no amount of post hoc data analysis can overcome the fact that even without the early mortality signal, this design could not have definitively answered the question of mortality benefit. I think a step-up trial is the design that needs to be considered despite the difficulties with designing such a trial. Thank you.

DR. STOLLER: Thank you, Dr. McCormack.

Dr. Medoff?

DR. MEDOFF: Yes. This is a Ben Medoff. I voted no. I didn't feel the data reached the standard laid out by the FDA for mortality advantage and echo many of the reasons expressed by the others on this committee, namely the potential effects of withdrawal of the steroids and the fact that the trial was not designed to answer the

mortality questions directly also. Thank you.

DR. STOLLER: Thank you, Dr. Medoff.

Dr. Redlich?

(No response.)

DR. STOLLER: Dr. Redlich, perhaps you're muted.

(No response.)

DR. STOLLER: We'll come back to Dr. Redlich.

Dr. Shapiro?

DR. SHAPIRO: I voted no for the reasons stated, although I would say that it is encouraging. We know that steroids are a double-edged sword. It could reduce the inflammation leading to tissue destruction at the expense potentially of fighting infections. The fact that even if this was a withdrawal effect, the inflammatory component and destruction seems to be pretty important. So if we continue to focus on this subgroup of exacerbators, we could design a study to prove its mortality benefit.

DR. STOLLER: This is Dr. Stoller. I'm

remiss again in not reminding everyone to please state your full name, so shame on me. This is James Stoller. I voted no, and I have to say that I struggled with this because this was a very difficult decision. Again, like many of you, as a practicing lung doc, we all hunger for a drug that will favorably impact the mortality of our patients.

I'm quite happy that a triple-drug single inhaler is available for compliance reasons and others that have been stated, however, I think the bar was very high on this, both by guidance, criteria, and the fact that the replicate studies, at best, in some very small subset post hoc analyses were perhaps consistent with but not overall consistent with the mortality benefit in studies that were designed to show a mortality benefit, albeit in a different patient population.

So much has been said before. I think it was very difficult to discount the possibility that the 90-day separation was attributable to anything other than the adverse impact of ICS withdrawal,

and I think we've amply discussed the daunting challenges of a step-up trial that would show a mortality benefit.

So the good news is that drugs like this are available to our patients, and as others have said, although a mortality label would be nice, perhaps it's icing on the cake. Clinicians have access to this drug and to the data in the public domain. So I'll stop there.

Dr. Tracy, and then we'll come back to Dr. Redlich. Please state your full name.

DR. TRACY: Dr. James Tracy. I voted no for most of the reasons previously discussed. Overall, I'm not sure that the overall survival benefit met the necessary standards. I was also concerned about the lack of type 1 control.

That being said, I really do think that there is a benefit for this. I think, as has been alluded to by a couple of the other commenters, that most of the stuff seems to be appropriately addressed and that there's definitely a benefit to this therapy. Sometimes from a regulatory

standpoint, we look at this thing as a one-and-done kind of thing, but in practical reality of clinical practice, it's never a one-and-done thing. You see where things work out, and who benefits and who doesn't benefit. Then, obviously if there's a down side in the case of pneumonia or such things, you adjust therapy based on that.

The last thing I'll say is I found the labeling issue to be very confusing, and I'm not sure exactly what the end labeling would be, but I thought that the labeling overstated what we were trying to get across here. Thank you very much.

DR. STOLLER: Thank you, Dr. Tracy.

Dr. Redlich, are you available.

DR. REDLICH: This is Dr. Carrie Redlich. Can you hear me?

DR. STOLLER: Yes.

DR. REDLICH: Sorry. I'm not sure what the problem was. I also voted no for the many reasons that have been stated. It did not meet the FDA standard. I don't think I need to restate the other reasons.

DR. STOLLER: Okay. Thank you, Dr. Redlich.

I think that completes our voting list. Before we adjourn, let me turn again to the FDA and ask whether there are any last comments from the FDA, please?

DR. KARIMI-SHAH: Thanks, Dr. Stoller. This is Banu Karimi-Shah. I have no other comment other than to say, on behalf of the entire review team here at FDA, I just wanted to extend my deepest gratitude to the committee members for their participation in this meeting today. We acknowledge the preparation that was required for this meeting, and not only reading the briefing document as is sort of per usual, but watching the prerecorded presentations. Your diligence and preparation was apparent, and we are greatly appreciative.

We understand that this allows for a focused and streamlined discussion, which is really helpful to us in our decision making of this really important topic. We also understand that all of you took time away from your very busy schedules in

this very challenging time. And again, a very special thanks to you, our chair, Dr. Stoller, for running a very organized meeting in this new virtual format. I daresay we're going to finish a few minutes ahead of schedule, so, thank you again on behalf of all of us here at FDA.

Adjournment

DR. STOLLER: Thank you, Dr. Karimi-Shah.

I'll take the chairman's prerogative for just a final comment, which is to thank everyone and to thank my colleagues on the committee. I thought the conversation was very robust and thoughtful. I know many of you, and this was a very informed, robust discussion.

I want to thank the sponsor. I think that were it not for carefully designed studies, we wouldn't have the answers and availability of agents like this. Again, I stated before that I'm appreciative of the fact that the drug is available, although perhaps wasn't able to endorse its mortality benefit for reasons stated.

I want to thank the FDA staff. I thought

that the analyses and the briefing documents and the presentations, like those of the sponsor, were very careful, very clear, and very informative. Then I want to thank the public and our commenters whose comments, as always, really inform the discussion and try to provide a real context.

So with those concluding remarks and with three minutes to spare before are appointed adjournment, we will now adjourn the meeting with thanks to everyone. Thank you very much.

(Whereupon, at 3:57 p.m., the meeting was adjourned.)