FDA Briefing Document
Pulmonary-Allergy Drugs Advisory Committee Meeting

August 31, 2020

sNDA 209482: fluticasone furoate/umeclidinium/vilanterol fixed dose combination to reduce all-cause mortality in patients with chronic obstructive pulmonary disease

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the supplemental New Drug Application (sNDA) 209482, for fluticasone furoate/umeclidinium/vilanterol, as an inhaled fixed dose combination, for the reduction in all-cause mortality in patients with COPD, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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DIVISION MEMORANDUM

Date: August 4, 2020

From: Banu A. Karimi-Shah, MD, Deputy Director
Sally Seymour, MD, Director
Division of Pulmonology, Allergy, and Critical Care (DPACC), Office of Immunology and Inflammation (OII), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC)

Subject: Overview of the FDA background materials for the supplemental New Drug Application (sNDA) 209482/S-008, TRELEGY ELLIPTA (fluticasone furoate [FF], umeclidinium [UMEC], vilanterol [VI] inhalation powder), at a dose of 100/62.5/25 mcg (once-daily), to evaluate the proposed claim of decreased all-cause mortality (ACM) in patients with chronic obstructive pulmonary disease (COPD)

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on August 31, 2020. As members of the PADAC you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States, as well as the evaluation of important claims to be added to approved product labeling. The upcoming meeting is to discuss a supplemental New Drug Application (sNDA) from GlaxoSmithKline Pharmaceuticals (GSK, or the Applicant), in which the Applicant has submitted data to evaluate the proposed claim that treatment with TRELEGY ELLIPTA reduces all-cause mortality (ACM) in patients with COPD. This is an important topic for discussion and an area of unmet medical need, as there are no approved therapies which have been shown to reduce ACM in patients with COPD.

Introduction

TRELEGY ELLIPTA (Trelegy) is a fixed-dose triple combination inhalation powder containing fluticasone furoate (FF), umeclidinium (UMEC), and vilanterol (VI). Trelegy includes three therapeutic modalities to treat COPD: an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta-agonist (LABA), respectively. Trelegy is approved for the maintenance treatment of patients with COPD. The Clinical Studies section (Section 14) of the US package insert (USPI) describes the efficacy of Trelegy with respect to lung function, acute exacerbations of COPD (AECOPD), and health-related quality of life (i.e., St. George's Respiratory Questionnaire, SGRQ).

This memorandum summarizes data submitted by GSK to evaluate the proposed claim that treatment with Trelegy reduces all-cause mortality (ACM) in patients with COPD. To support this claim, the Applicant has submitted analyses of the results of a randomized, double-blind, partial factorial, active control trial (**I**nfor**M**ing the **PA**thway of **C**OPD **T**reatment: IMPACT) of Trelegy (FF/UMEC/VI). Subjects were randomized to FF/UMEC/VI, FF/VI, or UMEC/VI, respectively. Specifically, the Applicant cites the results for FF/UMEC/VI versus UMEC/VI

(ICS/LAMA/LABA vs. LAMA/LABA) to support their assertion that Trelegy reduces ACM. Based on this comparison, the benefit in ACM proposed by the Applicant is attributed to the addition of FF (the ICS). Based on the Agency's analyses, there are several statistical and clinical uncertainties in the interpretation of the ACM data, and whether these data provide substantial evidence to support the proposed claim that Trelegy reduces ACM in patients with COPD.

We have convened this meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) to draw on the expertise of the panel members, so that we may better address these uncertainties in our regulatory decision-making process. Major discussion points for the advisory committee members include: 1) the statistical persuasiveness of the ACM results in IMPACT, as a single trial, 2) the timeframe of efficacy observed in the IMPACT trial, 3) the evidence across the IMPACT, SUMMIT, and TORCH trials to support the efficacy of fluticasone on ACM, 4) the potential effect of ICS removal on IMPACT results, and 5) the generalizability of these results to the care of patients with COPD in clinical practice. We ask that the committee members consider each of these issues to determine whether the results of IMPACT support the addition of the proposed labeling claim to Section 14 (Clinical Studies) of the USPI.

This Division Memorandum will provide a high-level overview of the regulatory history, IMPACT trial design, ACM results, and the statistical and clinical issues with the data that warrant the committee's consideration with regard to each of these discussion points. A more detailed discussion is provided in the Agency's Clinical and Statistical Briefing Document.

Regulatory History

Trelegy was initially approved in 2017 for the long-term, once-daily maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired, or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.

The IMPACT trial was a large, 1-year, partial factorial trial, specifically designed to demonstrate the contribution of FF and UMEC to the triple combination in reducing acute exacerbations of COPD (AECOPD). Based on the results of the IMPACT trial, the indication for Trelegy was amended to: the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD and also to reduce exacerbations of COPD in patients with a history of exacerbations. To comply with updated labeling practices, and harmonize indications across COPD products, the Division initiated labeling changes to generalize the indication statement for Trelegy in 2019, to its current language: for the maintenance treatment of COPD.

Many of the statistical and clinical issues to be discussed before the committee were raised with the Applicant through regulatory interactions. The original statistical review of the IMPACT trial recommended control of the probability of Type I error for secondary endpoints, referencing mortality, at the 0.01 level. Prior to submission of the ACM supplement under discussion (i.e., the pre-sNDA meeting), the Agency raised this issue again, noting the lack of multiplicity control, since ACM analyses were not part of the statistical hierarchy, and ACM was designated as an

"other" endpoint. The Agency noted that this lack of control for multiple endpoints would need to be considered carefully in the setting of a single trial without replicate evidence from another COPD trial to confirm the finding. The Applicant noted plans to include supportive data for ICS efficacy on ACM from two previous trials (SUMMIT and TORCH), as it was the Applicant's assertion that the ACM benefit for Trelegy relied primarily on the efficacy contribution of the ICS as well.

From a clinical perspective, preliminary review of the IMPACT results had revealed that there may be an unexpected early separation in the survival curves when comparing FF/UMEC/VI to UMEC/VI. It was this early separation and the design of IMPACT (discussed below) which raised concern for the potential effect of ICS removal on the interpretation of the ACM results. Therefore, the Agency requested subgroup analyses based on pre-study ICS use in IMPACT, and also asked that the Applicant provide a discussion in the sNDA submission for the potential impact of abrupt stepdown of therapy (i.e., ICS removal) among those with pre-study triple therapy or pre-study ICS therapy who were randomized to a non-ICS-containing dual therapy.

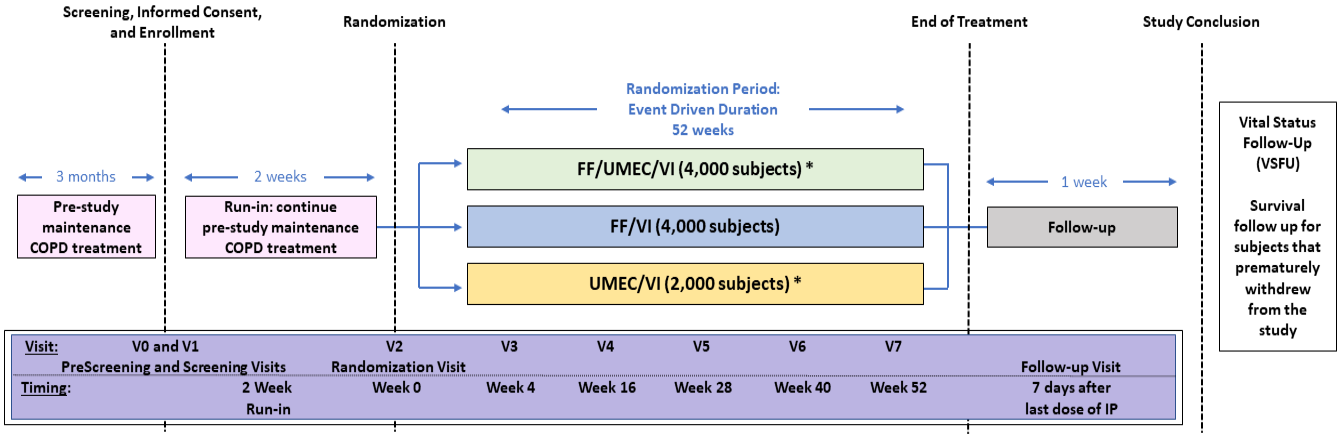
Approach to the Analysis of All-Cause Mortality

The IMPACT trial has been reviewed in detail by the Agency for the approval to expand the indication for Trelegy as described above. Therefore, this memorandum will focus on the design, endpoints, and results which relate to the ACM discussion. Review of the ACM results from IMPACT revealed several statistical and clinical issues with respect to interpretation of the data. Due to these uncertainties in the context of a single trial, the Agency examined additional ACM data from the SUMMIT and TORCH trials, two trials which were designed with the primary objective of evaluating ACM in COPD. SUMMIT and TORCH both evaluated ICS-containing dual therapies. Notably, these trials were of longer duration, with more mortality events. A summary of their trial designs and results is presented to place the results of IMPACT in context.

IMPACT Trial Design

IMPACT was a randomized, double-blind, parallel group, active control, partial factorial trial that evaluated the efficacy and safety of a fixed-dose combination (FDC) of FF/UMEC/VI compared to FF/VI or UMEC/VI on AECOPD among 10,355 symptomatically uncontrolled, moderate-to-very severe COPD patients with a history of exacerbations despite their current COPD maintenance medications. After a 2-week run-in period, in which patients continued their pre-study COPD medications, patients were randomized 2:2:1 to either FF/UMEC/VI, FF/VI, or UMEC/VI, respectively, for 52 weeks. Patients who experienced pneumonia or an exacerbation during the run-in were not randomized. A schematic of the trial design is shown in Figure A.

Figure A. IMPACT: Trial Schematic



Source: Agency. Modified from Applicant's submitted materials for study CTT116855 (IMPACT). *The comparison of these treatment arms provides data on the efficacy of fluticasone furoate on trial endpoints; Abbreviations: FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; FF/VI: fluticasone furoate/vilanterol; UMEC/VI: umeclidinium/vilanterol; VSFU: vital status follow-up; V: visit; IP: investigational product; COPD: chronic obstructive pulmonary disease

Any pre-study inhaled COPD daily maintenance medication was considered acceptable for enrollment in IMPACT and continued until the date of randomization. In this study design, a subset of patients could have been randomized to a treatment arm in which they received fewer medications during the trial than before entry, despite uncontrolled symptoms and high COPD severity. For example, randomization of subjects on pre-study maintenance triple therapy (i.e., pre-study ICS, LAMA, and LABA) randomized to UMEC/VI (LAMA/LABA) would result in the abrupt removal of ICS therapy without the addition of any therapeutic modality. Analogously, randomization of subjects on any pre-study COPD maintenance regimen that included ICS would lead to abrupt removal of the ICS when randomized to the UMEC/VI arm. Within this pre-study ICS subset, the isolated effect of this ICS removal intervention can be explored in the UMEC/VI versus FF/UMEC/VI comparison. In IMPACT, the Applicant analyzed this subset of subjects with pre-study ICS who underwent abrupt ICS removal together with ICS-naïve subjects who could not undergo ICS removal (only ICS addition). IMPACT did not account for the possibility that abrupt ICS removal could influence mortality in the design or analysis model. These design and analysis elements of IMPACT will be important for the committee to consider as we examine the ACM results further in the context of other trials and by pre-study medication subgroups (i.e. those who were treated with pre-study ICS and those who were pre-study ICS-naive).

IMPACT All-Cause Mortality Analysis

The primary endpoint in IMPACT was the annual rate of on-treatment moderate-to-severe AECOPD, with co-primary comparisons of FF/UMEC/VI with the two dual products, FF/VI and UMEC/VI. Multiplicity across the two co-primary and the key secondary treatment comparisons was controlled with an appropriate hierarchical testing strategy. All tests within the predefined statistical testing hierarchy for primary and secondary endpoints achieved statistical significance, with $p<0.001$.

Beyond the pre-specified primary and secondary outcomes, there was a long list of pre-specified 'other' endpoints, which included ACM. ACM was evaluated with two pairwise comparisons: FF/UMEC/VI versus UMEC/VI and FF/UMEC/VI versus FF/VI. The analysis was based on a

Cox proportional hazards (PH) model, with covariates of gender and age. The Kaplan-Meier probabilities of having an event for each treatment arm over time were also presented. No adjustments for multiplicity were made for these other comparisons.

The Agency used what is designated in the briefing document as the ITT+VS+VSFU dataset to perform the ACM analysis. This dataset includes both on- and off-treatment follow-up data, as well as any additional vital status follow-up data on patients who withdrew from the study (gathered after the study, as part of this supplemental application). This dataset provides complete follow-up in 99.6% of the randomized population, and while it includes data gathered after the trial was unblinded, it provides the most complete mortality data on all patients who were randomized, and therefore the most reliable results.

IMPACT All-Cause Mortality Results

The IMPACT trial enrolled a population of COPD subjects who were primarily Caucasian males, with an average age of 65 years, similar to other COPD registration trials. Smoking history and the proportion of current versus former smokers were similar across treatment arms.

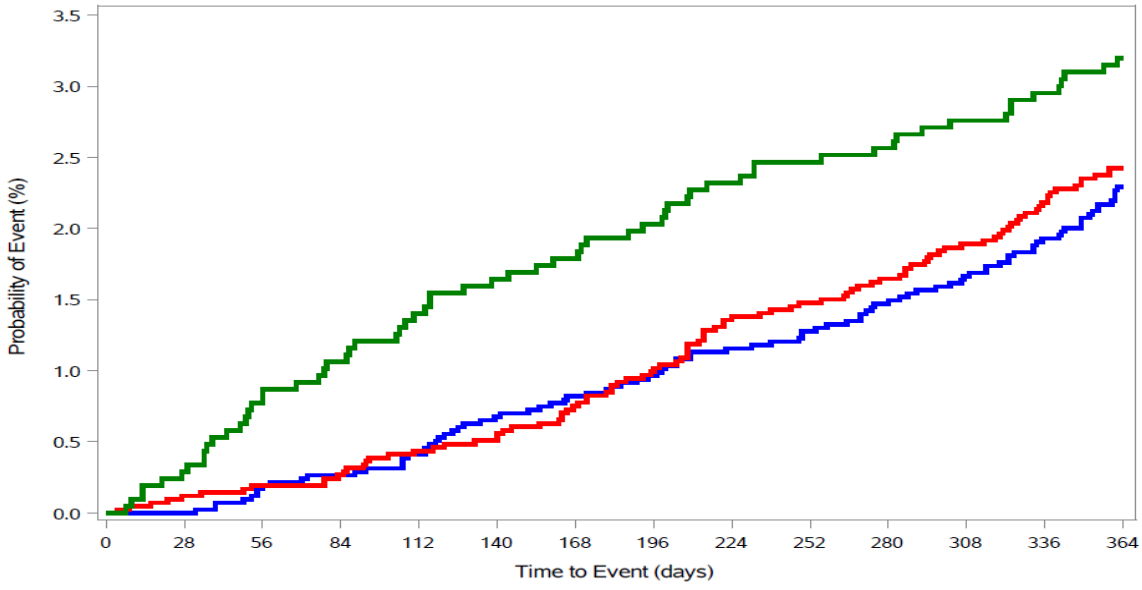
The results of the exploratory ACM analysis of IMPACT using the most complete vital status follow-up are presented in Table A and Figure B below.

Table A. IMPACT: All-cause Mortality Results at 52 Weeks (ITT+VS+VSFU)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Number of subjects with event (%)	98 (2.4)	109 (2.6)	66 (3.2)
All-cause Mortality Analysis of FF/UMEC/VI versus Comparator (column)			
Hazard Ratio for ACM[1]		0.89	**0.72**
95% CI		0.68, 1.17	**0.53, 0.99**
p-value (Cox PH model – main)		0.387	**0.042**
p-value (Log-rank test -supplemental)		0.405	0.048

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_primary.sas. [1]These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. Cox model includes age and gender as covariates. Comparisons in **bold text** provide data to inform the contribution of FF on ACM endpoints as part of the FF/UMEC/VI FDC. (*Table 12 in Clin/Stats Briefing Document*); Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; CI: confidence interval; FF/UMEC/VI: fluticasone furoate 100 µg /umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

Figure B. IMPACT: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Day:	0	28	56	84	112	140	168	196	224	252	280	308	336	364
FF/UMEC/VI:	4151	4150	4142	4137	4131	4119	4113	4107	4097	4092	4082	4073	4062	3919
FF/VI:	4134	4129	4123	4118	4111	4106	4095	4082	4065	4060	4050	4040	4027	3848
UMEC/VI:	2070	2063	2052	2045	2037	2030	2027	2021	2013	2008	2004	1999	1995	1914

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_kmplot.sas. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. *(Figure 5 in the Clin/Stats Briefing Document);* Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

As shown in Table A, 273 subjects died during the 52-week duration of the IMPACT trial, with 2.4% mortality among subjects administered FF/UMEC/VI, compared to 3.2% among subjects administered UMEC/VI. The exploratory Cox proportional hazards analysis of the ACM data yielded a hazard ratio (HR) for ACM of 0.72 (95% CI 0.53 to 0.99) comparing FF/UMEC/VI with UMEC/VI, with a nominal p-value of 0.042. This comparison attributes the effect of Trelegy on ACM to the addition of FF, the ICS component.

Given that the evaluation of the effect of ICS on ACM was one of a long list of exploratory analyses of 'other endpoints' for which there was no Type I error control, the analyses could be subject to bias and/or due to chance. Therefore, we ask the committee to consider the persuasiveness of the IMPACT ACM findings in the setting of examining multiple exploratory endpoints.

