Request to Amend the TRELEGY™ ELLIPTA® Label to
Include Data on the Reduction in Risk of All-Cause Mortality in Patients with COPD

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GlaxoSmithKline
Pulmonary-Allergy Drugs Advisory Committee

Introduction, C. Elaine Jones, PhD, GlaxoSmithKline

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I'm Elaine Jones, the Medicines Development Leader for Trelegy Ellipta at GlaxoSmithKline.
I would like to present findings from our large, well-controlled, prospective study, IMPACT, that supports a proposed label change to include data for the reduction in risk for all-cause mortality for Trelegy in patients with COPD.

I would like to thank the Advisory Committee and the Agency for this opportunity to present the data. I would also like to acknowledge, that while there are areas of agreement between the FDA and GSK, there are some differences which we will highlight during the presentation and offer our perspective.

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Here is our agenda. After my introductory remarks, Dr. David Lipson, the physician responsible for this project, will review the relevant clinical data that support our proposed label change for Trelegy.

Dr. Robert Wise will discuss the importance of both mortality as an endpoint and the inclusion of these data in the label to prescribers.

I will then conclude our presentation.

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Trelegy is a triple inhaled therapy approved for the maintenance treatment of patients with chronic obstructive pulmonary disease or COPD. Trelegy contains 3 different classes of medications.

Fluticasone furoate, or FF, an inhaled corticosteroid.

Umeclidinium, or UMEC, a long-acting muscarinic antagonist.

And Vilanterol, or VI a long acting beta2-adrenergic agonist.

It is delivered in a single inhaler and is taken once a day.

Since its approval in September 2017, it has been prescribed to approximately seven hundred and ten thousand patients in the United States. 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 2019 and that is the focus of this advisory committee meeting.

The safety profile of Trelegy is consistent with the data submitted in the exacerbation supplement. Consequently, only the efficacy data from the all-cause mortality endpoint will be discussed during this presentation.

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Moving on to Chronic Obstructive Pulmonary Disease, or COPD. This is a progressive lung disease that affects approximately 16 million people in the United States. COPD is an umbrella term used to describe patients with emphysema and/or chronic bronchitis.

While there is no cure for COPD, it is considered preventable since most cases are associated with smoking.

Patients with more advanced COPD have an increased risk of exacerbations and hospitalizations. And we know that hospitalizations are associated with increased mortality. In fact, COPD is the 4th leading cause of death in the United States.

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Based on US Medicare data in patients 65 years of age and older, COPD exacerbation events lead to significant healthcare utilization, including 15.4 million office visits and seven hundred and 39 thousand hospitalizations per year.

The risk of readmission and death remain elevated for an extended period of time following hospitalization for a COPD exacerbation. To illustrate this, 64% are readmitted within one year, and over one quarter die within that time period.

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Additional data in a primary care population, demonstrating the significance of exacerbations, comes from a natural history study by Rothnie in nearly 100,000 patients demonstrating 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 increase so does the proportion of patients who die. 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.

In fact, a number of trials have evaluated the effect of pharmacotherapy on hospitalized COPD exacerbations and mortality in patients with COPD, including our own trials, TORCH and SUMMIT. I would like to give you some context around these studies.

TORCH was the first mortality study conducted in six thousand, one hundred and twelve patients with COPD, however it was initiated over 20 years ago. TORCH showed a 17.5% 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. The inhaled corticosteroid studied in TORCH was fluticasone propionate and the long-acting beta agonist was salmeterol.

Fluticasone propionate and fluticasone furoate are different molecules. Fluticasone furoate and fluticasone propionate are not salts or pro-drugs of fluticasone, they are not metabolized to fluticasone and share no common metabolites.

As these are different molecules and the standard of care and treatment guidelines have changed, in particular, there were no LAMAs 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 fluticasone furoate and vilanterol, 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 fluticasone furoate and vilanterol, and the individual components in more than 16,000 patients compared to placebo. The primary endpoint in 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. On the x-axis is the time to death and on the y-axis is the probability of dying. The SUMMIT study had four arms and presented here is placebo in black, vilanterol in blue, fluticasone furoate in light blue and the combination of fluticasone furoate and vilanterol in red.

I am going to focus on the comparison of the combination of fluticasone furoate and vilanterol with placebo as this was the pre-defined primary comparison.

Patients in SUMMIT were required to have moderate airflow limitation and heightened cardiovascular risk, however they were not required to have a history of COPD exacerbations in order to enter the study. Evaluation of this particular patient population, while it showed a 12% reduction in the risk of all- cause mortality, did not allow for the treatment effect to reach statistical significance.

However, if we look at the all-cause mortality results in the patients in the SUMMIT study who would have met the entry criteria for IMPACT, a population with frequent moderate exacerbations or at least one hospitalized exacerbation, we see a much larger reduction in the risk of dying.