Figure B provides visualization of the IMPACT ACM data by demonstrating the probability of ACM over 52 weeks by treatment arm. It is notable that there is an early separation between the FF/UMEC/VI and UMEC/VI curves which occurs by ~90 days, after which the curves appear to follow a more parallel course. While the interpretation of these curves at different timepoints was not a prespecified analysis and should be approached with caution, this appearance of the curves suggests the difference in ACM was limited to the first 90 days of the trial, and that the event rates across treatment arms were similar after this initial period of divergence. In order to examine

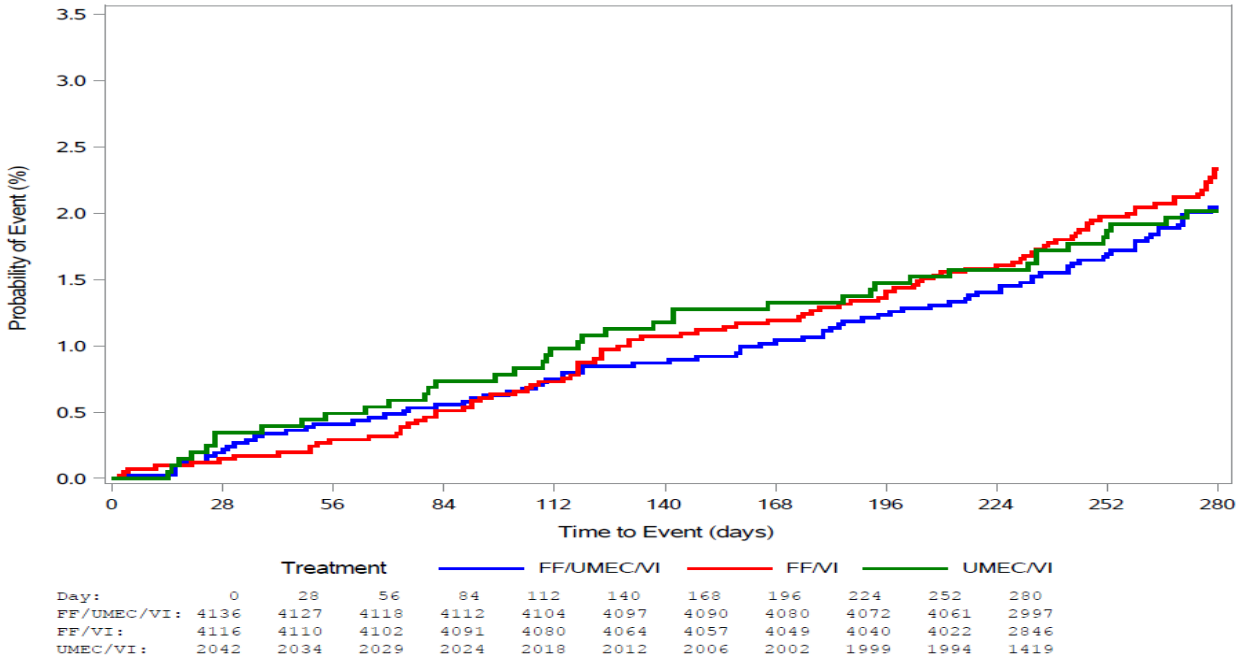
further this visual trend of early mortality in the UMEC/VI arm, the Agency requested analyses of ACM at earlier timepoints in the IMPACT trial. See Table B and Figure C below.

Table B. IMPACT: All-cause Mortality Results at Various Timepoints (ITT+VS+VSFU)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Day 30: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator (column)			
Number of subjects with event at Day 30, n (%)	0	5 (0.1)	7 (0.3)
Hazard Ratio for ACM 95% CI		N/A N/A	**N/A** **N/A**
Day 60: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator (column)			
Number of subjects with event at Day 60, n(%)	9 (0.2)	8 (0.2)	18 (0.9)
Hazard Ratio for ACM 95% CI		1.12 0.43, 2.90	**0.25** **0.11, 0.55**
Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator			
Number of subjects with event at Day 90, n (%)	12 (0.3)	13 (0.3)	25 (1.2)
Hazard Ratio for ACM 95% CI		0.92 0.42, 2.01	**0.24** **0.12, 0.47**
After Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator Excluding first 90 Days			
Number of subjects with available data after Day 90	4135	4116	2042
Number of subjects with event after Day 90, n (%)	86 (2.1)	96 (2.3)	41 (2.0)
Hazard Ratio for ACM 95% CI		0.88 0.66, 1.18	**1.02** **0.7, 1.48**

Source: Statistical reviewer. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints as part of the FF/UMEC/VI FDC. (*Table 13 Clin/Stats Briefing Document);* Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg, N/A: not applicable

Figure C. IMPACT: Probability of All-cause Mortality After Day 90 by Treatment Arm (ITT+VS+VSFU)



Day:	0	28	56	84	112	140	168	196	224	252	280
FF/UMEC/VI:	4136	4127	4118	4112	4104	4097	4090	4080	4072	4061	2997
FF/VI:	4116	4110	4102	4091	4080	4064	4057	4049	4040	4022	2846
UMEC/VI:	2042	2034	2029	2024	2018	2012	2006	2002	1999	1994	1419

Source: Statistical reviewer. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.(*Figure 6 Clin/Stats Briefing Document)* Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

These ACM data at different timepoints suggest a high early event rate in the UMEC/VI arm, reinforcing the visual trend suggested by the Kaplan-Meier curve (Figure B). By the Day 90 timepoint, 1.2% of subjects in the UMEC/VI arm had died, compared to 0.3% of the FF/UMEC/VI arm, yielding an observed hazard ratio for ACM in the FF/UMEC/VI versus UMEC/VI comparison of 0.24 (95% CI of 0.12 to 0.47). To explore this trend further, the Agency examined the data excluding this initial 90-day period of risk. The comparison of events after Day 90 translate to a hazard ratio of 1.02 (95% CI 0.7 to 1.48) for the comparison of FF/UMEC/VI to UMEC/VI, and the curves no longer show separation (Figure C). While we recognize the limitations of this analysis (which is based on the post-randomization variable of surviving to Day 90), this data suggests that FF (the ICS component of FF/UMEC/VI) did not show efficacy on ACM after this initial 90-day period, and leads to a plausible interpretation that the overall observed ACM difference (Table A, Figure B) may have been due to the early separation during the initial 90 days.

From a clinical perspective, this early timeframe of effect of an ICS on ACM is unexpected and not consistent with previous COPD trials (e.g. SUMMIT and TORCH). While the exact mechanism by which ICS would improve ACM is unknown, data suggest that severe AECOPD are a risk factor for mortality.[1,2] If the efficacy of ICS on ACM in COPD relied on a mechanism such

[1] Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31

[2] Siafakas NM, Vermeire P, Pride NB, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. Eur Respir J 1995;8:1398-420.

as prevention of severe AECOPD events, the timeframe of efficacy might be expected to follow a pattern of gradual accumulation, since severe exacerbations are rare events. This gradual timeframe of efficacy was not observed in the FF/UMEC/VI versus UMEC/VI comparison in IMPACT. While these analyses are exploratory, they raise questions as to the reasons behind the early timeframe of treatment separation, why the treatment effect is not persistent over the entire trial duration, and whether these early events in the UMEC/VI arm could be attributed to ICS removal effects in subjects treated with pre-study ICS, rather than attributing them to improved mortality in the Trelegy arm due to the FF component. Given our statistical concerns with the persuasiveness of the results, and the clinical inconsistencies with the proposed benefit of ICS on ACM in this single trial, the Agency examined additional ACM data from the SUMMIT and TORCH trials. These trials were designed with a primary objective of assessing ACM in patients with COPD, and their treatment arms allowed for an assessment of the contribution of fluticasone to ACM in COPD. The Agency examined the mortality results of these previous trials to provide additional context within which to consider the observed results of the IMPACT trial.

IMPACT, SUMMIT, TORCH: Evidence Across Trials for the Efficacy of Fluticasone on All-Cause Mortality

SUMMIT was a multinational, randomized, double-blind, parallel group, placebo-controlled, full factorial design trial with an event-driven duration that evaluated the efficacy and safety of a FDC of FF/VI compared to its components and placebo on all-cause mortality endpoints among 16,485 subjects with moderate COPD and cardiovascular risk factors. The treatment arms in SUMMIT included FF/VI, FF, VI, and placebo. The primary endpoint was time to death from any cause (at the Common End Date, after 1000 death events) comparing FF/VI vs. placebo.

TORCH was a 3-year, multicenter, randomized, double-blind, placebo-controlled, full factorial design trial designed to provide primary evidence of the efficacy of the FDC of fluticasone propionate 500 µg /salmeterol 50 µg (FP/SAL), with respect to survival in subjects with moderate-to-very severe COPD. The treatment arms in TORCH included FP/SAL, FP, SAL, and placebo. The primary endpoint in TORCH was all-cause mortality in the 3 years post-randomization in all subjects randomized to treatment, comparing FP/SAL to placebo.

Important differences between trials must be kept in mind when comparing across the trials. The baseline characteristics of subjects in the IMPACT trial indicate a clinically uncontrolled COPD population in terms of lung function, symptoms, and exacerbation history. Compared to the IMPACT trial, the baseline characteristics of subjects in the SUMMIT trial describe a less severe population with better lung function and symptom control, and – most importantly – a lower proportion of patients with frequent exacerbations. TORCH also included a lower proportion of frequent exacerbators compared to the IMPACT trial. Consistent with disease severity in each trial, the IMPACT trial included a higher proportion of subjects with pre-study ICS as part of their COPD maintenance medications prior to enrollment, as compared with SUMMIT and TORCH.

The ACM results for all three trials are presented below for comparison (see Table C).

Table C. All-cause Mortality Across Trials: Pairwise Treatment Comparisons That Isolate the Effect of ICS on ACM in IMPACT, SUMMIT and TORCH

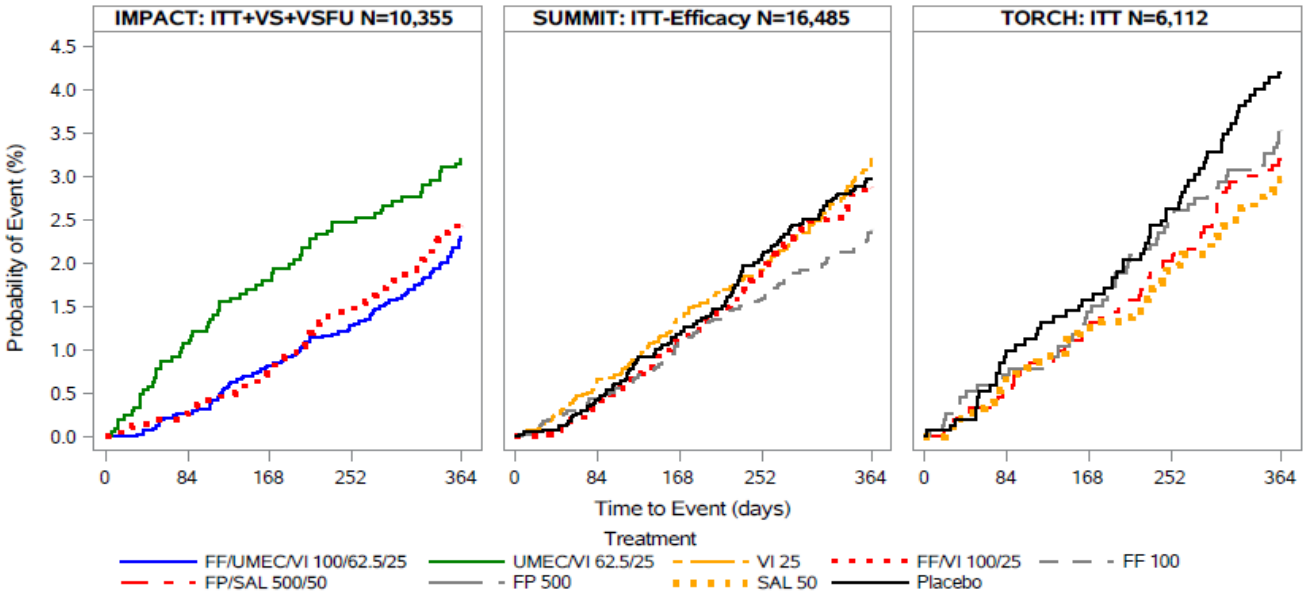
Study	IMPACT N = 10,355	SUMMIT N = 16,485		TORCH N = 6,112	
Data for Relevant All-cause Mortality Comparisons					
ICS Comparison(s)	FF/UMEC/VI vs. UMEC/VI	FF/VI vs. VI	FF vs. Pbo	FP/SAL vs. SAL	FP vs. Pbo
Number of Patients in Comparison	6221	8239	8246	3054	3057
Number of Mortality Events in Comparison	164	511	526	398	477
All-cause Mortality Analyses					
Hazard Ratio	0.72	0.91	0.91	0.95	1.06
95% CI	0.53 to 0.99	0.77 to 1.09	0.77 to 1.08	0.78 to 1.15	0.88 to 1.25

Source: Reviewer, adapted from Applicant's submitted materials. Note: Values are based on the ITT-E population for SUMMIT, the ITT population for TORCH, and the ITT+VS+VSFU population for IMPACT, isolating only those subjects in the corresponding treatment arms that isolate the contribution of the ICS component. Data presented are from each study's analysis at study end: IMPACT's analysis at 52 weeks, SUMMIT's analysis at the CED, with a median duration of 1.8 years, and TORCH's analysis at 156 week *(Table 16 Clin/Stats Briefing Document)*
Abbreviations: FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg; VI: vilanterol 25 µg; FF: fluticasone furoate 100 µg; FP/SAL: fluticasone propionate 500 µg salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo CI: confidence interval; CED = common end date

Notably, both TORCH and SUMMIT were designed specifically to evaluate mortality. SUMMIT and TORCH both examined ACM over a longer duration than IMPACT, both included a higher number of mortality events (193-275 events per treatment arm, as compared to 66-109 events per treatment arm in IMPACT, or roughly three times the statistical information) to inform the determinations of efficacy, and both failed to achieve a statistically significant result in their primary analysis of ACM, as well as in analyses that isolated the effect of the ICS component.

Given the early ACM events observed in IMPACT, in addition to evaluating the primary efficacy analysis from TORCH and SUMMIT, the Agency also requested efficacy analyses conducted at the 52-week timepoint for TORCH and SUMMIT for comparison of early ACM trends. Kaplan-Meier ACM curves over 52 weeks for IMPACT, SUMMIT, and TORCH are displayed in Figure D; this 52-week timeframe represents the entire duration of the IMPACT trial and the first year of the SUMMIT and TORCH trials.

Figure D. All-cause Mortality Across Trials: Probability of All-cause Mortality over 52 Weeks by Treatment Arm in IMPACT, SUMMIT, and TORCH (including on- and off-treatment data)



Source: Reviewer program M:\NDA 209482\Analysis\ALL\reviewer programs\kmfig.sas
All data and treatment arms from each study are used in the analysis; plots are truncated at Day 364. *(Figure 11 Clin/Stats Briefing Document)* Abbreviations: ITT-E: intention to treat, efficacy; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg; VI: vilanterol 25 µg; FF: fluticasone furoate 100 µg; FP/SAL: fluticasone propionate 500 µg/salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo CI: confidence interval; CED = common end date

We note the limitations of these exploratory cross-study comparisons; however, descriptively we can see that the early separation of the curves in the IMPACT trial is notably different that the observed curves in the SUMMIT and TORCH trials, where no such early separation occurs.

In summary, multiple trials and analyses have failed to show a mortality benefit for ICS in COPD. ACM analyses from TORCH and SUMMIT – designed to evaluate mortality and each including data on roughly three times the mortality events of IMPACT – failed to show a statistically significant effect. We acknowledge that these trials involved different COPD patient populations and used different comparisons to evaluate the ICS effect (i.e., ICS versus placebo and ICS/LABA versus LABA rather than ICS/LABA/LAMA versus LABA/LAMA), and that the fluticasone study drug evaluated in TORCH was fluticasone propionate. Nevertheless, TORCH and SUMMIT provide the most reliable independent data to inform the proposed ACM efficacy claim based on IMPACT. The additional ACM results from TORCH and SUMMIT are considered critical in light of the uncertainties about the persuasiveness of the results from IMPACT, a single trial. Whether the totality of evidence from IMPACT, SUMMIT, and TORCH supports the claim that addition of fluticasone furoate, as a component of Trelegy, improves mortality in COPD is an important issue for the committee's consideration.

The Effect of ICS Removal in IMPACT

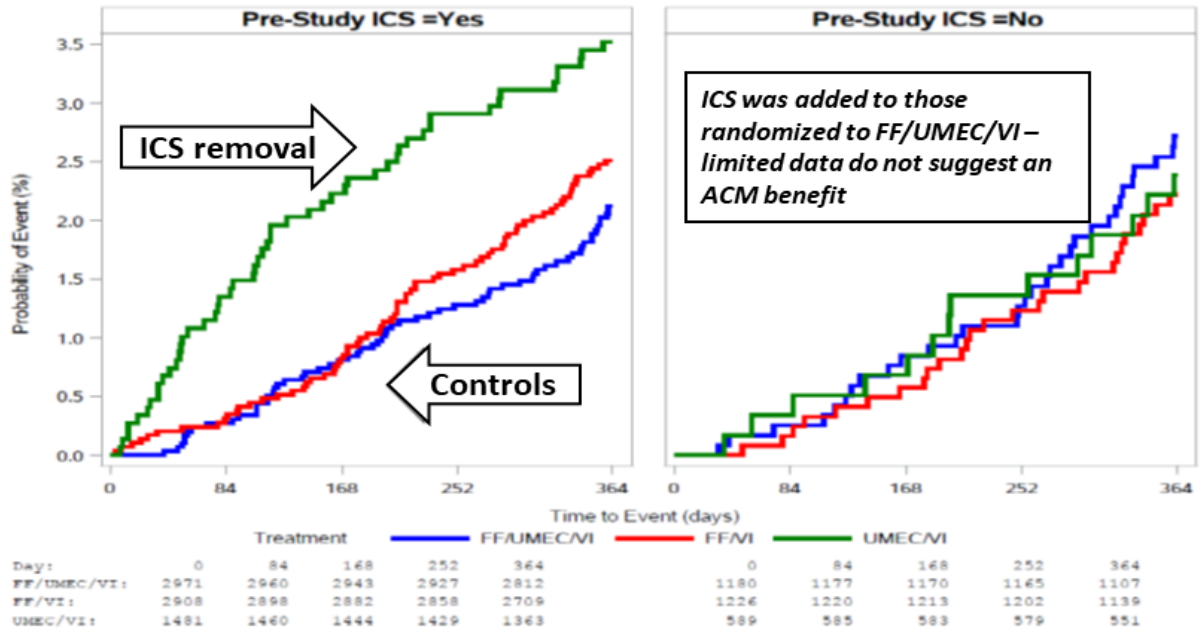
Due to the unexpected early separation in the UMEC/VI treatment arm in IMPACT (Figure B, Figure D), and a protocol design which could result in abrupt removal of ICS in patients who were treated with ICS pre-study and then randomized to the UMEC/VI arm, the Agency questioned

whether the observed effect of ICS on ACM could be due to ICS removal. In order to explore this question, we examined the data using pre-study ICS and ICS-naïve subgroups. Subjects with ICS as a component of their pre-study COPD regimen comprised 71% of the randomized population of IMPACT, with the majority using either ICS/LABA or ICS/LABA/LAMA. The subjects with pre-study ICS continued ICS if randomized to FF/UMEC/VI or FF/VI, or had ICS removed if randomized to UMEC/VI. The effect of ICS removal can be explored by the UMEC/VI versus FF/UMEC/VI comparison in this pre-study ICS subgroup.

Kaplan-Meier curves for the ACM analysis stratified by pre-study ICS therapy are shown below (see Figure E). The results in the left panel suggest that subjects who underwent ICS-removal as an intervention (i.e., those randomized to UMEC/VI) had higher early and total probability of death compared to the subjects that continued ICS (i.e., those randomized to FF/UMEC/VI). In contrast, a mortality difference is not observed in the right panel, which represents those patients who were ICS-naïve pre-study. While the ICS-naïve subgroup comprised only ~30% of the trial population, and was underpowered to detect a difference in ACM, the lack of a trend towards a mortality difference in the FF/UMEC/VI versus UMEC/VI comparison in this pre-study ICS-naïve subgroup (i.e., a difference that would be attributable to the addition of fluticasone furoate) creates additional uncertainty regarding the proposed labeling claim. The effect of pre-study ICS and ICS removal is an important issue for the committee's consideration.

As part of our data exploration surrounding ICS removal as an intervention in IMPACT, the additional terms of pre-study ICS status and pre-study ICS status by treatment interaction were added to the main analysis model of treatment, adjusting for age and gender. This post-hoc analysis resulted in a p-value of 0.08 for the interaction of pre-study ICS with the pairwise comparison of FF/UMEC/VI versus UMEC/VI, suggesting the treatment effect may differ according to pre-study ICS status. These results, while exploratory in nature, suggest that interpretation of the ACM results from IMPACT using the overall population may be difficult, and that it may instead be more appropriate to consider the subgroup analyses by pre-study ICS status.

Figure E. IMPACT: Pre-study ICS Subgroups: Probability of All-cause Mortality Over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_kmplot_ics.sas. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. (*Figure 17, Clin/Stats Briefing Document*). Abbreviations: ITT: intention-to-treat; VS: end of study vital status; VSFU: vital status follow-up; Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-Study ICS = No: subjects without pre-study ICS-containing therapy; FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg /vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

The Agency also examined the data from the SUMMIT and TORCH trials by pre-study ICS use and found the magnitude of the ICS removal effect to be less, though still supportive of the IMPACT findings noted above. In comparison to IMPACT, these two studies recruited less severe COPD patients and a lower proportion of patients with pre-study ICS, and their study designs allowed for longer run-in periods on short-acting medications alone. Although the magnitude of the observed ICS removal effect on ACM at study end was lower in SUMMIT and TORCH than in IMPACT, this lower magnitude could potentially be attributed to SUMMIT and TORCH's longer duration, attrition during the run-in of both trials, and to less severe patient populations undergoing ICS removal. Similar to IMPACT, the ICS-naïve subgroup results from SUMMIT and TORCH do not provide evidence that would support a claim of mortality benefit attributable to the addition of ICS. These results are provided in the Appendix of the Clinical and Statistical Briefing Document.

When examined from the standpoint of ICS removal, the results from IMPACT may suggest a safety risk to patients with uncontrolled COPD despite pre-study ICS therapy who underwent ICS-removal (i.e., randomized to UMEC/VI) compared to those remaining on ICS-containing therapy (i.e., those randomized to FF/UMEC/VI). To examine the effect of ICS-removal, the Agency examined the hazard ratio of UMEC/VI vs. FF/UMEC/VI, considering the triple therapy as the active control, and the UMEC/VI arm as the intervention of ICS-removal. Under this "flipped" interpretation that describes the potential effects of ICS-removal, subjects with pre-study ICS randomized to UMEC/VI demonstrated a hazard ratio for death of 1.64 (95% CI 1.15 to 2.38) compared to those randomized to FF/UMEC/VI (i.e. ICS continuation) at Week 52. Notably, under this same "flipped" interpretation, subjects with pre-study ICS randomized to UMEC/VI

(i.e., ICS removal) demonstrated a hazard ratio for death of 5.0 (95% CI 2.27 to 11.11) compared to those randomized to FF/UMEC/VI (i.e., ICS continuation) at Day 90. These are exploratory analyses where the 90-day time period of evaluation was in part data-driven and therefore may be subject to bias, and there is considerable uncertainty around the estimates due to the small numbers of events. Nevertheless, the results are striking, with a point estimate that would suggest a potentially clinically significant, five-fold increased risk of mortality attributable to ICS removal in this COPD patient population from baseline to Day 90.

ICS Removal in COPD and the Clinical Relevance of the IMPACT ACM results

The Clinical and Statistical Briefing Document provides a summary of the data surrounding ICS removal in COPD in Section 4.5.8. Extensive literature suggests that removal of ICS leads to various degrees of clinical deterioration in COPD patients, correlating roughly with their baseline severity and exacerbation history. Multiple non-randomized studies and a few randomized trials suggest worsening FEV1 and AECOPD outcomes upon removal of ICS from patients in COPD cohorts who were not enriched for severity or exacerbations. These early suggestive results led to larger randomized-withdrawal trials with a goal of determining what clinical scenarios might allow for ICS removal among patients with few or no exacerbations in the prior year; these trials showed non-inferiority on moderate-to-severe AECOPD endpoints, but the largest trial and a meta-analysis suggested a trend towards an early increase of severe AECOPD events after removal of ICS. None of these later ICS-removal trials were powered to assess mortality differences, and none of them recruited subjects with severity of disease comparable to IMPACT.

Randomized withdrawal trials can be used to obtain information to support the efficacy of a drug. However, in IMPACT, the patients had uncontrolled, moderate-to-very severe COPD. It is important to note that abrupt removal of ICS in symptomatic patients is not generally consistent with standard clinical practice. The IMPACT trial was designed to understand the contribution of the ICS and the LAMA to the triple combination with respect to reducing exacerbations; ICS removal occurred within the context of this specific objective and trial design. In a clinical practice setting, the question of interest is whether advancing from double to triple therapy provides for a clinically meaningful effect. In this particular application, the question of interest is whether advancing from double therapy (UMEC/VI) to triple therapy (FF/UMEC/VI), or adding the ICS FF, improves ACM in COPD. We ask the committee to discuss whether IMPACT, as designed, could answer this question, and whether that answer would be generalizable to clinical practice.

Summary

The purpose of this PADAC meeting is to discuss the adequacy of the data submitted by GSK to support the claim that Trelegy Ellipta reduces all-cause mortality (ACM) in COPD. The key statistical and clinical issues for discussion are summarized below:

1. Statistical Persuasiveness of the ACM Results in IMPACT

The ACM analysis including all vital status follow-up data comparing FF/UMEC/VI versus UMEC/VI produced a hazard ratio of 0.72 (95% CI: 0.53, 0.99) and a nominal p-value of 0.042. However, IMPACT was not designed as a mortality study, and the evaluation of ACM was not

performed under strict Type I error control. We acknowledge that all analyses of primary and secondary endpoints were statistically significant, that mortality is a clinically important outcome, and that many (but not all) of the exploratory analyses of "other" endpoints had nominal p-values below the 0.05 threshold. Nevertheless, the ACM evaluation was one of a long list of exploratory analyses. It would not be unusual to find nominal p-values below 0.05 just by chance when evaluating multiple exploratory endpoints, and such analyses may also be subject to substantial random high bias.

The statistical persuasiveness of the ACM results attributable to the ICS component in IMPACT should be considered in the context of other uncertainties which have been discussed in this memorandum and are described below. These uncertainties include the early efficacy timeframe observed in IMPACT, the ACM results from the SUMMIT and TORCH trials, and the concerns with respect to the effects of ICS removal versus ICS addition from the exploratory pre-study ICS subgroup analyses of IMPACT.

2. Evidence across IMPACT, SUMMIT, TORCH for the Efficacy of Fluticasone on ACM

Due to the uncertainties in our analysis of IMPACT, the Agency examined two previous trials to provide additional context. SUMMIT and TORCH were longer trials, specifically designed to evaluate mortality, with a larger number of death events, and thus more power and precision to detect as statistical difference in ACM. Both trials did not show a mortality benefit attributable to ICS. Acknowledging the differences in the patient populations and comparisons to evaluate the ICS effect, these are the trials which provide the most reliable independent data to help inform the proposed claim based on IMPACT and are considered critical in light of the uncertainties about the persuasiveness of the results from this single trial. In light of the evidence from these two trials, we ask the committee to consider whether the evidence presented in IMPACT as a single trial supports the claim that addition of fluticasone furoate, as a component of Trelegy, improves mortality in COPD.

3. Efficacy Timeframe of the IMPACT Results

The observed early efficacy timeframe for the FF/UMEC/VI versus UMEC/VI comparison in IMPACT raises uncertainty in the interpretation of the ACM results. Time-to-event visualizations show separation between the UMEC/VI arm and the two ICS-containing arms (i.e., FF/UMEC/VI and FF/VI) within the first 90 days. With exclusion of the first 90 days of data, the treatment benefit is not observed. While these analyses are exploratory and thus subject to bias, they suggest that the observed difference at trial completion was driven by the early events. This is not consistent with previous studies regarding the efficacy of ICS in COPD. Clinically, the efficacy of ICS in COPD relies on prevention of moderate-to-severe AECOPD. Severe AECOPD have been associated with increased mortality. While trials of ICS on ACM in COPD have proposed that prevention of severe AECOPD events could lead to decreased ACM, previous findings do not suggest that such an effect would occur within a 90-day timeframe. Conversely, previous data on ICS-removal do suggest an almost immediate clinical deterioration in COPD that persists over time among vulnerable patients with uncontrolled and frequently exacerbating COPD.

We ask the committee to consider the clinical significance and relevance of this observed efficacy timeframe, and whether the observed early efficacy timeframe of these results could be consistent with a deleterious effect of ICS removal on ACM among patients with symptomatic and uncontrolled COPD.

4. The Effect of ICS Removal in IMPACT

Due to the unexpected early separation in the UMEC/VI treatment arm in IMPACT, and the protocol design which could result in abrupt removal of ICS in patients who were treated with pre-study ICS and then randomized to the UMEC/VI arm, the Agency examined the data by pre-study ICS and ICS-naïve subgroups. Those subjects who underwent ICS-removal as an intervention (i.e., those randomized to UMEC/VI) had higher early and total probability of death compared to the subjects that continued ICS (i.e., those randomized to FF/UMEC/VI). In contrast, a mortality difference was not observed in those patients who were ICS-naïve pre-study, and therefore had ICS added via randomization to the FF/UMEC/VI arm. A potential difference between these subgroups was also suggested by an analysis yielding a p-value of 0.08 for the interaction between treatment and pre-study ICS status. We ask the committee to discuss this evaluation of subgroups and whether the overall ACM results are reliable given the trial design and the notable differences in pre-study ICS subgroup behavior.

5. Clinical Generalizability of the IMPACT Results

The overall results of the comparison of FF/UMEC/VI vs. UMEC/VI in IMPACT yielded a HR of 0.72 (95% CI 0.53, 0.99), with an ACM benefit attributable to FF (the ICS component). If clinicians interpreted the proposed labeling claim on face value based on the ACM analysis of FF/UMEC/VI versus UMEC/VI (without consideration of pre-study ICS subgroups), then these data might imply that initiation of ICS therapy in ICS-naïve patients with a history of AECOPD will improve survival in those patients.

However, 71% of the subjects in the IMPACT trial already had pre-study ICS therapy, and could not have had ICS initiated as part of the IMPACT trial. As a result, the relevance of this population to informing a clinical decision about the addition of ICS in ICS-naïve patients is unclear. If the observed difference on ACM for FF/UMEC/VI vs. UMEC/VI was driven by the potential harm of removing an ICS from uncontrolled patients, then the proposed labeling claim would be misleading. Examination of the 29% of subjects in the IMPACT ICS-naïve subgroup, in whom ICS addition was possible, provides the most relevant data to inform the clinical question of whether the addition of fluticasone furoate to UMEC/VI improves ACM. While underpowered, these data from the ICS-naïve subgroup of do not provide evidence of benefit in the FF/UMEC/VI vs. UMEC/VI comparison. While trial design differences may limit cross-study comparisons, analogous ICS-naïve subgroup data from TORCH and SUMMIT do not demonstrate the benefit of fluticasone addition on ACM, despite longer trial durations and more death events. Whether these results are generalizable to patients in clinical practice, in whom health care providers are considering the benefit of adding a therapy, is an important question. The majority of patients in IMPACT entered the study on pre-study ICS and could be randomized only to ICS removal or ICS continuation (but not ICS addition). Therefore, it warrants the committee's consideration as to

whether the trial design of IMPACT had inherent limitations in its ability to answer the clinically relevant question: does the addition of FF to UMEC/VI decrease ACM?

This meeting is being held in virtual format. Therefore, the committee will be provided the briefing document as well as Applicant and Agency's presentations to view in their entirety prior to the meeting. On the day of the PADAC meeting, summary presentations will be provided by the Applicant followed by the Agency, with the opportunity for the panel members to ask clarifying questions. There will be an Open Public Hearing followed by a further opportunity for discussion and voting questions. We ask that you think through the following "draft points to consider" as you review the briefing materials:

Draft Points to Consider

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:
    a. The exploratory nature of the ACM analysis, the lack of Type I error control, and the strength of evidence in IMPACT
    b. Whether the ACM results from IMPACT are persuasive in light of the additional ACM data from fluticasone comparisons provided by SUMMIT and TORCH
    c. The observed timeframe of the IMPACT results, i.e., the early separation in survival

2. Discuss the implications of pre-study ICS use and ICS-removal on the interpretation of the ACM data in the IMPACT trial. Include the following elements in your discussion:
    a. The clinical understanding of the contribution of ICS to COPD therapy and the effects of ICS removal in patients with uncontrolled COPD and frequent exacerbations
    b. The implications of randomization to study drugs that do not contain ICS among patients with uncontrolled COPD despite pre-study ICS therapy
    c. The observed timeframe of the IMPACT results, i.e., the early separation in survival
    d. The pre-study ICS subgroup data from SUMMIT and TORCH, in light of the differences from IMPACT in study design and patient population

3. Discuss the generalizability of the IMPACT ACM data to relevant clinical practice decisions about fluticasone furoate (FF) as add-on therapy in COPD. Include the following elements in your discussion:
    a. The clinical relevance and persuasiveness of the ACM results from fluticasone comparisons among the ICS-naïve subgroups of IMPACT, SUMMIT, and TORCH
    b. The clinical relevance of data from the pre-study ICS subgroup to inform decisions regarding the addition of FF
    c. The clinical relevance of the IMPACT trial design and its ability to assess the benefit of adding FF
    d. The clinical implications of the proposed labeling claim in light of the submitted data

4. Discuss whether 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.

Clinical and Statistical Briefing Document for the Pulmonary Allergy Drugs Advisory Committee Meeting

August 31, 2020

Fluticasone furoate, umeclidinium, and vilanterol inhalation powder
TRELEGY ELLIPTA
NDA 209482/S-0008

Proposed Dose: Fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, fixed dose combination

Proposed Indication:
Improvement in All-cause mortality labeling claim

Clinical Reviewer: Robert Busch, M.D., M.M.Sc.
Statistical Reviewer: Susan Duke, M.S., M.S.

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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Glossary

Medication Class Acronyms

ICS	inhaled corticosteroid
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
ICS/LABA	therapy that includes both an inhaled corticosteroid and long-acting beta-agonist; whether supplied as fixed dose combinations or separately
LABA/LAMA	therapy that includes long-acting beta-agonist and long-acting muscarinic antagonist; whether supplied as fixed dose combinations or separately
ICS/LABA/LAMA	therapy that includes inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist; triple therapy; whether supplied as fixed dose combinations or separately

Medication Acronyms

FF	fluticasone furoate 100 mcg, an ICS
UMEC	umeclidinium 62.5 mcg, a LAMA
VI	vilanterol 25 mcg, a LABA
FF/VI	fixed dose combination of fluticasone furoate 100 mcg and vilanterol 25 mcg, an ICS/LABA
UMEC/VI	fixed dose combination of umeclidinium 62.5 mcg and vilanterol 25 mcg, a LABA/LAMA
FF/UMEC/VI	fixed dose combination of fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, an ICS/LABA/LAMA
FP	fluticasone propionate 500 mcg, an ICS
SAL	salmeterol 50 mcg, a LABA
FP/SAL	fixed dose combination of fluticasone propionate 500 mcg and salmeterol 50 mcg, and ICS/LABA
PBO	placebo

Withdrawal Risk Subgroups Defined by Pre-study Therapy

Exploratory Subgroups at Risk of ICS removal

Pre-study ICS	subjects whose pre-study therapy included inhaled corticosteroid
Pre-study triple	subjects whose pre-study therapy included inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist

Exploratory Subgroups not at Risk of ICS removal

ICS-naïve	subjects whose pre-study therapy did not include inhaled corticosteroid

Additional Acronyms

ACM	all-cause mortality
AECOPD	acute exacerbation of COPD
cAMP	cyclic 3′,5′-adenosine monophosphate
CAT	COPD Assessment Test
CED	common end date
CV	cardiovascular
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
DMC	data monitoring committee
eCRF	electronic case report form
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
IND	investigational new drug application
IP	investigational product
ISOLDE	Inhaled Steroids in Obstructive Lung Disease
ITT	intent to treat
ITT	intent-to-treat efficacy
MDI	metered-dose inhaler
Pbo	Placebo
PH	proportional hazard
PK	pharmacokinetics
Sev AECOPD	severe acute exacerbation of COPD
SGRQ	St. George's Respiratory Questionnaire
sNDA	supplemental new drug application
VS	vital status
VSFU	vital status follow-up
USPI	United States Prescribing Information

1. Introduction and Regulatory Background

1.1. Product Information

TRELEGY ELLIPTA inhalation powder is a fixed-dose combination (FDC) of fluticasone furoate, an inhaled corticosteroid (ICS), umeclidinium bromide, a long-acting muscarinic antagonist (LAMA), and vilanterol trifenatate, a long-acting beta-agonist (LABA), developed by GlaxoSmithKline (GSK, or the Applicant) for delivery using a breath-actuated multi-dose dry powder inhaler. The dry powder inhaler delivers fluticasone furoate 100 mcg (FF), umeclidinium 62.5 µg (UMEC), and vilanterol 25 µg (VI) per actuation from the mouthpiece.