Shown here is a Kaplan Meier plot of the patients from the SUMMIT study who would have met the IMPACT entry criteria. Again, shown on the x-axis is the time to death and on the y-axis is the probability of dying.

This post-hoc analysis shows that in this population in SUMMIT who met the entry criteria for IMPACT with regard to history of exacerbations, which was nearly three thousand five hundred patients, we see a clinically meaningful reduction in the risk of all-cause mortality of 34%. The FDA briefing document notes that there is a lack of separation at one year for all-cause mortality in the overall SUMMIT study. However, when you look at the data for the exacerbating population in SUMMIT, there was separation at one year as shown here. These data provide evidence that this frequently exacerbating population, who are the patients most at risk of dying, provides the ability to see the treatment benefit of fluticasone furoate and vilanterol combination on all-cause mortality.

The FDA suggest 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 would be required to power for a larger true treatment effect – this is illustrated in the SUMMIT exacerbating population where we see a 34 % reduction with 59 events on FF/VI combination and 89 events on placebo.

Recalling the Rothnie natural history study data and this data from SUMMIT in patients with a history of exacerbations, I would now like to present the COPD exacerbation and mortality data from IMPACT.

I will start with the exacerbation data. The forest plot shown here, represents moderate and severe COPD exacerbation data, for the comparisons of Trelegy versus UMEC/VI in the top portion and Trelegy versus FF/VI in the bottom portion.

For both comparisons looking at moderate and severe COPD exacerbations, the point estimates and 95% confidence intervals are to the right of the vertical dotted line and therefore favor Trelegy, demonstrating a statistically significant reduction in these events.

However, when looking at severe exacerbations, only the comparison of Trelegy with UMEC/VI reached a statistically significant reduction of 34%.

The data I previously shared from Rothnie showed an association between severe COPD exacerbations and mortality. Because of this association and considering the data showing a reduction in severe exacerbations seen with Trelegy it is not surprising that Trelegy demonstrated a reduction in all-cause mortality compared with UMEC/VI in the IMPACT study. Consequently, this pairwise comparison of Trelegy versus UMEC/VI will be our main focus in today's presentation.

I would now like to show you the all-cause mortality data we would like to include in the Trelegy label.

Shown here are the data that we are proposing to include in the Trelegy label. Of note, this is revised wording submitted during the review and takes into consideration post hoc sub-group analyses requested by the FDA post submission.

All-cause mortality, on and off treatment, was a pre-specified endpoint with a pre-specified analysis plan. It was not an exploratory endpoint. The data is proposed to be included as text only and is in a similar format to the other "other" endpoint data already included in the Trelegy label.

For ease of presentation, I am showing the mortality data included in this proposed label text in a tabular format.

There was a 28% reduction in risk of all-cause mortality for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset.

There was a 39% reduction in risk of all-cause mortality for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset for those patients who were on an inhaled corticosteroid prior to the study.

There was no reduction in risk of all-cause mortality observed for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset in patients who were not on an inhaled corticosteroid prior to the study potentially due to the small sample size and low number of events.

The FDA has suggested that the mortality benefit observed in IMPACT was driven by abrupt inhaled corticosteroid withdrawal for those subjects randomized to UMEC/VI. This is an area where we do not agree with the FDA and Dr Lipson will address this in his presentation.

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 studies section of the Trelegy label given the medical importance of a mortality endpoint.

Dr. Lipson will now present the data supporting this label change in more detail.

Relevant Clinical Data, David Lipson, MD, GlaxoSmithKline

I'm David Lipson. I'm a practicing pulmonologist and the physician responsible for Trelegy at GlaxoSmithKline. I'll be reviewing the relevant data, which demonstrated the additional benefit of Trelegy to reduce the risk of all-cause mortality in patients with COPD.

Here is an overview of my presentation. I will focus on data from the IMPACT trial, including important aspects of the trial design and clinically relevant results supporting the mortality benefit observed with Trelegy. My presentation will also address the points raised in the Agency's memorandum.

I will discuss other trial design implications including issues of multiplicity, that impact the interpretation of the data. And finally, I will review additional analyses which support the overall data package and provide substantial evidence for the inclusion of reduction in the risk of mortality in the Trelegy label.

Let me first discuss the IMPACT trial design.

IMPACT was a randomized, double-blind, parallel-group, multicenter Phase 3 study designed to demonstrate superiority of triple therapy over effective dual inhaler therapies for the reduction in the rate of moderate and severe COPD exacerbations.

The intention-to-treat population included 10,355 patients with symptomatic COPD and a history of exacerbation and is one of the largest studies ever conducted in patients with COPD.

Twice as many patients were randomized to Trelegy and FF/VI, seen here in blue and red than to UMEC/VI, seen here in green, because the study was powered on exacerbations and it was hypothesized that there would be a greater magnitude of benefit between Trelegy and UMEC/VI than between Trelegy and FF/VI.

Patients received once daily treatment for 52 weeks and then had a 7-day follow-up.

Evidence from the IMPACT study is included in the Trelegy label.

As a reminder when IMPACT was designed in 2014, there was a controversy regarding the use of ICS in COPD and the relative benefits of triple therapy compared with dual therapies in patients with a history of exacerbations.

IMPACT allowed patients to enter the study on their current COPD medications. This was important because unlike previous studies, there was no artificial stabilization or washout of therapy during the run-in. This reflects clinical practice where patients switch treatment without a withdrawal period – a patient comes to the office and a change in therapy is made. So, to improve the generalizability of the results we allowed patients to remain on their current therapies as they came into the study. This was consistent with current medical practice and international guidelines.

Another important aspect of the study is that we evaluated the same molecules, in the same delivery device, with the same dosing regimen throughout the trial.

Thus, when we compare Trelegy with FF/VI, the only difference between the arms is the addition of the LAMA or umeclidinium. This helps us to understand what benefit UMEC adds to Trelegy.

Similarly, when you make the comparison of Trelegy with UMEC/VI, the only difference between those arms is the ICS fluticasone furoate, so one can "pull out" the contribution of the inhaled corticosteroid.

The inclusion / exclusion criteria were designed to enroll a COPD population that would typically be seen in clinical practice.

These patients had symptomatic COPD with a history of exacerbations, depending on the severity of their airflow limitation.

A current diagnosis of asthma was an exclusion criterion.

The IMPACT trial included clinically relevant prespecified endpoints to assess multiple aspects of COPD including lung function, quality of life, and exacerbation reduction.

However, given the severity of the patient population in the trial and the mortality associated with COPD, we did include all-cause mortality as a prespecified endpoint with a prospectively defined analysis plan.

We prospectively evaluated COPD hospitalizations and all-cause mortality given the importance of these endpoints to both patients and physicians.

All-cause mortality was included as an endpoint in a protocol amendment prior to the start of the study.

First, let me present the demographics of the IMPACT population.

Baseline demographics and disease characteristics show that the enrolled patients had moderate to very severe air flow limitation and the majority had a history of frequent exacerbations, typical of a symptomatic COPD population that we would see in clinical practice.

The mean age of patients in the trial was 65 years.

The majority of patients were male.

65% were former smokers and the remainder of patients were current smokers.

The mean post bronchodilator FEV_1 % predicted was 46%.

Only 18% of patients were reversible to albuterol, which is commonly seen in a population of patients with COPD.

70% of patients had 2 or more moderate or one or more severe, meaning hospitalized, COPD exacerbations in the prior year.

A quarter of the population had at least one hospitalization for COPD in the prior year.

And 40% of patients had 2 or more cardiovascular risk factors.

As you can see, these patients had advanced disease. And this is the exact population we were hoping to enroll in the trial.

You will recall that Dr. Jones showed you the association between COPD exacerbations and hospitalizations and how they relate to mortality. I would like to share with you the key data from IMPACT that addressed each of these aspects, starting with moderate to severe exacerbations.

Previously Dr. Jones presented a forest plot of the exacerbation data. What I am showing you here is a different way to view the data showing the modelled rate of exacerbations in each treatment arm and the percent reduction.

In IMPACT, Trelegy, as shown in blue, demonstrated a significant reduction in the rate of moderate and severe exacerbations compared with either dual therapy FF/VI, shown in red, or UMEC/VI, shown in green.

There was a 15% reduction in the rate of moderate and severe exacerbations in Trelegy compared to FF/VI.

And a 25% reduction with Trelegy compared with UMEC/VI as shown on the right, each with a p-value less than 0.001.

These results are included in the current labeling for Trelegy Ellipta.

Now I'd like to show you data also in the label on severe COPD exacerbations that required hospitalization, because we know that COPD hospitalization is highly associated with increased morbidity and mortality in patients with COPD.

Trelegy also reduced the annual rate of severe COPD exacerbations, meaning hospitalized exacerbations, compared to both dual therapies.

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

Trelegy reduced the rate of severe COPD exacerbations by 34% compared to UMEC/VI, shown in green, which was highly statistically significant.

This reduction in hospitalized exacerbations has tremendous clinical relevance for patients as we might expect that a reduction in COPD hospitalization could affect mortality.

In fact, we have performed a post-hoc analysis in IMPACT to investigate if mortality risk is associated with severe exacerbations. Results of this analysis show that during a severe exacerbation event the hazard ratio was 41.2 compared with the baseline period prior to an exacerbation event. Representing a 41-fold increase in the risk of dying during a severe exacerbation.