GSK submitted this supplemental new drug application (sNDA) for TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) to support a proposed labeling claim of a decrease in all-cause mortality (ACM), relying primarily on comparisons demonstrating the contribution of the ICS component.

TRELEGY ELLIPTA was initially approved on September 18, 2017 with an indication for the long-term, once-daily maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations and in whom additional treatment of airflow obstruction is desired, or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.

The indication for TRELEGY ELLIPTA was amended on April 24, 2018 after approval of an sNDA relying on data from trial CTT116873 (IMPACT). The amended indication for TRELEGY ELLIPTA was for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD and also to reduce exacerbations of COPD in patients with a history of exacerbations.

In an effort to clarify and harmonize labeling across approved COPD products, the Division initiated labeling changes in 2019 for COPD drugs – including TRELEGY ELLIPTA – to provide a more general indication in line with current labeling practice, with efficacy results with respect to specific COPD endpoints (e.g., lung function, exacerbations, and quality of life measures) described in Section 14 of the U.S. package insert. As a result of this change, the current United States Prescribing Information (USPI) for TRELEGY ELLIPTA lists the following indication, amended on May 15, 2019: For the maintenance treatment of patients with COPD.

1.2. Proposed Labeling Claim

The Applicant proposes to amend Section 14 Clinical Trials of the USPI for TRELEGY ELLIPTA with all-cause mortality data from the IMPACT trial (referred to as Trial 3 in the USPI). The

Applicant's initially proposed labeling is included below, as well as the Applicant's revision to the proposed labeling that was submitted during the course of the sNDA review.

Initial Proposed Labeling Change

Survival: In Trial 3, treatment with TRELEGY ELLIPTA significantly reduced the risk of all-cause mortality, including on- and off-treatment data, by 27.7% compared with umeclidinium/vilanterol (vital status confirmed in 99.6% of patients at Week 52) (Table #). The reduction in risk of all-cause mortality was 11.3% with TRELEGY ELLIPTA compared with fluticasone furoate/vilanterol; however, this result was not statistically significant.

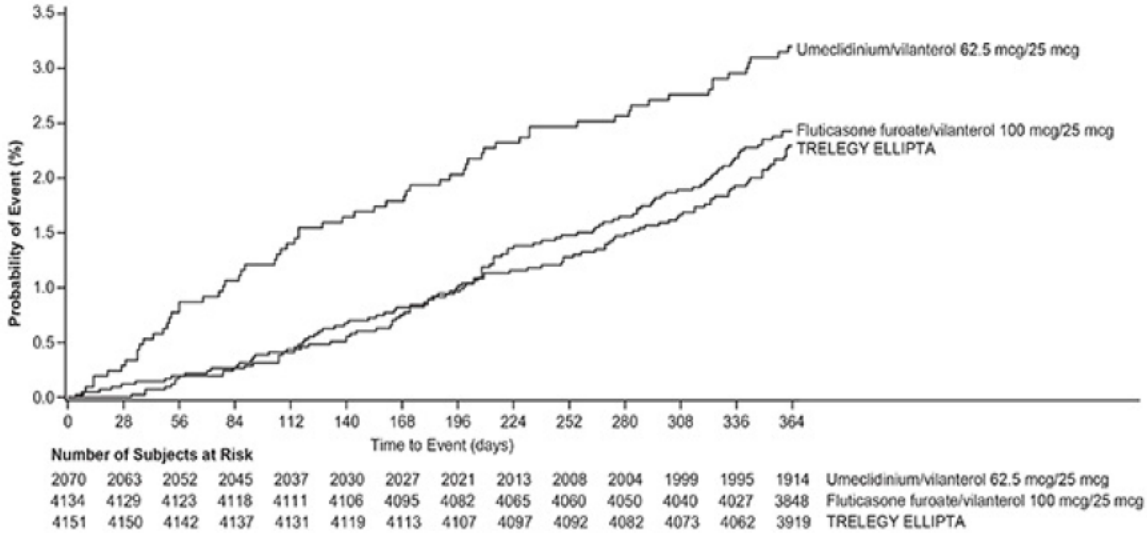
Table #. Reduction in All-Cause Mortality (Trial 3)

Treatment	n	Hazard Ratio vs. Comparator (95% CI)	Reduction in Risk (95% CI)	P-Value
TRELEGY ELLIPTA	4,151			
UMEC/VI	2,070	0.72 (0.53, 0.99)	27.7% (1.2, 47.1)	0.042
FF/VI	4,134	0.89 (0.67, 1.16)	11.3% (-16.5, 32.5)	0.387

CI = Confidence Interval; UMEC/VI = Umeclidinium/Vilanterol 62.5 mcg/25 mcg; FF/VI = Fluticasone Furoate/Vilanterol 100 mcg/25 mcg.

Treatment with TRELEGY ELLIPTA improved survival with a significant reduction in the risk of all-cause mortality, on- and off-treatment, over time compared with umeclidinium/vilanterol (Figure #).

Figure #. Kaplan-Meier Plot of Time to All-Cause Mortality (Trial 3)



Analyses of on-treatment all-cause mortality were also conducted, and results were consistent with the above results. Treatment with TRELEGY ELLIPTA significantly reduced the risk of on-treatment all-cause mortality by 42.1% (95% CI: 11.9, 61.9; P = 0.011) compared with umeclidinium/vilanterol. The reduction in risk of all-cause mortality was 5.5% (95% CI: -40.2, 36.3) with TRELEGY ELLIPTA compared with fluticasone furoate/vilanterol; however, this result was not statistically significant.

Revised Proposed Labeling Change
On April 23, 2020, the Applicant submitted the following revision to the proposed labeling changes:

Survival: In Trial 3, treatment with TRELEGY ELLIPTA reduced the risk of all-cause mortality by 27.7% (95% CI: 1.2, 47.1; P = 0.042) compared with umeclidinium/vilanterol (on- and off-treatment data). The reduction in risk of all-cause mortality was 11.3% (95% CI: -16.5, 32.5; P = 0.387) with TRELEGY ELLIPTA compared with fluticasone furoate/vilanterol (on- and off-treatment data). Vital status was confirmed in 99.6% of patients at Week 52.
In Trial 3, 71% of all subjects were on ICS therapy at Screening. Despite ICS therapy, these subjects had more severe COPD as indicated by history of severe exacerbations (≥1 in the prior year, 27.4% versus 21.8% not on ICS). Post-hoc subgroup analyses of all-cause mortality were conducted for subjects on ICS therapy at Screening and for those not on ICS. In the ICS subgroup, TRELEGY ELLIPTA reduced the risk of all-cause mortality by 39.3% (95% CI: 12.6, 57.8) compared with umeclidinium/vilanterol; the clinical relevance of these results is unknown. In the non-ICS subgroup, the evaluation of all-cause mortality was limited by the small sample size.

1.3. Brief Clinical Background

COPD is a serious, common, preventable, progressive lung disease involving chronic inflammation of the airways and lung parenchyma caused by exposure to particulate matter or gases. COPD is characterized by irreversible airflow obstruction and persistent respiratory symptoms. Tobacco smoke exposure is the most frequent cause of COPD in the United States by an overwhelming margin. COPD is the fourth leading cause of mortality worldwide[1-4]. Almost 15.7 million Americans report a diagnosis of COPD[5], and COPD has been the third or fourth leading cause of death in the United States from 2012-2017 as per data from the National Vital Statistics System[6-11]. Currently, there is no cure for COPD, nor any therapeutic intervention that definitively halts or reverses disease progression.

The major pathophysiologic drivers of airflow obstruction in COPD are chronic inflammation of the airways and lung parenchymal destruction in response to chronic noxious stimuli. While the most common stimulus in the United States and Europe is tobacco smoke exposure, biomass fuel exposure also causes a significant global burden of COPD. Airway inflammation is commonly neutrophilic and causes increased mucus production and airway wall thickening, both of which contribute to airflow obstruction by narrowing the bronchial lumen.

Emphysematous lung parenchymal destruction and the resultant loss of elastic recoil of the lung contribute to airflow obstruction by decreasing airway tethering, which can cause airways to narrow or collapse.

The clinical course of COPD is heterogeneous and includes both chronic daily symptoms and acute disease exacerbations. COPD often presents as clinically heterogeneous constellations of symptoms and deficits in different patients; classic descriptive phenotypes of COPD derived from these constellations include chronic bronchitis and emphysema. Disease heterogeneity occurs despite the unifying inciting event of tobacco smoke exposure. Patients with equal smoking histories often differ broadly in disease severity measures, degree of emphysema, quality of life, degree of debility from COPD, and in the frequency of acute exacerbations of COPD (AECOPD). Comorbidities, genetic factors, occupational exposures, environmental exposures, and gender influence the likelihood of acquiring COPD and disease manifestations.

Regardless of overarching clinical presentation, the symptomatic burden of COPD is significant. Almost all patients with COPD experience chronic and persistent symptoms such as dyspnea, cough, increased mucus production, and exercise limitation. As the disease progresses over time and increases in severity, patients may develop more debilitating symptoms: muscle wasting, dyspnea with minimal exertion or even at rest, cyanosis and resting hypoxemia with supplemental oxygen dependence, secondary pulmonary hypertension, and chronic respiratory failure requiring mechanical ventilatory support. These progressive symptoms negatively impact a patient's health-related quality of life[12] and lead to loss of independence[13] and productivity[5,14].

Clinicians use spirometry to diagnose COPD and judge the severity of airflow obstruction in patients with COPD[1,15]. Demonstration of significant irreversible airflow obstruction confirms the diagnosis, while the degree of airflow obstruction compared to predicted normal values determines severity. Recent international guidelines for COPD diagnosis and management include an assessment of both chronic symptoms and frequency of disease exacerbations as an adjunct classification to better characterize COPD severity[1].

Moderate-to-severe acute exacerbations of COPD (ModSev AECOPD) involve significant worsening of COPD symptoms requiring additional medical intervention[16,17]. Well-designed studies link increased frequency of ModSev AECOPD to disease sequelae such as decreased quality of life[18], while severe acute exacerbations of COPD (Sev AECOPD) are more directly linked to increased disease progression[19], morbidity, and mortality[20,21]. Some patients with COPD still experience frequent ModSev AECOPD despite the concomitant use of multiple FDA-approved maintenance therapies designed to reduce the rate of ModSev AECOPD.

Despite advancements in the understanding of COPD, symptomatic treatment, and prevention of exacerbations, COPD mortality remains high[6-11]. To date, no drug has been shown to improve all-cause mortality in COPD. A therapy which decreases all-cause mortality in COPD would address a substantial unmet need in the treatment of patients with COPD.

1.4. Tables of Currently Available Treatments for Proposed Indications

Currently, there are no FDA-approved therapies that decrease mortality in COPD.

Smoking cessation is the most important intervention for treatment of COPD. Smoking cessation is critical to prevent COPD progression[22,23] and COPD-related mortality[24,25], in addition to providing an all-cause mortality benefit and decreasing the risk of cardiovascular- and cancer-related death[26]. In addition to smoking cessation, oxygen supplementation decreases mortality among patients with COPD and resting hypoxemia.

International guidelines recommend inhaled medications as first-line medical therapy for symptomatic treatment of COPD[1,15] due to their low systemic exposure and favorable toxicity profile. Inhaled medication classes for maintenance treatment of COPD include long-acting beta-agonists, long-acting muscarinic antagonists, and inhaled corticosteroids, often prescribed in combination (see Table 1). Short-acting inhaled medications approved for the treatment/prevention of bronchospasm are routinely prescribed for patients with COPD. Oral medications are generally prescribed for specific subpopulations of COPD, or for patients who do not respond adequately to inhaled medications.

Patients with COPD use long-acting inhaled medications as primary maintenance therapy for COPD symptoms and to decrease the rate of exacerbations. Long-acting beta agonists (LABA), long-acting muscarinic antagonists (LAMA), and combination LABA/LAMA products are a mainstay of COPD treatment, providing improvement in airflow obstruction and symptomatic improvement. Inhaled corticosteroids (ICS) are used in combination with LABA to decrease the frequency of AECOPD and improve airflow obstruction. If clinically indicated by severity and exacerbation frequency, physicians often prescribe an ICS/LABA in conjunction with a LAMA, also known as “triple therapy.” Providers prescribe numerous approved and currently marketed drug products and delivery devices for LABA, LAMA, LABA/LAMA, ICS/LABA, and ICS/LABA/LAMA in the U.S. (See Table 1).

In summary, the current treatment armamentarium for COPD is extensive and provides significant efficacy with respect to improvement in lung function and AECOPD prevention for most patients, especially for those with early or less severe disease. No therapy cures COPD, no therapy reverses progression of airflow obstruction or emphysema, and there are no FDA-approved therapies that have been shown to decrease mortality.

Table 1. Summary of Treatment Armamentarium for COPD

Class	Drug Substance	Representative Trade Names
Single ingredient treatments		
SABA	Albuterol (salbutamol)	ProAir, Proventil, Ventolin,
LABA, inhaled	Arformoterol tartrate, formoterol fumarate, indacaterol maleate, olodaterol hydrochloride, salmeterol xinafoate	Brovana, Perforomist, Arcapta Neohaler, Striverdi Respimat, Serevent
LAMA, inhaled	Aclidinium bromide, glycopyrrolate, tiotropium bromide, umeclidinium bromide, revefenacin	Tudorza Pressair, Seebri Neohaler, Spiriva HandiHaler, Spiriva Respimat, Incruse Ellipta, Yupelri
PDE-4 inhibitor	Roflumilast	Daliresp
Methylxanthine	Theophylline	Theophylline, Theo-24, Theochron, Elixophyllin
Combination treatments		
ICS/LABA	Budesonide/ formoterol, fluticasone propionate/ salmeterol, fluticasone furoate/ vilanterol	Symbicort, Advair Diskus, Advair HFA, Breo Ellipta
LABA/LAMA	Formoterol / glycopyrrolate, glycopyrrolate/ indacaterol, olodaterol / tiotropium, umeclidinium / vilanterol	Bevespi Aerosphere, Utibron Neohaler, Stiolto Respimat, Anoro Ellipta, Duaklir
ICS/LABA/LAMA	Fluticasone furoate/ umeclidinium / vilanterol	TRELEGY ELLIPTA
Inhaled SABA/short-acting anticholinergic	Albuterol sulfate/ ipratropium bromide	Duoneb, Duoneb HFA, Combivent Respimat

Source: Reviewer-created table based on product labeling for currently approved medications indicated for COPD.
Abbreviations: LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist. ICS: inhaled corticosteroid; PDE: phosphodiesterase 4; SABA, short-acting beta-agonist

The Role of Inhaled Corticosteroids in COPD

The all-cause mortality efficacy data in this sNDA rely on the contribution of the ICS component of TRELEGY ELLIPTA – an ICS/LABA/LAMA – compared to a LAMA/LABA. ICS have an established role in the maintenance treatment of COPD due to their anti-inflammatory effects and effects on rates of AECOPD; however, large randomized controlled trials spanning three years or more have failed to demonstrate a statistically significant mortality benefit with the use of ICS alone or in combination with a LABA[27,28]. Indeed, one study observed a numerically higher mortality among those randomized to ICS alone compared to placebo[27].

Despite a recognized clinical benefit, the appropriate use of ICS in COPD is still controversial[29-33], partly because of a safety signal identified in clinical trials showing increased incidences of pneumonia and pneumonia requiring hospitalization in users of ICS-containing products. In addition, negative effects on COPD control (e.g., lung function and patient-reported outcome measures) after abrupt discontinuation of ICS (i.e., ICS removal) are well-documented[34-42]. Randomized controlled trials of ICS removal have observed inconsistent effects on ModSev AECOPD endpoints[38,43-45], although some trials and meta-analyses may suggest trends towards higher rates of Sev AECOPD[46,47]. It is important to note that the larger randomized ICS-removal trials have primarily enrolled participants without a history of frequent AECOPD. These symptomatically less severe participants without frequent exacerbations represent a

population in which ICS removal might be clinically indicated. However, no well-powered randomized clinical trial has explored the effect of abrupt ICS removal on all-cause mortality across the spectrum of COPD severity, much less in participants with inadequately controlled COPD and a high proportion of frequent exacerbators despite ongoing inhaled therapy.

1.5. Availability of Proposed Active Ingredient in the United States

TRELEGY ELLIPTA is a triple fixed-dose combination product containing fluticasone furoate, umeclidinium, and vilanterol. The initial marketing approval of TRELEGY ELLIPTA occurred in 2017. Components of TRELEGY ELLIPTA are available as approved monoproducts (e.g., fluticasone, umeclidinium) or as part of approved dual fixed dose combinations (e.g., fluticasone furoate/vilanterol, umeclidinium/vilanterol).