Severe exacerbations are highly statistically significantly associated with an increase risk of dying, with the risk returning to baseline after about 90 days following the end of the event.

All-cause mortality is a clinically relevant endpoint as it is associated with worsened COPD disease state, especially when a patient is hospitalized for an exacerbation.

And showing a reduction in mortality for COPD has been of interest to clinicians and researchers for many years.

The IMPACT trial has now provided that evidence.

Let me start with the original on and off treatment all-cause mortality analysis from IMPACT as presented in the NEJM. These included deaths in patients who withdrew from treatment and those who withdrew from the study.

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Time is presented on the x-axis and the probability of death is on the y-axis. Trelegy, seen in blue, FF/VI in red and UMEC/VI in green.

We saw a statistically significant 29% reduction in the risk of all-cause mortality for Trelegy compared with UMEC/VI. We also saw 10% reduction in risk for Trelegy compared with FF/VI although this comparison was not statistically significant.

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In this analysis 574 patients or about 5.5% had missing vital status data at Week 52 of the trial. These patients were censored at their last known alive date.

In order to account for these missing data, GSK performed a rigorous global collection of missing vital status at Week 52. An independent committee external to the study monitored the number of patients in whom vital status had been obtained. They were blinded to both treatment and whether patients were alive or dead. The committee made the determination to stop data collection when they felt no more data could be obtained. The majority of those missing vital status were due to data privacy regulations or inability or refusal to re-consent.

Following this effort, we were only missing vital status for 42 patients at Week 52, of the more than 10,000 patients randomized in the trial.

This includes 9 patients on Trelegy, 18 on FF/VI, and 15 on UMEC/VI.

Now let me show you the results for the dataset with additional follow-up.

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The collection of the additional follow-up data did not change our findings. We see a clear separation in the Trelegy arm in blue from the UMEC/VI group in green with a 28% reduction in the risk of dying on Trelegy versus UMEC/VI and a p-value of 0.042.

There was also a numerical reduction in the risk of dying of 11% for Trelegy compared to FF/VI, illustrating the contribution of the LAMA, UMEC to the overall treatment effect.

While the all-cause mortality effect seems to be driven by the ICS component, the data suggest there is a further contribution from UMEC. Thus, the greatest benefit is seen when all three components of Trelegy are taken together.

GSK concur with the Agency that missing data are not considered a critical issue with only 0.4% of patients not having complete follow-up for mortality through one year.

Now I would like to share with you the causes of death in the IMPACT study.

Deaths within the study were independently adjudicated.

The rate of death was 21.5 per 1000 patient years in the Trelegy arm, 22.8 in the FF/VI arm and 29 in the UMEC/VI arm.

Not surprisingly, based on the demographics of the population, the most common causes of death were cardiovascular and respiratory. We saw lower rates of both cardiovascular and respiratory deaths on Trelegy compared to UMEC/VI.

It is important to note that when patients come off randomized therapy, they can go on any therapy that is prescribed. In fact, 45% of those on UMEC/VI who discontinued treatment were prescribed triple therapy and 22% were prescribed an ICS/LABA.

Therefore, two-thirds of patients went onto an ICS regimen after discontinuing UMEC/VI. By including off-treatment data we are no longer comparing Trelegy with only UMEC/VI.

So, I would like to show you the magnitude of effect when patients are on-treatment.

This figure represents the Kaplan Meier probability plot for on-treatment all-cause mortality from IMPACT.

The plot shows a clear separation between Trelegy and UMEC/VI with a 42% reduction in the risk of on-treatment all-cause mortality with a p-value of 0.011.

There was also a numerical reduction in the risk of dying of 5% for Trelegy compared with FF/VI.

Having just presented the benefit of Trelegy on survival, I will now discuss some of the trial design implications from IMPACT that are important to the evaluation of these data.

First, I would like to remind you that we used active comparators as there was no placebo arm in the trial. Therefore, we are seeing the benefits of Trelegy in IMPACT, not against placebo but against two dual therapy medications that are approved for the maintenance treatment of COPD.

Now, I would like to discuss exploratory analyses presented by the Agency in their briefing document excluding data from the first 30, 60 and 90 days of treatment to explore the time course of mortality.

We agree with the agency that these exploratory analyses are limited as they could represent a healthy survivor effect and should be interpreted with caution. The agency note that these analyses suggest a

potential trend of early mortality events in the UMEC/VI arm. Let me show you a graph that shows there was not an early surge in mortality events on UMEC/VI.

This figure shows the cumulative number of deaths on the UMEC/VI arm over the course of the study.

There is not a sudden bolus of deaths in the UMEC/VI arm. The events occur gradually over the course of the study, in fact 89% of the deaths occurred after the first 30 days on the UMEC/VI arm.

These data do not show an abrupt increase in deaths in patients randomized to UMEC/VI.

Let me now address multiplicity.

All-cause mortality was a predefined 'other' endpoint in the trial without adjustment for multiplicity.

Let me take a moment to address why multiplicity adjustments in clinical trials are considered important. Multiplicity adjustments are performed to avoid a study being declared successful when only a few endpoints have hit a p-value < 0.05 without the context of how many endpoints were tested.

However, if the context is understood, that is to say, the number of analyses performed and how many had a significant outcome, then valid scientific conclusions can still be drawn from results that have not been adjusted for multiplicity.

It is also important to understand that we are not singling out the all-cause mortality results simply because they were positive by chance.

This slide shows all of the 34 pre-defined efficacy endpoints which evaluated Trelegy with UMEC/VI in the overall IMPACT population. These endpoints are grouped into categories of Exacerbations, All-Cause Mortality, Lung Function and Patient-Reported Outcomes. All but one directionally favored Trelegy. 29 had a p-value < 0.05 in favor of Trelegy, including 23 that had a p-value < 0.001. The ones that did not have a p-value < 0.05 are those that we would not necessarily expect to show a benefit with the addition of a steroid to a dual bronchodilator, as the benefits were primarily driven by improvements in lung function which are maximized by the dual bronchodilators.

Given that the results directionally favored Trelegy in 33 of 34 endpoints, we are not singling out all-cause mortality.

Finally, I would like to show further analyses which support the all-cause mortality benefit with Trelegy.

As a reminder, IMPACT was a large, global, multicenter, well controlled trial with more than 10,000 patients across 37 countries.

There was no single pre-defined subgroup that was driving our findings. This is important because these characteristics help address concerns about bias and chance findings associated with a single trial.

This slide shows the all-cause mortality results by pre-defined subgroups, including gender, age, race, geographical region, and background disease characteristics.

While I recognize that there is a lot of data on this slide, what I would like you to focus in are the point estimates in the center of the figure. As you can see most of the point estimates are to the right of the vertical dotted line favoring Trelegy.

These data further support the robustness of this single trial and show that no single pre-defined subgroup is driving the all-cause mortality findings. Again, this is important because these characteristics help address concerns about bias and chance findings associated with a single trial.

We also looked at whether there was an effect by ICS or triple use at screening as separate post-hoc analyses.

Not surprisingly, given that IMPACT enrolled a population of frequently exacerbating COPD patients, most, 71%, were on an ICS-containing medication at screening either as a triple, dual or mono therapy. While 29% of patients came into the trial on a non-ICS regimen.

Recall that there was a 2:2:1 randomization scheme in the trial. Because of this randomization scheme only approximately 14% of patients overall would have actually undergone ICS withdrawal.

One of the concerns raised by the FDA is that abrupt ICS withdrawal would make patients less stable. If this were true, one would expect to see a deterioration in lung function and or health status. So, let me now show you the data on FEV_1 and SGRQ that demonstrate this is not the case in IMPACT.

These graphs present change from baseline in trough FEV_1 over the study. The panel on the left presents the results of those on an ICS at screening and the one on the right those who were not on ICS at Screening. Trelegy is presented in blue, UMEC/VI in green and FF/VI in red.

As anticipated in a progressive disease, FEV_1 declines over time in all treatment groups with the treatment difference remaining consistent.

If abrupt removal of ICS was making patients unstable as suggested by the FDA, you would expect an early effect on the baseline FEV_1 for those on UMEC/VI (as shown in green on the left-hand figure). However, that is not what was observed indicating that there was no abrupt deterioration in lung function from baseline because of ICS withdrawal.

These graphs present change from baseline in SGRQ over the study, which was measured at weeks 4, 28 and 52. 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 at screening and the one on the right those who were not on ICS at screening.

Again as suggested by the FDA, if removal of ICS was making patients unstable you would expect a deterioration from baseline in health status, with an increase in the SGRQ score, for those on UMEC/VI (shown in green in the left-hand figure). This was not what was observed. These data also suggest that the health status improved regardless of the removal of the ICS.

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This figure shows the results of time to first severe exacerbation by ICS use, with ICS use at screening in the left-hand panel and no ICS use at screening in the right-hand panel.

In table 21 of the FDA briefing document, the Agency suggest that this analysis indicates that ICS removal resulted in an increase in severe exacerbations in patients receiving ICS at screening who were randomized to UMEC/VI. Of note, there is a numerical reduction in risk for Trelegy compared with UMEC/VI irrespective of ICS use at screening. However, this analysis ignores all subsequent severe exacerbations. Let me show you the analysis of rate of severe COPD exacerbations which captures all severe exacerbations and was a pre-defined secondary endpoint.