1.6. Mechanism of Action

The approved USPI for TRELEGY ELLIPTA contains the following information regarding mechanism of action:

> TRELEGY ELLIPTA
> TRELEGY ELLIPTA contains fluticasone furoate, umeclidinium, and vilanterol. The mechanisms of action described below for the individual components apply to TRELEGY ELLIPTA. These drugs represent 3 different classes of medications (an ICS, an anticholinergic, and a LABA), each having different effects on clinical and physiological indices.
>
> Fluticasone Furoate
> Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown.
>
> The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Inflammation is an important component in the pathogenesis of COPD. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as NFkB, and inhibition of antigen-induced lung eosinophilia in sensitized rats. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

Umeclidinium

Umeclidinium is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical in vitro as well as in vivo studies, prevention of methacholine- and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

Vilanterol

Vilanterol is a LABA. In vitro tests have shown the functional selectivity of vilanterol was similar to salmeterol. The clinical relevance of this in vitro finding is unknown.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenergic agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

1.7. Important Safety Issues With Consideration to Related Drugs

The primary focus of this sNDA and the Advisory Committee Meeting is the contribution of the ICS component of TRELEGY ELLIPTA (i.e., fluticasone furoate) to the all-cause mortality endpoint through the comparison of FF/UMEC/VI versus UMEC/VI in the IMPACT trial.

While no ICS is approved as stand-alone therapy in COPD, multiple COPD trials have observed consistent safety risks of ICS in placebo-controlled or active-controlled comparisons. The

Warnings and Precautions section of most ICS drug labeling includes the recognized risks of ICS use in COPD:

- Increased risk of pneumonia
- Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infections and ocular herpes simplex)
- Candida albicans infections of the oropharynx
- Decreases in bone mineral density
- Glaucoma
- Cataracts
- Risk of hypercorticism and adrenal suppression with very high dosages or at regular dosage in susceptible individuals

In addition to the labeled risks of ICS use, the clinical effects of ICS removal have been a topic of debate in the COPD scientific literature[34-41,43,45-62]. Multiple peer-reviewed publications suggest that removing ICS from a COPD maintenance regimen may lead to clinical deterioration in lung function[34-36,38,45,59] and other clinically relevant endpoints, especially among COPD patients with markers of higher disease severity and frequent exacerbations. Randomized trials powered specifically to examine AECOPD rates after ICS removal have largely focused on subsets of COPD patients with better symptomatic control[39,45,59], analogous to the clinical situation of removing the ICS component of a COPD medication regimen in a patient exhibiting clinical signs of disease control. In addition, none of these ICS removal studies were designed to demonstrate a mortality benefit or to rule out a mortality risk attributable to ICS removal. These issues are discussed further in Section 4.5.2 Pre-study Therapy and ICS Removal in IMPACT, and Section 4.5.8 ICS Removal in COPD. Defining the extent of detrimental effects of ICS removal in symptomatically controlled and uncontrolled subsets of patients with COPD has been a source of uncertainty in clinical practice and clinical trials.

Reviewer's Comment*: The phrase "ICS removal" has been used deliberately throughout this document in place of phrases such as "ICS discontinuation" or "ICS withdrawal" to describe the situation in which ICS therapy is stopped or removed from a patient's regimen. This terminology was chosen because both "discontinuation" and "withdrawal" have well-defined regulatory meanings related to a subject's disposition within a trial. The potential effect of protocol-mandated ICS removal (e.g., through randomization to the LAMA/LABA arm when a subject was receiving ICS pre-study) and its effects on the interpretation of efficacy results from the IMPACT trial merit discussion by the Advisory Committee.*

1.8. Summary of Regulatory Activity Related to Submission

Numerous regulatory interactions occurred during the drug development of TRELEGY ELLIPTA and its components. Regulatory interactions relevant to the proposed all-cause mortality claim for TRELEGY ELLIPTA are summarized below. For the summary of the eight additional interactions regarding the IMPACT trial design and the initial approval of TRELEGY ELLIPTA, see Section 5.2Regulatory History Appendix.

Comments from statistical review of IMPACT trial protocol on November 12, 2014

- The Division recommended defining and justifying the causal estimand of interest for the IMPACT trial and justifying that the estimand is meaningful and can be estimated with minimal and reasonable assumptions. The Division suggested a "de facto treatment effect" estimand, incorporating data from all primary and key secondary efficacy endpoints regardless of whether they discontinue the initially assigned randomized treatment or whether they fail to actively maintain contact with their investigational site.
- The Division stated that the presentation of results with missing data will be a review issue, and suggested techniques to establish consistent and effective data collection.
- The Division emphasized the importance of collection of mortality data after withdrawal of treatment, and stated that presentation of results with missing data for the mortality endpoint would be a review issue. The Division also suggested that the patient consent form include permission to collect mortality/survival data after patient withdrawal from treatment.
- The Division noted that the Sponsor proposed to assess secondary endpoints while controlling the probability of Type I error at 0.05. The Division recommended control of the probability of Type I error for secondary endpoints in study CTT116855, referencing mortality, at the 0.01 level.

Reviewer's Comment*: Two important points not discussed during the Sponsor's interactions with the Agency prior to conducting the IMPACT trial influence the present discussion of all-cause mortality:*

- *The appropriate duration for all-cause mortality assessment or clinical design elements that would allow the IMPACT study to provide substantial evidence of an all-cause mortality benefit in COPD.*
- *The potential risks of protocol-mandated ICS removal (i.e. through the randomization of a subject receiving pre-study ICS therapy to a treatment arm with no ICS) among symptomatic COPD patients with a history of exacerbations.*

Pre-sNDA meeting minutes for TRELEGY ELLIPTA all-cause mortality application on March 13, 2019

- The Division inquired whether the Applicant's proposed application fundamentally relied on the premise that the ICS component of FF/UMEC/VI contributed to the observed all-cause mortality results, or whether the Applicant also proposed some efficacy of the UMEC component on all-cause mortality. The Applicant replied that their understanding of the all-cause mortality data relied primarily on the efficacy contribution of the ICS component and noted plans to include supportive data for ICS efficacy on all-cause mortality from two previous factorial design mortality trials in COPD: TORCH and SUMMIT.
- The Division notified the Applicant that the review of the submitted all-cause mortality claims for TRELEGY ELLITPA would rely on the intention-to-treat plus vital status data including both on- and off-treatment deaths, as well as the intention-to-treat plus vital status follow-up data including on- and off-treatment deaths plus additional post hoc vital status collection.
- The Division requested subgroup analyses of all-cause mortality by pre-study therapy measures (e.g., presence/absence of pre-study triple therapy, presence/absence of pre-study ICS-containing therapy) at multiple timepoints.
- Given that severe exacerbation events are a risk factor for mortality in COPD, the Division also requested analogous subgroup analyses of severe exacerbation endpoints by pre-study therapy measures.
- The Division noted potential statistical issues with the all-cause mortality analyses, including the lack of multiplicity control, since the all-cause mortality analyses were not part of the statistical testing hierarchy for IMPACT. The Division also noted the lack of statistically significant replicate data showing an all-cause mortality benefit of ICS from another COPD trial for confirmatory support.
- The Division requested that the Applicant discuss the potential impact of abrupt ICS removal on the ACM analysis results including the early separation of Kaplan-Meier mortality curves. The Division also requested that the Applicant discuss the event rates among subjects who received pre-study ICS therapy and were randomized to non-ICS containing regimens compared to ICS-naïve subjects.
- The Division requested additional discussion of the potential impact of abrupt "step-down" of COPD therapy (i.e., ICS removal or LAMA-removal) among those with pre-study triple therapy randomized to a dual therapy.
- The Division requested tipping point analyses of the primary analysis to evaluate the effect of missing data on the trial results.
- The Division questioned whether the assumption of proportional hazards (PH) was appropriate in the IMPACT trial. If this assumption were violated by the trial, the Division noted that this would increase uncertainty in the primary analysis results, and invalidate sensitivity analyses relying on the assumption of PH.
- In post-meeting comments, the Division notified the Applicant that, should they choose to include data from TORCH and SUMMIT as supportive data for their sNDA, analogous subgroup analyses of these trials might be necessary for review.

2. Sources of Clinical Data and Review Strategy

2.1. Tables of Clinical Trials

Table 2. Clinical Trials of Fluticasone for All-cause Mortality in COPD

Study Identifier, Design and Duration	Treatments	Number (ITT†)	Characteristics of Enrolled Population	Study Primary and Key Secondary Efficacy Endpoints
CTT116855 (IMPACT) *NCT02164513* R, DB, MC, PG, AC, partial factorial, 52-week duration JUN 2014 to JUL 2017	FF/UMEC/VI* FF/VI UMEC/VI*	4,145 4,133 2,070	• Moderate-to-Very Severe COPD by FEV1 • Current/former smokers (≥10 pack-year) • History of ModSev AECOPD in the prior year • CAT≥10, indicative of poor symptom control • Any maintenance medication for ≥3 months	1° Rate of ModSev AECOPD FF/UMEC/VI vs. UMEC/VI 2° Rate of ModSev AECOPD FF/UMEC/VI vs. FF/VI
HZC113782 (SUMMIT) *NCT01313676* R, DB, MC, PG, PC, factorial, event driven stop date, ~4-year duration JAN 2011 to JUL 2015	FF/VI* FF VI* Pbo	4,121 4,135 4,118 4,111	• Moderate COPD by FEV1 • Current/former smokers (≥10 pack-years) • mMRC >2, indicative of dyspnea • Documented history of CV disease marker • No requirement for history ModSev AECOPD in the previous year • Any maintenance medication	1° Risk of All-cause Mortality (TTD) FF/VI vs. Pbo 2° Rate of decline in FEV1 FF/VI vs. Pbo 2° Non-inferiority in risk of MACE FF/VI vs. Pbo
SCO30003-01 (TORCH) *NCT00268216* R, DB, MC, PG, PC, factorial, 156-week duration SEP 2000 to NOV 2005	FP/SAL* FP SAL* Pbo	1,533 1,534 1,521 1,524	• Moderate-to-Severe COPD by FEV1 • Current/former smokers (≥10 pack-years) • Protocol-mandated discontinuation in case of worsening with suggested criteria for frequent AECOPD as reason for discontinuation	1° Risk of All-cause Mortality (TTD) FP/SAL vs. Pbo 2° Rate of ModSev AECOPD FP/SAL vs. Pbo 2° Quality of Life by SGRQ FP/SAL vs. Pbo

Source: Reviewer. *In addition to placebo-controlled comparisons of fluticasone, the comparison of these treatment arms provides data on the efficacy of fluticasone on trial endpoints.
†In the SUMMIT trial, the primary analysis population presented was labeled ITT-E, which excluded subjects randomized by excluded investigators
Abbreviations: AC, active controlled; AECOPD, acute exacerbations of COPD; COPD, chronic obstructive pulmonary disease; DB, double blind; FEV1, forced expiratory volume in one second; FF, fluticasone furoate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; FF/VI, fluticasone furoate/vilanterol; FP, fluticasone propionate; FP/SAL, fluticasone propionate/salmeterol; ITT, intention-to-treat; MACE, major adverse cardiovascular event; MC, multicenter; mMRC: modified Medical Research Council score; ModSev, moderate to severe; Pbo, placebo; PC, placebo-controlled; PG, parallel group; QoL, quality of life; R, randomized; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire Score; TTD, time to death; UMEC/VI, umeclidinium/vilanterol; VI, vilanterol

2.2. Review Strategy

This sNDA relies primarily on analyses of ACM data including on- and off-treatment data, on- and off-study data, and post hoc vital status follow-up (VSFU) data from trial CTT116855 (IMPACT). To further explore ACM data in COPD trials that included ICS (fluticasone) and to provide further information to rely on the ACM result of a single trial (IMPACT), supplementary data are presented from two previous mortality-focused trials in COPD: HZC113782 (SUMMIT) and SCO30003-01 (TORCH). Analogous primary analyses of ACM and subgroup analyses of ACM by pre-study medication relying on data from SUMMIT and TORCH provide supplementary data to inform the efficacy of fluticasone on ACM endpoints in COPD, to examine further the effect of ICS removal in the setting of varying COPD patient populations and medication run-ins, and for comparison of trial designs and durations when evaluating ACM.

The protocols for the IMPACT, SUMMIT, and TORCH trials are summarized and reviewed in Sections 3.1, 3.2, and 3.3, respectively, including details of trial designs, trial objectives, approaches to pre-study ICS treatment, and medication run-in strategies. The IMPACT trial did not examine ACM as a primary efficacy endpoint or as a key secondary efficacy endpoint. ACM was an "other" endpoint and was not included in the statistical multiplicity gatekeeping hierarchy of the IMPACT trial. Therefore, the primary efficacy results of annual rate of exacerbations (reviewed under sNDA 209482), as well a list of all the endpoints analyzed, have been included in the Appendix for the Advisory Committee's reference. The body of this review focuses on the analyses of ACM.

Sections 4.1 through 4.3 summarize the demographics, baseline disease characteristics, and subject disposition from IMPACT, SUMMIT, and TORCH, respectively.

The ACM data from the IMPACT, SUMMIT, and TORCH trials are presented in Sections 4.4.1, 4.4.2, and 4.4.3, respectively, followed by a discussion of ACM across trials in Section 4.4.4.

Section 4.5 presents further analyses of the ACM data by pre-study medication subgroup. Section 4.5.1 provides a conceptual framework for discussing ICS removal in COPD trials. Section 4.5.2 provides a discussion of the potential effects of ICS removal on the overall interpretation of the IMPACT ACM data. Exploratory subgroup analyses of the IMPACT ACM data by pre-study medication subgroup are presented in Sections 4.5.3 and 4.5.4, with an emphasis on Section 4.5.4 IMPACT: All-cause Mortality and Pre-study ICS. Section 4.5.5 reports pertinent interactions and discussions of the Independent Data Monitoring Committee (IDMC) regarding early mortality and ICS removal concerns. To further inform the interpretation of the ACM data, subgroup analyses of severe AECOPD endpoints are also presented in Section 4.5.6. Section 4.5.7 summarizes additional ACM analyses by pre-study medication subgroups and potential ICS removal effects in SUMMIT and TORCH data. The full discussion of differences in study design and trial run-in, the presentation of pre-study medication subgroup results, and discussion of potential ICS removal effects in SUMMIT and TORCH are presented in Appendices5.5.5 through 5.5.6 and 5.6.5through 5.6.6, respectively. Finally, Section 4.5.8

provides a summary of the relevant background literature on ICS removal to provide scientific context to the potential effect of ICS removal in IMPACT, SUMMIT, and TORCH.

The statistical and clinical issues for discussion are detailed in Section 4.6. Topics include: the statistical persuasiveness of the ACM results from the IMPACT trial, the evidence across trials (i.e. IMPACT, SUMMIT, and TORCH) for the efficacy of fluticasone on ACM, and the timeframe of efficacy with respect to ACM in IMPACT. These are summarized in 4.6.1, 4.6.2, and 4.6.3, respectively. The potential effect of ICS removal in IMPACT, SUMMIT, and TORCH is then summarized in 4.6.4. Finally, Section 4.6.5 considers the generalizability of the IMPACT trial's ACM data and the proposed efficacy claim to clinical practice. An integrated summary is provided to conclude the briefing document.

3. Design and Conduct of Pivotal Trials

3.1. Trial CTT116855 (IMPACT)

The design of this 52-week multi-national, randomized, double-blind, active-controlled trial proposed to provide primary evidence of the efficacy of TRELEGY ELLIPTA, an FDC of fluticasone furoate 100 µg (FF), umeclidinium 62.5 µg (UMEC), and vilanterol 25 µg (VI), on the rate of moderate to severe (ModSev) acute exacerbations of COPD (AECOPD) compared to a FDC of FF/VI and a FDC of UMEC/VI among persons with moderate to very severe COPD with uncontrolled symptoms and a history of AECOPD in the prior year.

Trial Designation: CTT116855 (IMPACT)
Trial Title: A phase III, 52-week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety, and tolerability of the fixed dose triple combination TRELEGY ELLIPTA (FF/UMEC/VI) with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease
National Clinical Trials Registry Number: NCT02164513
Trial Dates: June 30, 2014 to July 17, 2017
Trial Sites: 971 sites in 37 countries, including 257 sites in the United States
Trial Report Date: January 10, 2018

3.1.1. IMPACT: Objectives

The primary objective was:

- To evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of ModSev AECOPD compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD

Secondary objectives were:

- To evaluate the long-term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapy of FF/VI or UMEC/VI
- To evaluate the efficacy of FF/UMEC/VI to reduce AECOPD compared with UMEC/VI in the subset of subjects with a blood eosinophil count ≥150 cells/µL

Other objectives were:

- To evaluate the patient perspective of the efficacy of FF/UMEC/VI in subjects with COPD
- To evaluate the population pharmacokinetic profiles of FF, UMEC, and VI in subjects with COPD
- To collect blood samples for a genetics research study

Reviewer's Comment: *Assessment of all-cause mortality was not stated as an objective of the IMPACT trial.*

3.1.2. IMPACT: Design

Trial CTT116855 (IMPACT) was a randomized, double-blind, parallel group, active control trial that evaluated the efficacy and safety of an FDC of FF/UMEC/VI compared to FF/VI or UMEC/VI on AECOPD endpoints among 10,355 symptomatically uncontrolled COPD patients with a history of exacerbations despite the use of COPD maintenance medications.

A schematic of the trial is shown in Figure 1 below.