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This figure shows the results of the rate of severe exacerbation by ICS use at screening in the left-hand panel and no ICS use at screening in the right-hand panel. You will note that the rate of exacerbations is higher in both treatment arms for those patients previously on an ICS reflecting the severity of this population

There is a 35% reduction in the rate of severe exacerbations with Trelegy relative to UMEC/VI regardless of ICS use at screening. As the reduction in rate of severe exacerbations was the same irrespective of ICS use at screening, abrupt ICS withdrawal cannot be driving these results.

Now, let me show you mortality results by ICS at screening.

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On the left of this slide is a Kaplan Meier curve for time to death for patients who were on an ICS-containing medication at screening.

In these patients, we see a significant benefit with Trelegy compared with UMEC/VI.

On the right is the same curve for those who were not on an ICS at baseline.

We see no all-cause mortality treatment effect in patients who were not on an ICS-containing medication at screening, potentially due to the small sample size and low number of events. These are patients with less severe disease as evidenced by lower exacerbation rates and a lower number of deaths. The low number of events in this smaller subgroup analysis result in reduced precision as evidenced by the wide confidence intervals.

So, Trelegy demonstrated an additional benefit of improved survival compared to UMEC/VI in those patients who came into the trial on an ICS.

These patients had more advanced COPD as indicated by a higher rate of hospitalization in the prior year despite being on an ICS and thus were at greater risk of dying than those who did not.

Let me now show you the rates of moderate to severe exacerbations by medication at study entry to further illustrate their enhanced risk.

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The annual rates of exacerbations over the duration of the trial for those patients coming in on a triple therapy were higher regardless of randomized treatment, ranging from 1.2 to 1.7 per year, than those on LAMA monotherapy. These patients had lower annual rates of exacerbation, ranging from 0.6 to 0.7.

Therefore, we clearly see differences in disease severity within subpopulations of IMPACT. Perhaps this is to be expected as international treatment recommendations suggest the use of ICS in patients with more advanced disease.

This degree of disease severity is why we believe we are seeing the survival benefit with Trelegy versus UMEC/VI for those who were on an ICS at screening.

Let me now show you the all-cause mortality data for the most severe patients, those who came in on triple therapy.

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On this slide is a Kaplan Meier curve for time to death for patients who were on a triple ICS/LAMA/LABA medication at screening.

While impact is not powered to look at subgroups, this subgroup comprises 40 % of the population and thus we believe these data are informative.

Those patients who were maintained on a triple therapy with Trelegy after randomization, seen here in blue, have a trend towards improved survival compared to those who were randomized to either an ICS/LABA (in red) or to a LAMA/LABA (in green). Although these comparisons did not reach statistical significance, they suggest that symptomatic patients who mirror the inclusion criteria of IMPACT have better survival than those who have either the LAMA or ICS component removed from their treatment regimen. This helps demonstrate the benefit of both the LAMA and the ICS in the triple combination of Trelegy.

Now to summarize what you have heard during this presentation.

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We acknowledge that all-cause mortality was an other endpoint with no adjustment for multiplicity with a p-value of 0.042. 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.

I would now like to summarize key aspects from the IMPACT study that provide confidence in the substantial evidence of effectiveness. IMPACT was a well-designed, well-conducted large, global, multi-center trial. All-cause mortality was a pre-defined endpoint with a pre-specified analysis plan. These data are reliable and of high quality with independent adjudication of deaths and there was minimal missing data.

33 of 34 pre-defined efficacy endpoints directionally favored Trelegy compared with UMEC/VI in the overall IMPACT population, 29 with a p-value less than 0.05 with 23 of these having a p-value less than 0.001. We have not singled out all-cause mortality.

In addition, we have demonstrated clinical plausibility between all-cause mortality and reduction of severe COPD exacerbations. Indeed, in IMPACT, there was a 34% reduction in the rate of severe COPD exacerbations, supporting the plausibility that the risk of death would also be reduced. The data from a similar population to that in IMPACT from the SUMMIT study, an exacerbating population also provide directly relevant supportive data.

In summary, Trelegy is already approved by the FDA to treat exacerbations in patients with COPD. And today we have presented substantial evidence demonstrating that Trelegy provides the additional benefit of reducing all-cause mortality in patients who were previously taking an ICS.

Specifically, we have shown data from IMPACT that demonstrate a statistically significant and clinically important 28% reduction in the risk of all-cause mortality with Trelegy compared with UMEC/VI. There was a statistically significant and clinically important 39% reduction in the risk of all-cause mortality with Trelegy compared with UMEC/VI in those patients on an ICS at screening. There was no effect that was seen in those patients not on an ICS at screening.

Finally, the effect on all-cause mortality seen with Trelegy is not due to abrupt ICS withdrawal but rather demonstrates the benefit of an ICS in this patient population.

These data provide substantial evidence that Trelegy reduces the risk of all-cause mortality in a symptomatic population with COPD and a history of exacerbation.