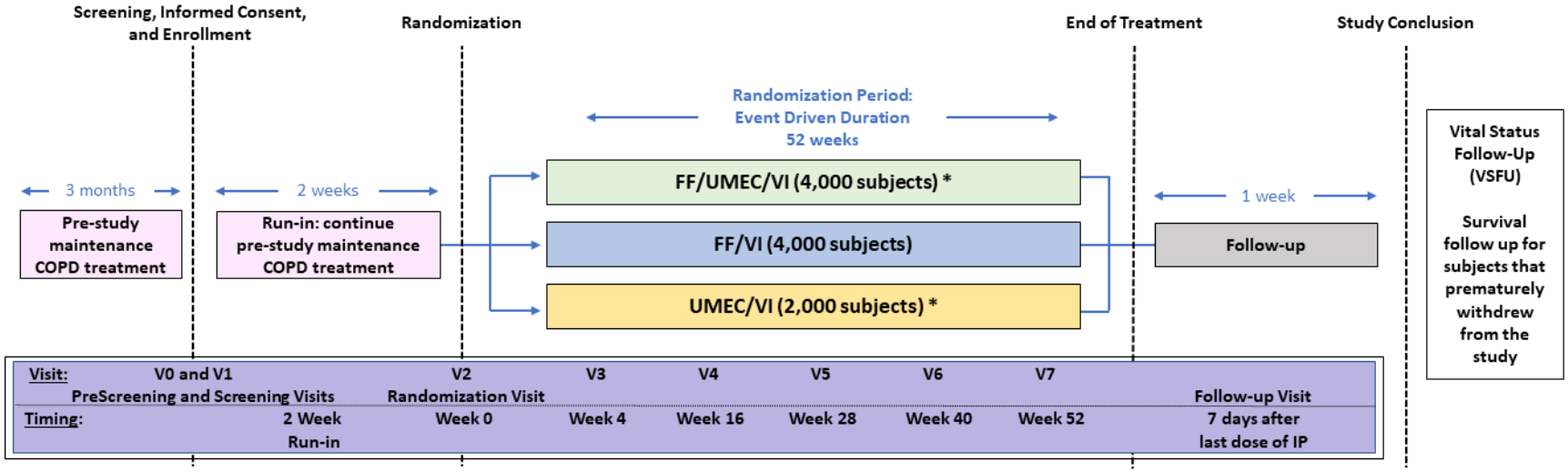
Reviewer's Comment*: The initial approval of TRELEGY ELLIPTA relied on proof of pharmaceutical equivalence of TRELEGY ELLIPTA to its approved UMEC and FF/VI components and on clinical data showing substantial evidence of efficacy on lung function endpoints from two randomized, double-blind, placebo-controlled 12-Week trials of UMEC versus placebo added to open-label FF/VI (trial 200109 [NCT01957163] and trial 200110 [NCT02119286]). This initial approval was limited to patients receiving "FF/VI for airflow obstruction and exacerbations in whom additional treatment of airflow obstruction was desired" or for those "already receiving UMEC and an FDC of FF/VI", based on the data provided from the enrolled population of trials 200109 and 200110. The design of the IMPACT trial's enrolled population, run-in strategy, and randomization strategy were intended to provide efficacy data to expand the indication to include patients with any COPD maintenance medication regimen. Specifically, the IMPACT trial was designed for the purpose of understanding the contribution of the ICS (FF)*

and LAMA (UMEC) to the FDC product, with respect to COPD exacerbations. Whether this trial design is adequate to support a claim of improvement in ACM due to ICS is an important issue for the Advisory Committee's consideration.

Trial Duration and Clinical Visits

As shown in Figure 1, the IMPACT trial comprised a 2-week run-in period, a 52-week investigational product (IP) treatment period with scheduled trial visits every 12 weeks starting at Week 4, and an additional safety follow-up by telephone call or clinic visit 7 days after the final treatment period visit or IP discontinuation. Efficacy assessments were collected at scheduled clinic visits during Weeks 4, 16, 28, 40, and 52. The IMPACT trial initially assessed all-cause mortality endpoints at study conclusion for subjects who maintained enrollment throughout the trial. Additional post hoc data-gathering and analyses of all-cause mortality – including vital status follow-up of subjects who withdrew from the IMPACT trial – occurred after study conclusion in the setting of this planned sNDA submission.

Figure 1. IMPACT: Trial Schematic



Source: Agency. Modified from Applicant's submitted materials for study CTT116855 (IMPACT).
*The comparison of these treatment arms provides data on the efficacy of fluticasone furoate on trial endpoints
Abbreviations: FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; FF/VI: fluticasone furoate/vilanterol; UMEC/VI: umeclidinium/vilanterol; VSFU: vital status follow-up; V: visit; IP: investigational product; COPD: chronic obstructive pulmonary disease

3.1.3. IMPACT: Inclusion and Exclusion Criteria

Inclusion Criteria

Important inclusion criteria are summarized as:

- Outpatient male or female subjects ≥40 years of age
- Diagnosis of COPD by 2004 American Thoracic Society/European Respiratory Society guidelines
- Post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio of ≤0.7
- COPD severity commensurate with one of the following:
  - A post-bronchodilator FEV1 <50% predicted normal and a documented history of ≥1 ModSev AECOPD in the previous 12 months

    OR
  - A post-bronchodilator FEV1 ≥50% and <80% predicted normal and a documented history of frequent exacerbations (≥2 moderate AECOPD or ≥1 severe AECOPD in the previous 12 months)
- Daily maintenance medication for the treatment of COPD for at least 3 months prior to screening (pre-study medication)
- Current or former tobacco smoker with ≥10 pack-year history
- Score of ≥10 on the COPD Assessment Test (CAT) at screening

***Reviewer's Comment**: The trial population included COPD patients with a history of AECOPD and uncontrolled symptoms (CAT score ≥ 10) despite the use of chronic maintenance medications (e.g., ICS/LABA, ICS/LAMA, LABA, LAMA, LABA, LAMA/LABA, or additional medication combinations) for three months or longer. The three-month maintenance medication requirement plus the run-in period on maintenance medications (see below) demonstrates that – at randomization – the subjects exhibited uncontrolled COPD despite steady state, chronic maintenance medication use.*

Exclusion Criteria

Important exclusion criteria are summarized here:

- Pneumonia or ModSev AECOPD that has not resolved at least 14 days prior to screening and at least 30 days following the last dose of oral/systemic corticosteroids.
- A pneumonia or ModSev AECOPD during the run-in period
- A respiratory tract infection that had not resolved at least 7 days prior to screening
- Abnormal chest x-ray
- Long-term oxygen therapy at rest ≥3L/min
- Medically unable to withhold albuterol/salbutamol for the 4-hour period prior to spirometry testing at each visit

- Acute phase of pulmonary rehabilitation within the last 4 weeks or who plan to enter the acute phase of pulmonary rehabilitation during the study
- Use of the following medications prior to screening:
  - Long-term antibiotic therapy
  - Systemic corticosteroids within 30 days
  - Any other investigational drug within 30 days or 5 half-lives
- Alpha-1 antitrypsin deficiency as the underlying cause of COPD
- Other respiratory disorders including active tuberculosis, lung cancer, sarcoidosis, pulmonary hypertension, and others
  - Subjects with a current diagnosis of asthma were included; subjects with a prior history of asthma could be included if they had a current diagnosis of COPD
- Lung volume reduction surgery within the previous 12 months
- Risk factors for pneumonia including immune suppressions or neurologic disorders affecting the upper airway, among others
- Any other uncontrolled, clinically significant abnormalities in any organ system that, in the opinion of the Investigator, would affect the efficacy or safety analysis if exacerbated during the study. Additional examples included:
  - Unstable liver disease
  - Unstable cardiac disease
  - Abnormal and clinically significant electrocardiogram findings
  - Cancer not in remission for at least 5 years
- History of allergy or hypersensitivity to any study drug or component
- Women who are pregnant, lactating, or planned to become pregnant during the study

3.1.4. IMPACT: Treatments and Concomitant Medications

Eligible subjects were randomized to one of the following study treatments administered by oral inhalation once daily for 52 weeks:

Treatment Groups

- TRELEGY ELLIPTA (FF/UMEC/VI, 100/62.5/25 µg)
- UMEC/VI (62.5/25 µg)
- FF/VI (100/25 µg)

Reviewer's Comment*: While these three medications represent the assigned treatment groups in IMPACT, the interpretation of the randomized intervention for each patient may differ based on additional pre-randomization factors, as described in Sections 3.1.5 and 4.5.2, below.*

Randomization and Blinding

The randomization strategy in the IMPACT trial was adequate. Randomization was conducted using an interactive voice response system. The blinding in the IMPACT trial was adequate. The dry powder inhalers for each study drug were identical in appearance. Each dry powder inhaler contained the study medications in two "strips." Each inhaler contained excipients of lactose and magnesium stearate.

Concomitant Medications

The IMPACT protocol required pre-study COPD maintenance medication use at entry, and these medications were continued through the run-in period. All COPD medication used within 3 months prior to screening and during the study were recorded in the electronic case report form (eCRF). All non-COPD medications taken during the study and any changes to concomitant medications were recorded in the eCRF, other than non-study supplied albuterol/salbutamol.

In addition to investigational products, the protocol allowed for the use of the following concomitant medications and therapies for COPD:

- Study-supplied rescue medication
  - salbutamol and/or ipratropium as MDI or nebules
- Short courses (<14 days) of systemic corticosteroids for the treatment of AECOPD and/or pneumonia
- Short courses (<14 days) of antibiotics for the treatment of AECOPD and/or pneumonia
- Any COPD medication deemed medically necessary for the short-term treatment (≤14 days) of a ModSev AECOPD
- Mucolytics such as acetylcysteine
- Long-term oxygen therapy

The protocol also allowed for the use of the following non-COPD medications:

- Vaccinations including influenza, pneumonia, and shingles vaccines
- Medications for rhinitis, topical and ophthalmic corticosteroids, localized corticosteroid injections, beta-blockers, cough suppressants, anti-depressants, smoking cessation, allergy immunotherapy, and anxiolytics
- Short courses (<14 days) of antibiotics for the treatment of AECOPD and/or pneumonia
- Continuous positive airway pressure therapy for sleep apnea

Restricted Medications

The protocol did not allow subjects to use the following therapies during the randomized period:

- Phosphodiesterase-4 inhibitors (e.g., roflumilast)
- Long-term systemic antibiotic therapy
- Non-study drug inhaled and systemic corticosteroids outside of the context of treatment of a ModSev AECOPD

- Non-study drug long- and short-acting muscarinic antagonists
- Non-study drug long- and short-acting beta-2 agonists
- Theophylline
- Cromoglycate and nedocromil inhalers
- Zafirlukast, montelukast, or zileuton
- Acute phase of pulmonary rehabilitation

3.1.5. IMPACT: Pre-study Medications and Run-in

Pre-study Medications

Enrolled and eligible subjects were required to have stable pre-study COPD maintenance medications over the 3 months prior to enrollment. They were to continue these therapies through enrollment and run-in.

Run-in Period

During the run-in period, the subjects continued their existing pre-study COPD medications along with short-acting beta-agonist rescue medication and attended a screening visit. Subjects experiencing a pneumonia event or an AECOPD during the run-in were not randomized. At the end of this run-in, eligible subjects attended a randomization visit and were randomized in a 2:2:1 ratio to FF/UMEC/VI, FF/VI, or UMEC/VI once daily, respectively.

***Reviewer's Comment**: Any pre-study inhaled COPD daily maintenance medication was considered acceptable for enrollment in IMPACT and continued until the date of randomization. Because of this design choice – and despite subjects' history of AECOPD and clinical markers suggesting a potential need for increased COPD maintenance therapy – subjects in IMPACT could have been randomized to a regimen that removed medication classes (e.g. removed a chronic medication such as an ICS) or that included fewer medications than their pre-study maintenance regimen.*

For example, randomization of subjects on pre-study maintenance triple therapy (i.e., pre-study ICS, LABA, and LAMA medications) randomized to UMEC/VI (LAMA/LABA) would result in the abrupt removal of ICS therapy without the addition of any therapeutic modality. Analogously, randomization of subjects on any pre-study COPD maintenance regimen that included ICS would lead to abrupt removal of the ICS when randomized to the UMEC/VI arm. This concept is detailed further in Section 4.5.2. The protocol did not include provisions to prevent or mitigate the risk of protocol-mandated removal of medications in symptomatic subjects receiving pre-study triple therapy, nor to prevent or mitigate a protocol-mandated ICS removal in symptomatic subjects receiving pre-study ICS as part of their COPD maintenance medications.

3.1.6. IMPACT: Efficacy Endpoints and Safety Assessments

Primary Endpoint

The primary efficacy endpoint for the IMPACT trial was the annual rate of on-treatment ModSev AECOPD defined in a manner consistent with previous drug development programs. The primary endpoint had the following co-primary treatment comparisons:

- Annual rate of on-treatment ModSev AECOPD comparing FF/UMEC/VI with UMEC/VI
- Annual rate of on-treatment ModSev AECOPD comparing FF/UMEC/VI with FF/VI

Key Secondary Endpoints

- Change from baseline in trough FEV1 at Week 52 comparing FF/UMEC/VI with FF/VI
- Change from baseline St George's Respiratory Questionnaire Score (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI
- Time-to-first on-treatment ModSev AECOPD comparing FF/UMEC/VI with FF/VI and with UMEC/VI
- Annual rate of on-treatment ModSev AECOPD comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with blood eosinophil count ≥150 cells/µL
- Time-to-first on-treatment ModSev AECOPD comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with blood eosinophil count ≥150 cells/µL
- Annual rate of on-treatment severe (Sev) AECOPD comparing FF/UMEC/VI with FF/VI and with UMEC/VI

Other Efficacy Endpoints

All-cause mortality was one of a long list of roughly 30 'Other' efficacy endpoints, and there were planned pairwise comparisons of FF/UMEC/VI with both FF/VI and UMEC/VI for nearly all of these endpoints.

Reviewer's Comment*: The mortality endpoint was not included in the original design of this 52-week study. As noted in amendment 2, dated April 10th, 2014, ACM was added as an 'other efficacy endpoint'.*

Safety Assessments

The safety assessments of the IMPACT trial have been reviewed during prior submissions, and the schedule of safety assessments during the trial were judged to be adequate for the stated objectives of the trial.

3.1.7. IMPACT: Statistical Methodology

This section focuses on statistical methods for evaluating ACM, the endpoint of interest for this supplement. Statistical methods for the primary and secondary efficacy endpoints are not described in this document. For details of these methods, see the Agency's statistical review

submitted for TRELEGY ELLIPTA under NDA 209482/S-01 on April 11, 2018 by Dr. Jade (Yu) Wang.

ACM Statistical Methodology

ACM was evaluated with the two pairwise comparisons of FF/UMEC/VI versus UMEC/VI and FF/UMEC/VI versus FF/VI in a Cox PH model, with covariates of gender and age. The Kaplan-Meier probabilities of having an event for each treatment arm over time were also presented.

Approach to Control Type I Error Rate

The study was designed and powered to evaluate the primary endpoint of annual rate of on-treatment moderate/severe exacerbations. Multiplicity across the two co-primary and the key secondary treatment comparisons was controlled with an appropriate hierarchical testing strategy. All tests within the predefined statistical testing hierarchy for primary and secondary endpoints achieved statistical significance, with $p<0.001$.

Beyond the pre-specified primary and secondary outcomes, there was a long list of pre-specified 'other' endpoints, most of which were assessed with respect to two pairwise comparisons, as detailed above. No adjustments for multiplicity were made for these other comparisons. Furthermore, a large number of additional exploratory analyses were described in the clinical study report (see Appendix 5.4.2).

Reviewer's Comment: *Given that the evaluation of the effect of ICS on ACM was one of a long list of exploratory analyses of 'other endpoints' for which there was no Type I error control, it is difficult to interpret the results (e.g., estimates, confidence intervals, and p-values) from this analysis. We acknowledge that all analyses of primary and secondary endpoints were statistically significant, that mortality is a clinically important outcome, and that many (but not all) of the exploratory analyses of 'other' endpoints had nominal p-values below the 0.05 threshold. Nevertheless, the ACM evaluation was one of a very large number of exploratory analyses. It would not be unusual to find nominal p-values below 0.05 just by chance when evaluating multiple exploratory endpoints, and such analyses may also be subject to substantial random high bias.*

Pre-specified Efficacy Analysis Populations

The protocol defined four analysis populations: All subjects enrolled, intent-to-treat (ITT), pre-dose electrocardiogram and Transitional Dyspnea Index. The ITT population comprised all randomized subjects, excluding those who were randomized in error and did not receive a dose of study medication. As illustrated in Figure 1, the duration of subject participation was divided into four phases: pre-treatment, on-treatment, post-treatment, and post-study. In this trial, all pre-planned primary efficacy analyses were based on the ITT population using data collected on-treatment.

Follow-up for Mortality in All-Cause Mortality Analyses

All ACM analyses of the IMPACT trial included all randomized subjects, excluding those randomized in error. However, analyses differed in terms of the amount of vital status follow-up that was included. The following analyses were designated by the Applicant:

- Intent-to-treat (ITT): These analyses are "on-treatment" analyses, i.e., they exclude subject data after study drug discontinuation. These analyses include complete follow-up for mortality through Week 52 in 79.2% of the randomized population and were designated by the Applicant and in this review as "ITT."
- Intent-to-treat plus vital status from off-treatment data (ITT+VS): These analyses additionally include vital status follow-up after treatment discontinuation, i.e., they include both on- and off-treatment mortality data. These are "on-study" analyses, i.e., vital status follow-up after study withdrawal missing in patients who dropped out of the study before Week 52. These analyses include complete follow-up for mortality through Week 52 in 94.5% of the randomized population and were designated by the Applicant and in this review as "ITT+VS."
- Intent-to-treat plus vital status follow-up (ITT+VS+VSFU): These analyses include both on- and off-treatment follow-up data, as well as any additional vital status follow-up data in patients who withdrew from the study gathered after the study completed as part of this sNDA. These analyses include complete follow-up for mortality through Week 52 in 99.6% of the randomized population and were designated by the Applicant and in this review as "ITT+VS+VSFU."

Reviewer's Comment*: We note that the term intention-to-treat (ITT) has various definitions but is often used to imply an evaluation including follow-up of all randomized patients regardless of treatment discontinuation. In this case, the Applicant is using the term "ITT" in a different manner, in designating an on-treatment analysis of ACM. We are using "ITT" as the Applicant has defined to avoid confusion created by differences between the Agency and Applicant presentations.*

For the evaluation of treatment effects on mortality in COPD, the Agency is primarily interested in the evaluation of an estimand utilizing a treatment policy strategy for treatment discontinuation, i.e., the difference between FF/UMEC/VI and UMEC/VI in survival regardless of adherence to treatment.[63,64] Therefore, there are substantial limitations to both the ITT and ITT+VS analyses, in that they exclude vital status follow-up data in randomized patients and rely on strong and unverifiable (missing-at-random) assumptions about the subsequent missing data.

The ITT+VS+VSFU analysis provides the most complete mortality data on all patients who were randomized and therefore provides the most reliable results, with the least assumptions, for evaluating treatment effects of interest on mortality. Therefore, this analysis is the primary

focus of the Agency's analyses and discussion. While the ITT+VS+VSFU analysis includes data gathered and analyzed after the trial was unblinded, and caution should be exercised in its interpretation, it provides the most complete dataset available for analysis.