Thank you. Dr. Wise will now present his clinical perspective.

Clinical Perspective, Robert A. Wise, MD, Johns Hopkins University School of Medicine

My name is Bob Wise. I am a professor of medicine and a pulmonologist at Johns Hopkins University School of Medicine. I am a being paid for my time as a consultant to the sponsor, but I have no financial interest in the outcome of these deliberations.

The question before us today is whether the data regarding the effect of Trelegy compared to a dual bronchodilator on all-cause mortality should be included in the prescribing information. That is to say, we must consider whether prescribing physicians should be given the information that you have seen presented by Dr. Lipson. It is important that providers who prescribe or dispense Trelegy be permitted access to this information in a format that is approved by the FDA.

As a pulmonary physician, I care for patients with COPD in both the inpatient and the outpatient setting. All too frequently these patients die during or in the period following a severe hospitalized exacerbation. As you have seen this morning these events are both morbid and mortal. There are few treatments that we can offer that will improve survival and currently no pharmacotherapies.

In trying to determine whether this information should be provided to prescribing physicians, there are two threshold questions that must be answered in the affirmative.

First, is this information IMPORTANT?

Second, is this information TRUE?

It should be obvious that a reduction in mortality is a clinically important outcome. Improved survival is an overarching goal of public health and medical care. Improved survival is a goal of maintenance therapies in all chronic diseases. Thus, I think that there is little controversy that a reduction the risk of dying is clinically important to both patient and doctor.

Is the magnitude of the effect substantial? Is the effect size large enough that we should pay attention to it? Of course, there is no minimally important difference in survival. The prescription of treatments that prolong survival include a complex trade-off between effect size, costs, side-effects, functional status, and quality of life.

But I do want to point out that the effect size demonstrated here is comparable to maintenance treatments of chronic diseases such as diabetes and coronary heart disease.

Thus, I can easily conclude that the information about the effect of Trelegy compared to a dual bronchodilator on survival in a high-risk COPD population is IMPORTANT, and it is something that a practicing physician like myself should be aware of.

The annual all-cause mortality risk reduction with Trelegy versus UMEC/VI of 0.83% per year in the IMPACT study. The magnitude of the benefit is greater than that achieved with smoking cessation which has been widely accepted to effect mortality. This is the first pharmacologic therapy to prospectively demonstrate a survival benefit in patients with COPD.

The mortality reduction seen in the IMPACT study is also similar to, or greater than several approved medications in non-COPD studies, where the risk reduction varies between approximately 0.36% and 0.71% per year and where we accept that there is a clinically relevant benefit on survival.

The next threshold question to be considered is whether the mortality findings before us today are TRUE to a substantial degree of scientific certainty. This is a more challenging question as it involves consideration of several elements: internal validity, external validity, the precision of the data, and plausibility of the results.

The information that you have seen this morning is based on what is considered the highest level of medical evidence -- a randomized clinical trial. Moreover, the design of the trial was rigorous.

Treatments were randomly assigned.

The control group for the purpose of this analysis was active, a particularly high bar for comparison.

The participants were masked with respect to treatment assignment.

The outcome measure -- vital status -- was objective and not likely subject to reporting bias.

The outcome measure vital status and date of death was verified with clinical and administrative data and reviewed by a masked, independent, clinical endpoint committee.

There was nearly complete ascertainment of vital status in more than 99.6% of participants among the 10355 participants.

The analysis included both participants on-treatment and off-treatment, that is by intention to treat.

Thus, I can conclude that the evidence has a high degree of internal validity.

Can the information from IMPACT on mortality be applied to similar clinical populations?

The study population was global, comprising countries with different ethnicities, cultures, economies, environmental exposures, and healthcare systems.

The inclusion criteria were objectively defined and allowed a moderately wide range of high-exacerbation-risk COPD severity and pre-enrollment treatment.

The enrolled population was similar to other COPD cohorts and clinical trial populations in terms of smoking exposure, demographics, co-morbidities, and ventilatory impairment.

The study population was selected to have a high exacerbation risk based on the International COPD guidelines in effect at the initiation of the trial.

The only distinction that I am aware of is that the overall population had a somewhat lower mortality risk than other COPD populations, which makes the mortality benefit of Trelegy more striking.

Thus, I can conclude that the evidence is very likely applicable to a broad range of high-risk COPD patients.

How confident can we be that this data is not the result of chance alone?

The information is nominally statistically significant with $P < 0.05$. That is, the 95% confidence interval for the hazard of death does not include equality between Trelegy and dual bronchodilator treatment assignments.

The estimate of benefit is robust. That is --- the data stand up well to a worst-case scenario analysis where the missing data in Trelegy are assumed dead and all the missing data in dual bronchodilator are assumed living.

There is reasonably high presumption or pre-test probability that this finding is correct based on outcomes in other trials comparing ICS-containing treatments to as-needed short-acting bronchodilators or maintenance bronchodilators -- including SUMMIT. This prior data serves to strengthen the conclusion that this finding is NOT due to chance alone.

Thus, I can conclude that these findings are very unlikely to be the result of chance alone

Is it plausible that Trelegy treatment results in a lower risk of death than a dual bronchodilator?

We have a clear mechanistic causal pathway for this result.

We know that COPD exacerbations, particularly severe hospitalized exacerbations often precede death during or within the year after the event. Accordingly, it is logical that a reduction in exacerbations, especially severe exacerbations, would reduce death rates. In the IMPACT trial, Trelegy reduced the on-treatment risk of severe exacerbations by 34%, supporting the plausibility that the risk of death would also be reduced by a comparable 28% compared with UMEC/VI.

Thus, I can conclude that the findings are plausible.

In summary, I find that there is substantial evidence that experts would conclude that Trelegy does reduce all-cause mortality in patients with COPD with a risk of exacerbations.

Therefore, data on the effect of Trelegy on all-cause mortality should be made available to prescribers along with the other supporting data from the IMPACT trial that are in the current prescribing information. This information is important and is probative to a high degree of scientific certainty.

Thank you for your attention. Dr. Elaine Jones will now present closing remarks.

Summary and Conclusions, C. Elaine Jones, PhD, GlaxoSmithKline

Thank you, Dr. Wise. Let me take a moment to summarize what you have heard.

Trelegy is already approved by the FDA for the maintenance treatment of patients with COPD including a reduction in exacerbations. We have presented evidence demonstrating that Trelegy provides the additional benefit of reducing all-cause mortality in those patients taking an Inhaled Corticosteroid prior to entry into the IMPACT study.

Data from IMPACT, in over 10,000 patients, demonstrated statistically significant and important clinically relevant reductions in the risk of all-cause mortality with a 28% reduction for on- and off-treatment all-cause mortality for Trelegy compared with UMEC/VI. We also saw a 39% reduction in risk of all-cause mortality for Trelegy compared with UMEC/VI for those patients who were taking an ICS

prior to the study. There was no effect on all-cause mortality seen in patients who were not taking an ICS prior to the study, potentially due to the small sample size and low number of events.

We acknowledge that all-cause mortality was an other endpoint with no adjustment for multiplicity with a p-value of 0.042. 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.

I would, however, like to highlight some of the facets of the IMPACT study that provide confidence in the evidence of effectiveness. IMPACT was a well-designed, well-conducted large, global, multi-center trial. All-cause mortality was a pre-defined endpoint with a pre-specified analysis plan. The data are reliable and of high quality with independent adjudication of deaths and there was minimal missing data. In addition, we have demonstrated clinical plausibility between all-cause mortality and reduction of severe COPD exacerbations. Indeed, in IMPACT, there was a 34% reduction in the rate of severe COPD exacerbations, supporting the plausibility that the risk of death would also be reduced. The data from a similar population to that in IMPACT from the SUMMIT study, an exacerbating population also provide directly relevant supportive data.

Acknowledging the validity of the data from the IMPACT study, why is it important to include the all-cause mortality data in the Trelegy label.

It should be of little controversy that a reduction in the risk of dying is clinically important to both patients and doctors and reducing the risk of death remains a primary goal of medical care and public health organizations.

As Dr. Wise stated in his recording, the absolute annual all-cause mortality risk reduction with Trelegy versus UMEC/VI was 0.83% in the IMPACT study. The magnitude of the benefit is greater than that achieved with smoking cessation which has been widely accepted to effect mortality in patients with COPD. This is the first pharmacologic therapy to prospectively demonstrate a survival benefit in patients with COPD.

The mortality reduction seen in the IMPACT study is also similar to, or greater than several approved medications in non-COPD studies, where the risk reduction varies between approximately 0.36% and 0.71% per year and where we accept that there is a clinically relevant benefit on survival.

Consequently, we believe that these results and the context are of the utmost importance for physicians to know and to be included in the clinical studies section of the Trelegy label given the medical importance of a mortality endpoint.

As a reminder, shown here are the data that we are proposing to include in the Trelegy label. The data is proposed to be included in text format as shown on the right which is similar to the other "other" endpoint data already included in the Trelegy label.

There was a 28% reduction in the risk of all-cause mortality for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset.

There was a 39% reduction in the risk of all-cause mortality for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset for those patients who were on an inhaled corticosteroid prior to the study.

There was no reduction in all-cause mortality observed for Trelegy compared with umeclidinium/vilanterol in the on and off treatment dataset in patients who were not on an inhaled corticosteroid prior to the study, potentially due to the small sample size and low number of events.

I would like to thank the advisory committee and the agency for the opportunity to present this important data. Thank you.