Subgroup Analyses
Subgroup analyses for ACM were planned for the following subgroups:

- Demographic-related: gender, age, race (subgroup analyses by geographical region and body mass index are also presented in the main clinical study report (CSR)
- Medical history-related: exacerbation history, cardiovascular (CV) risk, smoking status, and pneumonia history.

Based on a request from the Agency, the Applicant conducted additional post hoc subgroup analyses on the following two subgroups:

- ACM by pre-study triple therapy
- ACM by pre-study ICS therapy

To assess for a potential interaction between treatment and pre-study triple therapy, ACM was evaluated in the two pairwise comparisons of FF/UMEC/VI compared with UMEC/VI and FF/UMEC/VI compared with FF/VI in a Cox PH model, with treatment and covariates of gender, age, pre-study triple therapy (yes or no), and the interaction term for treatment by pre-study triple therapy. This model is similar to the primary ACM analysis noted above, except for the addition of the last two terms. The Kaplan-Meier probabilities of having an event for each treatment arm over time by pre-study triple therapy were also presented.

A similar analysis was conducted for pre-study ICS therapy in the same pairwise comparisons in a Cox PH model, with treatment and covariates of gender, age, pre-study ICS (yes or no), and the interaction term for treatment by pre-study ICS. Similarly, Kaplan-Meier probabilities by pre-study ICS were also presented.

Additional Analysis Assessing Mortality over Time
Additional post hoc analyses of ACM for several time intervals (≤ 60 days, ≤ 90 days / > 90 days) were carried out to explore the potential time course of observed differences in mortality. These analyses were repeated based on subgroups defined by triple therapy use at Screening or ICS use at Screening.

Sensitivity Analysis
For sensitivity analysis, the PH assumption was examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the plot of ln (-ln[S(t)]) versus ln(t) was produced. Additionally, analyses using the Cox PH model without covariates and the logistic regression analyses without imputation were planned sensitivity analyses.

3.1.8. IMPACT: Additional Information

Independent Data Monitoring Committee
The IMPACT trial included an IDMC whose responsibility was to "protect the ethical and safety interests of subjects recruited into CTT116855 while protecting as far as possible the scientific validity of the data." The IDMC met periodically at predefined times based on study enrollment and no less than every 6 months. The IDMC consisted of three clinicians and a biostatistician, as well as a (b) (4) statistical data analysis center representative.

The IDMC received the study protocol, the investigator brochure, and other materials prior to their initial data review meeting. Each IDMC meeting after enrollment consisted of both open session and closed session meetings. The IDMC met in open session with members of GSK, who made brief data presentations and were available for questions if requested. The closed session meetings were not attended by GSK staff, and GSK employees did not participate in the decision-making of the IDMC.

Open meeting minutes were reviewed in-stream by the Applicant. Closed meeting minutes were available for review by the Applicant after the end of the study.

Compliance with Good Clinical Practices and Financial Disclosures
The Agency's prior review of the IMPACT trial did not note issues with compliance with Good Clinical Practices and financial disclosures that would influence the interpretation of the results of the IMPACT trial.

3.2. Trial HZC113782 (SUMMIT)

This multi-national, randomized, double-blind, placebo-controlled factorial design trial with event-driven duration attempted to provide primary evidence of the efficacy of fluticasone furoate/vilanterol (FF/VI), an FDC of fluticasone furoate 100 µg (FF) and vilanterol 25 µg (VI), on survival in subjects with moderate COPD and a history of – or risk factor for developing – cardiovascular disease compared to its components and placebo.

Trial Designation: HZC113782 (SUMMIT)
Trial Title: A Clinical Outcomes Study to compare the effect of Fluticasone Furoate/Vilanterol Inhalation Powder 100/25mcg with placebo on Survival in Subjects with moderate Chronic Obstructive Pulmonary Disease (COPD) and a history of or at increased risk for cardiovascular disease.
National Clinical Trials Registry Number: NCT01313676
Trial Dates: January 25, 2011 to July 15, 2015
Trial Sites: 1373 sites in 43 countries, including 358 sites in the United States of America
Trial Report Date: May 23, 2016

3.2.1. SUMMIT: Primary Objective

To prospectively evaluate the effect of FF/VI 100/25 once daily compared with placebo on survival in subjects with moderate airflow limitation due to COPD (50 to 70% predicted FEV1) and a history of, or at increased risk for, developing cardiovascular disease.

Reviewer's Comment: The primary objective of the SUMMIT trial was assessment of survival, measured as ACM, and this choice informed the trial design. While the primary comparison of FF/VI versus placebo does not provide evidence of the efficacy of FF on ACM, two comparisons in SUMMIT provide information on the efficacy of FF on ACM endpoints:

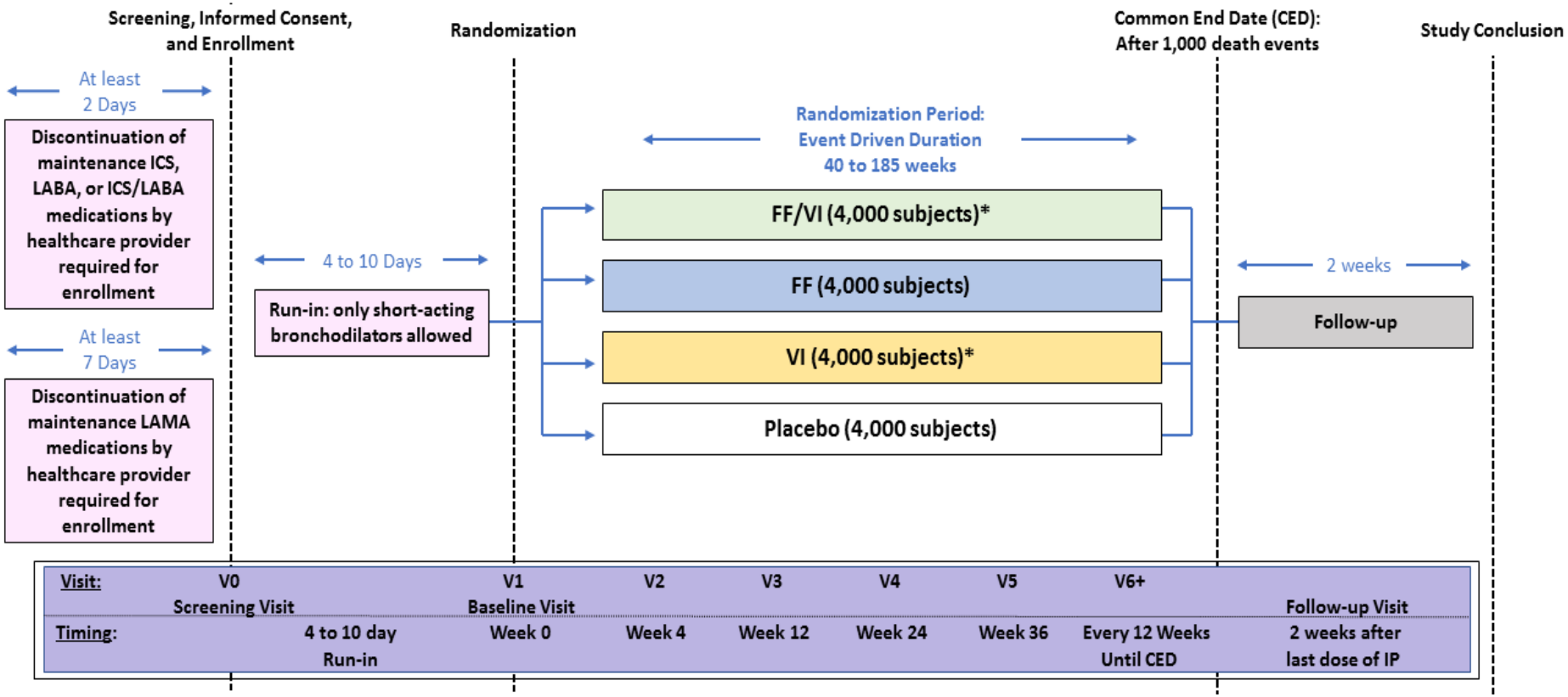
- *FF/VI versus VI*
- *FF versus placebo*

3.2.2. SUMMIT: Design

Trial HZC113782 (SUMMIT) was a multinational, randomized, double-blind, parallel group, placebo-controlled, factorial design trial with an event-driven duration that evaluated the efficacy and safety of a FDC of FF/VI compared to its components and placebo on all-cause mortality endpoints among 16,485 subjects with moderate COPD and cardiovascular risk factors.

A schematic of the trial is shown in Figure 2 below.

Figure 2. SUMMIT: Trial Schematic



Source: Agency. Modified from Applicant's submitted materials for study HZC113782 (SUMMIT).
*In addition to placebo-controlled comparisons of fluticasone, the comparison of these treatment arms provides data on the efficacy of fluticasone on trial endpoints
Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; ICS/LABA: inhaled corticosteroid/long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; FF/VI: fluticasone furoate/vilanterol; FF: fluticasone furoate; VI: vilanterol; CED: common end date; V: visit; IP: investigational product

3.2.3. SUMMIT: Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria for SUMMIT are presented in Appendix 5.5.2. Clinically relevant study design differences between SUMMIT and IMPACT are highlighted below.

Inclusion Criteria

The SUMMIT trial required spirometric documentation of COPD, FEV1 ≥50% and ≤70% predicted normal, confirmation of smoking history, and cardiovascular risk factors. Neither maintenance medication use nor a history of AECOPD in the prior year were required for enrollment.

Reviewer's Comment*: In contrast to IMPACT, the inclusion criteria for SUMMIT did not require demonstration of symptomatic and uncontrolled COPD. Requirements did not include a history of AECOPD in the prior year, and – other than a modified Medical Research Council dyspnea score threshold – the inclusion criteria did not require further demonstration of symptom severity. In addition, the SUMMIT trial's inclusion criteria did not specify a requirement for pre-study COPD maintenance treatment, although it did not specifically exclude subjects with pre-study COPD maintenance treatment from enrolling provided they followed the instructions for medication discontinuation during the pre-enrollment period and run-in (see Section 3.2.5 below).*

Exclusion Criteria

Importantly, subjects were excluded from the SUMMIT trial if they used particular medications (e.g., ICS, LABA, oral corticosteroids) within set time periods prior to enrollment, consistent with their pre-enrollment medication removal policy (see Section 3.2.5). In conjunction with this pre-enrollment medication removal, any subject who experienced a ModSev AECOPD or pneumonia event during the run-in period was also excluded.

Reviewer's Comment*: The required pre-enrollment discontinuation of inhaled maintenance medications as well as the 4- to 10-day run-in on only short-acting bronchodilators may have discouraged enrollment of subjects with uncontrolled COPD. See Section 3.2.5 for additional details of medication discontinuation prior to screening.*

3.2.4. SUMMIT: Treatments and Concomitant Medications

Details of randomization, blinding, and concomitant treatment rules in the SUMMIT trial are presented in Appendix 5.5.2. Clinically relevant study design differences between SUMMIT and IMPACT are highlighted below.

Treatment Groups

Eligible subjects were randomized to one of the following study treatments administered by oral inhalation once daily via dry powder inhaler from the date of randomization until the common end date, CED (~40-185 weeks):

- FF/VI (100/25 μg)
- FF (100 μg)
- VI (25 μg)
- Placebo (Pbo)

Reviewer's Comment*: Similar to the IMPACT trial, the SUMMIT trial allowed any pre-study COPD maintenance medication regimen. Because of this, subjects could potentially be randomized to a regimen that took medication modalities away (i.e. removed a chronic medication modality such as ICS) or that included fewer medications than their pre-study maintenance regimen. For example, randomization of subjects on pre-study maintenance ICS/LABA randomized to VI would result in removal of ICS therapy without the addition of any therapeutic modality. In contrast to IMPACT, however, SUMMIT required ICS removal prior to enrollment and SUMMIT also included a run-in period where only short-acting COPD medications were allowed.*

Randomization and Blinding

The randomization and blinding in the SUMMIT trial were adequate for the purposes of evaluating this sNDA. For further details, see Appendix 5.5.2.

Concomitant Medications

In addition to investigational products, the protocol allowed for the use of albuterol as a rescue medication, ipratropium and mucolytics as additional COPD therapy, short-term courses oral corticosteroids for the treatment of AECOPD, and short-term course of antibiotics for the treatment of AECOPD or pneumonia. The protocol allowed LAMA to be initiated for subjects who experienced a severe AECOPD or multiple moderate AECOPDs. Further details are presented in Appendix 5.5.2.

Restricted Medications

The protocol did not allow subjects to use the following therapies during the randomized period:

- Any ICS (other than investigational product)
- Any LABA (other than investigational product)

3.2.5. SUMMIT: Pre-study Medications and Run-in

The SUMMIT trial's handling of pre-study medications and run-in are relevant to the discussion of ACM, due to clinically notable differences compared to the study design of the IMPACT trial.

Pre-study Medications

The SUMMIT protocol did not require evidence of pre-study COPD maintenance medication use as an enrollment criterion, but subjects with pre-study COPD maintenance regimens were allowed to enroll.

As a protocol-specified criterion for enrollment, prior to the screening visit, the SUMMIT protocol required a potential subject's healthcare provider to discontinue any inhaled maintenance therapy for COPD other than short-acting bronchodilators. The protocol required discontinuation of ICS, LABA, and ICS/LABA medications for at least 2 days prior to enrollment, and discontinuation of LAMA medications for at least 7 days prior to enrollment. Within the limits of these pre-enrollment rules, all combinations of pre-study maintenance COPD medications were allowed.

The protocol addressed the timing of protocol-mandated maintenance medication prior to screening and informed consent in two ways. First, the SUMMIT protocol's Selection of Study Population (i.e., inclusion/exclusion criteria) section states the following (bold text maintained from protocol):

> ***Note regarding appropriate subject selection:***
> *Potential subjects should not have been withdrawn from medications necessary for their disease management solely for the purpose of enrolling in this study. Patients who were currently controlled on short-acting medications or who could be adequately managed with short-acting inhaled medications and oral therapies (including theophylline or roflumilast) based on physician opinion were appropriate subjects for this study.*

Second, the SUMMIT protocol's Critical Baseline Assessments section states the following (bold text maintained from protocol):

> ***No study related procedures may be performed until the informed consent form document has been reviewed with and signed by the subject****. A pre-screening visit may be required in order to administer and discuss the informed consent before any changes are made to the subject's current medication regimen. Washout of any prohibited medication, which is done only if deemed appropriate by the Investigator in discussion with the subject,* ***MUST NOT OCCUR prior to the informed consent being discussed and signed****. The informed consent may be administered and discussed at the screening visit if the subject does not take or has not taken any protocol excluded medication.*

Run-in Period

After informed consent, a screening visit, and enrollment, subjects entered a 4- to 10-day run-in period. During the run-in, subjects were only allowed to use inhaled short-acting bronchodilator medications for COPD control. Subjects with AECOPD during the run-in were not eligible to be randomized. At the end of this run-in, eligible subjects attended a randomization visit and were randomized in a 1:1:1:1 ratio to FF/VI, FF, VI, or placebo, once daily.

***Reviewer's Comment**: The required pre-study discontinuation of inhaled LAMA for ≥7 days, discontinuation of other inhaled COPD maintenance medications for ≥2 days, and the knowledge of a subsequent run-in allowing short-acting bronchodilators alone in the SUMMIT trial's moderate COPD population may have deterred enrollment of subjects who would be predicted to be at highest risk of detrimental ICS removal effects. The removal of pre-study inhaled COPD maintenance therapies during the run-in as well as the exclusion of subjects with an exacerbation during the SUMMIT trial's 4- to 10-day run-in may have excluded additional subjects (i.e., due to AECOPD or death events during those periods) at high risk of ICS removal effects. Because medication withdrawal may have occurred prior to trial enrollment and data collection, the trial's observed data on pre-randomization events may not be representative of all such events.*

3.2.6. SUMMIT: Primary Efficacy Endpoint

Primary Endpoint

- Time to death from any cause comparing FF/VI versus Pbo

Primary Endpoint Definition

The protocol mandated the recording of survival status data for each subject at every visit. In the case of subjects who prematurely withdrew from investigational product, the protocol mandated assessment of survival status at 3-month intervals by phone call or other form of contact.

All deaths occurring after randomization until the end of the study were reported as serious adverse events within 24 hours of the principal investigator becoming aware of the event.

The Investigator assigned a cause of death based on contact with the attending physician, details in the death certificate, autopsy findings, and any other available clinical evidence, and entered the cause of death in the eCRF. In addition, a Clinical Endpoint Committee performed categorization of cause of death after review of the eCRF data and additional information available. The cause of death reported by the Clinical Endpoint Committee formed the primary basis for all analyses involving cause of death.

3.2.7. SUMMIT: Statistical Methodology

Hypothesis tests for main effects used a 2-sided test at the 5% level of significance. Tests for interactions were 2-sided at the 10% level of significance. If assumptions of the proposed method of analyses are not met, alternative methods of analyses were to be used. The following pairwise comparisons were made in the original analysis:

- FF/VI versus placebo
- FF/VI versus VI

- FF/VI versus FF
- FF versus placebo
- VI versus placebo

The specific pairwise comparisons of interest to determine whether SUMMIT supports the Applicant's ACM claim from IMPACT are FF/VI compared with VI, and FF compared with placebo.

ACM was evaluated in a Cox PH model, with covariates of gender and age. The Kaplan-Meier probability of having an event and 95% CIs for each treatment arm were also presented.

Planned analyses to support the primary analysis were:

- Cox regression without covariates, which should give identical results to the Log Rank test.
- Cox regression with covariates, gender, age, region and participation in the Arterial Stiffness substudy (yes or no).

Pre-specified Efficacy Analysis Populations

SUMMIT's intent-to-treat efficacy (ITT-E) population is the population of interest for the review of ACM in the context of this sNDA.

The ITT-E population consisted of all subjects in the Safety Population, with the exception of 83 subjects recruited at 5 sites that were closed as the result of audit findings or information that implied the integrity of the data had been compromised. These subjects were excluded from the ITT-E population (and all efficacy analyses). The decision was formally documented prior to unblinding of the trial.

Re-analysis of SUMMIT to determine whether there is supporting evidence for IMPACT ACM Claim

Post hoc analyses of ACM (using the first 365 days of study data, to compare to IMPACT's one-year duration) included:

- Time to ACM including on- and off-treatment data (ITT-E)
- Analysis of ACM at the ≤ 90-Day timepoint using on-treatment data and on- and off-treatment data (ITT-E). These analyses were repeated based on ICS use at Screening.

3.3. Trial SCO30003-01 (TORCH)

This three-year, multicenter, randomized, double-blind, placebo-controlled factorial design trial attempted to provide primary evidence of the efficacy of fluticasone propionate/salmeterol (FP/SAL), an FDC of fluticasone propionate 500 µg (FP) and salmeterol 50 µg (SAL), on survival in subjects with moderate to very severe COPD compared to its components and placebo.

Trial Designation: SCO30003-01 (TORCH)
Trial Title: A multicenter, randomized, double-blind, parallel group, placebo-controlled study to investigate the long-term effects of salmeterol/fluticasone propionate (SERETIDE™/ VIANI™/ ADVAIR™) 50/500 mcg bd, salmeterol 50mcg bd and fluticasone propionate 500 mcg bd, all delivered via the DISKUS™/ ACCUHALER™ inhaler, on the survival of subjects with chronic obstructive pulmonary disease (COPD) over 3 years of treatment.
National Clinical Trials Registry Number: NCT00268216
Trial Dates: September 7, 2000 to November 8, 2005
Trial Sites: 466 sites in 42 countries, including 190 sites in the United States of America
Trial Report Date: July 13, 2006

3.3.1. TORCH: Primary Objective

To demonstrate a significant reduction in all-cause mortality in COPD subjects treated with fluticasone propionate/salmeterol compared with placebo, when added to usual COPD therapy.

Reviewer's Comment: The primary objective of the TORCH trial was assessment of survival, measured as ACM, and this choice informed the trial design. While the primary comparison of FP/SAL versus placebo does not provide evidence of the efficacy of FP on ACM, two comparisons in TORCH provide information on the efficacy of FP on ACM endpoints:

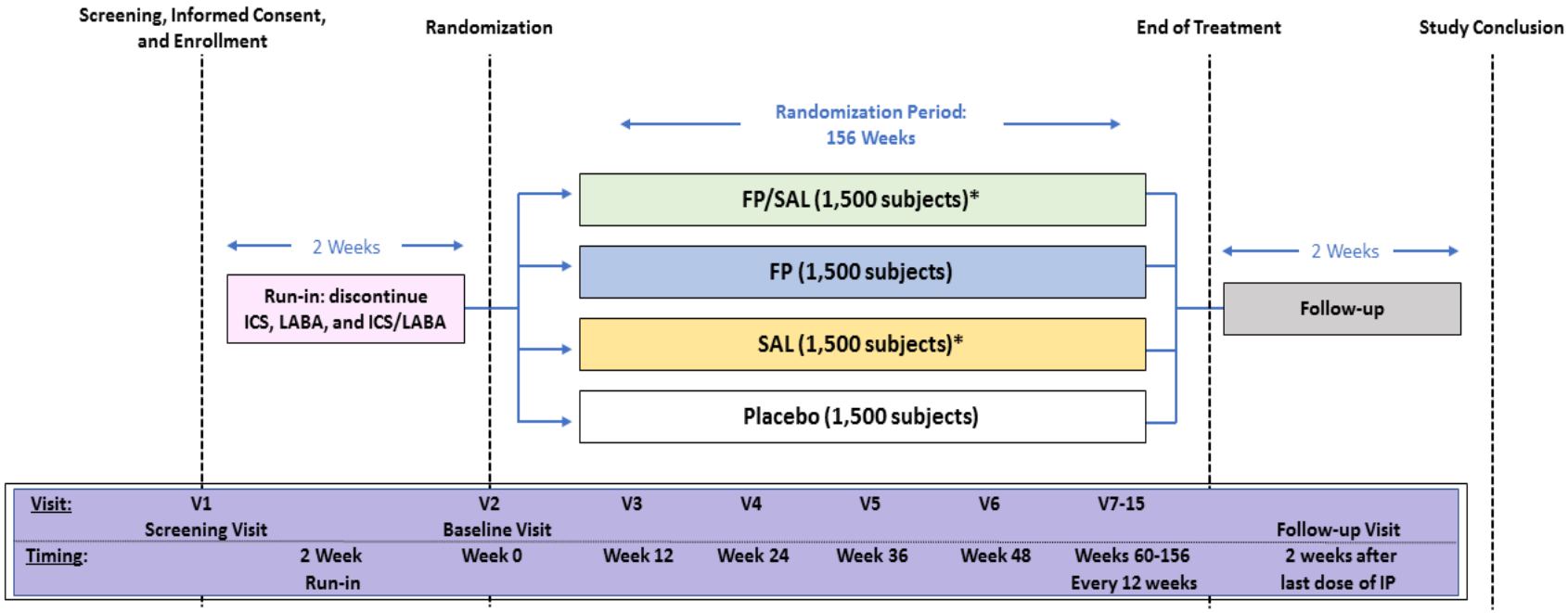
- *FP/SAL versus SAL*
- *FP versus placebo*

3.3.2. TORCH: Design

Trial SCO30003-01 (TORCH) was a multicenter, randomized, double-blind, parallel group, placebo-controlled, factorial design trial with a 156-week treatment duration that evaluated the efficacy and safety of an FDC of FP/SAL compared to its components and placebo on all-cause mortality endpoints among 6,184 subjects with moderate to severe COPD.

A schematic of the trial is shown in Figure 3 below.

Figure 3. TORCH: Trial Schematic



Source: Agency. Modified from Applicant's submitted materials for study SCO30003-01 (TORCH).
*In addition to placebo-controlled comparisons of fluticasone, the comparison of these treatment arms provides data on the efficacy of fluticasone on trial endpoints
Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; ICS/LABA: inhaled corticosteroid/long-acting beta-agonist; FP/SAL: fluticasone propionate/salmeterol; FP: fluticasone propionate; SAL: salmeterol; Pbo: placebo; V: visit; IP: investigational product

3.3.3. TORCH: Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria for TORCH are presented in Appendix 5.6.2. Clinically relevant study design differences between TORCH and IMPACT are highlighted below.

Inclusion Criteria

The TORCH trial required a spirometric assessment consistent with COPD, pre-bronchodilator FEV1 <60% predicted normal, confirmation of smoking history, and poor bronchodilator reversibility. Neither maintenance medication use nor a history of AECOPD in the prior year were required for enrollment.

Reviewer's Comment*: In contrast to IMPACT, the TORCH trial's inclusion criteria did not specify a threshold based on assessment of history of AECOPD in the prior year, nor did the criteria specify a threshold based on assessment of the patient's symptomatic burden by patient-reported outcome measurement tools such as the SGRQ. In addition, the TORCH trial's inclusion criteria did not specify a requirement for pre-study COPD maintenance treatment.*

Exclusion Criteria

The TORCH trial excluded subjects if they experienced an AECOPD in the run-in period, among other criteria.

3.3.4. TORCH: Treatments and Concomitant Medications

Details of randomization, blinding, and concomitant treatment rules in the TORCH trial are presented in Appendix 5.6.2. Clinically relevant study design differences between TORCH and IMPACT are highlighted below.

Treatment Groups

Eligible subjects were randomized to one of the following study treatments administered by oral inhalation twice daily via a dry powder inhaler for 156 weeks:

- FP/SAL (500/50 µg)
- FP (500 µg)
- SAL (50 µg)
- Pbo

Reviewer's Comment*: Similar to the IMPACT and SUMMIT trials, the TORCH trial allowed any pre-study COPD maintenance medication regimen. Because of this, subjects could potentially be randomized to a regimen that took medication modalities away (i.e. removed a chronic medication modality such as ICS) or that included fewer medications than their pre-study maintenance regimen. For example, randomization of subjects on pre-study maintenance ICS/LABA*

randomized to SAL would result in removal of ICS therapy without the addition of any therapeutic modality. In contrast to IMPACT, however, TORCH required ICS removal prior to randomization during a two-week run-in period where only short-acting COPD medications were allowed.

Randomization and Blinding

The randomization and blinding strategies in the TORCH trial were adequate for the purpose of evaluating this sNDA. For further details, see Appendix 5.6.2

Concomitant Medications

In addition to investigational products, the protocol allowed for the use of albuterol rescue medication, short-acting beta-agonists, short-acting muscarinic antagonists, theophyllines, and oral corticosteroids for the treatment of AECOPD. The protocol designated that all medication for other disorders may be used.

Restricted Medications

The protocol did not allow subjects to use the following therapies during the randomized period:

- Any ICS (other than investigational product)
- Any long-acting bronchodilators, including any LABA medication or LAMA medication (other than investigational product)
- Long-term oxygen use for ≥12 hours per day on entry
- Long-term use of oral corticosteroids, defined as continuous use for >6 weeks

3.3.5. TORCH: Pre-study Medications and Run-in

The TORCH trial's handling of pre-study medications and run-in are relevant to the discussion of ACM, due to clinically notable differences compared to the study design of the IMPACT trial.

Pre-study Medications

The TORCH protocol did not require evidence of pre-study COPD maintenance medication use as an enrollment criterion.

Run-in Period

The protocol required discontinuation of any pre-study ICS- and LABA-containing medications in subjects enrolled in TORCH for the duration of the two-week run-in period. Subjects experiencing an AECOPD during the run-in period were not randomized. At the end of this run-in, eligible subjects attended a randomization visit and were randomized in a 1:1:1:1 ratio to FP/SAL, FP, SAL, or placebo.

***Reviewer's Comment**: The removal of pre-study inhaled COPD maintenance therapies during the run-in as well as the exclusion of subjects who experienced an exacerbation during the TORCH trial's 14-day run-in may have excluded*

subjects (i.e., due to AECOPD or death events during this period) at high risk of ICS removal effects.

3.3.6. TORCH: Primary Efficacy Endpoints and Safety Assessments

Primary Endpoint

- ACM in the 3 years post-randomization amongst all subjects randomized to treatment comparing FP/SAL versus Pbo.

Primary Endpoint Definition

The protocol mandated recording of survival status of each subject at every visit. The protocol mandated assessment of survival status at 3-month intervals for subjects who prematurely withdrew from investigational product.

All deaths occurring after randomization until the end of the study were reported as serious adverse events within 24 hours. However, during long-term follow-up, only study drug-related deaths were reported in that manner.

The Investigator assigned a cause of death based on contact with the attending physician, details in the death certificate, autopsy findings, and any other available clinical evidence and entered it in the eCRF. In addition, a Clinical Endpoint Committee performed categorization of cause of death after review of the eCRF data and additional information available. The cause of death reported by the Endpoint Committee formed the primary basis for all analyses involving cause of death.

3.3.7. TORCH: Statistical Methodology

There were two interim analyses planned for this study, and for that reason the hypothesis tests for main effects used a 2-sided test that was adjusted downward so that the significance level for the overall study was 5%.

The following pairwise comparisons were made:

- FP/SAL versus placebo
- FP/SAL versus SAL
- FP/SAL versus FP
- FP versus placebo
- SAL versus placebo

The specific pairwise comparisons of interest to determine whether TORCH supports the Applicant's ACM claim from IMPACT are FP/SAL compared with SAL, and FP compared with placebo.

Difference in times to death from any cause between the combination-therapy group and the placebo group was analyzed with the use of the log-rank test (with stratification according to smoking status). A Cox PH model with covariates of smoking status, age, sex, baseline FEV1, body mass index, and region to estimate a hazard ratio was used as a supportive secondary analysis for the original submission.

Pre-specified Efficacy Analysis Populations

TORCH's intention-to-treat efficacy (ITT) population is the population of interest for the review of ACM in the context of this sNDA. The ITT was defined as all subjects who were randomized to treatment and who received at least one dose of trial medication. If any subjects inadvertently received a different treatment for the duration of the study, or were inadvertently given more than one treatment, their data were assigned to the treatment group to which they were originally randomized, irrespective of which treatment they actually took.

Re-analysis of TORCH to determine whether there is supporting evidence for IMPACT ACM Claim

Post hoc analyses of ACM (using the first 365 days of study data, to compare to IMPACT's one-year duration):

- Time to ACM including on- and off-treatment data (ITT).
- Subgroup analyses of time to ACM based on ICS use at Screening (yes/no) for ITT.
- Analysis of ACM at the ≤ 90-Day timepoint using on-treatment data and on- and off-treatment data (ITT). These analyses were repeated based on ICS use at Screening.

4. Review of Efficacy

4.1. Demographics

4.1.1. Demographics Across Trials

The IMPACT, SUMMIT, and TORCH trials included subjects with similar demographics of age and gender (Table 3). In addition, all three trials included a population who primarily identified as white. In contrast to baseline disease characteristics (see Section 4.2), there were no clinically significant differences in demographic characteristics across trials. While smoking history and the proportion of current versus former smokers differed across trials, the direct effect of these data on the interpretation of ACM from each trial is unclear.

Table 3. Demographics Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH

Characteristics	IMPACT n (%)	SUMMIT n (%)	TORCH n (%)
N	10,355	16,485	6,112
Sex			
Female	3,485 (34)	4,196 (25)	1,481 (24)
Male	6,870 (66)	12,289 (75)	4,631 (76)
Age			
Mean in years (SD)	65.3 (8.3)	65.2 (7.9)	65 (8.3)
Age group			
≤65 years	4,724 (46)	7,384 (45)	2,673 (44)
≥65 to <75 years	4,225 (41)	7,020 (43)	2,670 (44)
≥75 years	1,406 (13)	2,081 (13)	769 (13)
Smoking history			
Mean pack-years (SD)	46.6 (26.6)	40.8 (24.4)	48.5 (27.4)
Current	3,587 (35)	7,678 (47)	2,630 (43)
Former	6,768 (65)	8,807 (53)	3,482 (57)
Geographical region			
US	2,406 (23)	2,590 (16)	1,388 (23)
Not US	7,949 (77)	13,895 (84)	4,724 (77)
Race			
AI/AN	218 (2)	27 (<1)	N/A
Asian	1,679 (16)	2,723 (17)	769 (13)
Black or African American*	264 (3)	258 (2)	95 (2)
NHPI	7 (<1)	5 (<1)	N/A
White	8,083 (78)	13,357 (81)	5,006 (82)
Multiple**	103 (<1)	115 (<1)	N/A
Other or missing***	1 (<1)	0	242 (4)

Source: Reviewer. Adapted from data from Clinical Study Reports for IMPACT, SUMMIT, and TORCH. Note: IMPACT and TORCH used ITT population and SUMMIT used ITT-E population.
*Category title for SUMMIT trial was “African American or African Heritage”; category title for TORCH trial was “Black”
**Category title for SUMMIT was “Mixed race”; the TORCH trial did not make provision for data collection of multiracial individuals
***Data on subjects with race identification as American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or Multiple was not provided; data on subjects with race identification categorizations of “Other” and “American Hispanic” from the TORCH trial are presented for the TORCH trial as “Other” in this table
Abbreviations: AI/AN, American Indian or Alaska Native; ITT, intention to treat; NHPI, Native Hawaiian or Pacific Islander; US, United States

4.1.2. IMPACT: Demographics

There were no clinically meaningful differences between study arms in the collected demographic characteristics of subjects in the IMPACT trial (see Table 4). IMPACT enrolled a population of COPD subjects who were on average 65 years of age, primarily male, and primarily identified as white, similar to other COPD trials used to support marketing. Smoking history and proportion of current versus former smokers were similar across treatment arms.

Table 4. IMPACT: Demographic Characteristics, ITT Population

Characteristics	FF/UMEC/VI	FF/VI	UMEC/VI	Total
N	4,151	4,134	2,070	10,355
Sex				
Female	1,385 (33.4)	1,386 (33.5)	714 (34.5)	3,485 (33.7)
Male	2,766 (66.6)	2,748 (66.5)	1,356 (65.5)	6,870 (66.3)
Age				
Mean in years (SD)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
Age group				
<65 years	1,886 (45.4)	1,876 (45.4)	962 (46.5)	4,724 (45.6)
≥65 to <75 years	1,700 (41.0)	1,693 (41.0)	832 (40.2)	4,225 (40.8)
≥75 years	565 (13.6)	565 (13.7)	276 (13.3)	1,406 (13.6)
Smoking history				
Mean pack-years (SD)	46.7 (26.7)	46.4 (26.2)	47.0 (27.4)	46.6 (26.6)
Current	1,436 (35.0)	1423 (34.0)	728 (35)	3,587 (35.0)
Former	2,715 (65.0)	2711 (66.0)	1,342 (65)	6,768 (65.0)
Geographical region				
US	978 (23.6)	950 (23)	478 (23.1)	2,406 (23.2)
Not US	3173 (76.4)	3,184 (77)	1,592 (76.9)	7,949 (76.8)
Race				
Missing	0	1 (<1)	0	1 (<1)
AI/AN	87 (2.1)	86 (2.1)	45 (2.2)	218 (2.1)
Asian	668 (16.1)	676 (16.4)	335 (16.2)	1,679 (16.2)
Black or African American	122 (2.9)	99 (2.4)	43 (2.1)	264 (2.5)
Multiple	41 (<1)	45 (1.1)	17 (<1)	103 (<1)
NHPI	2 (<1)	3 (<1)	2 (<1)	7 (<1)
White	3,231 (77.8)	3,224 (78)	1,628 (78.6)	8,083 (78.1)

Source: Reviewer. Adapted from Agency's previous review of the IMPACT study under NDA 209482-S0001
All values are expressed as n (%) unless specified otherwise.
Abbreviations: AI/AN, American Indian or Alaska Native; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; NHPI, Native Hawaiian or Pacific Islander; SD, standard deviation; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

4.1.3. SUMMIT: Demographics

There were no clinically meaningful differences between study arms in the collected demographic characteristics of subjects in the SUMMIT trial (see Table 26, in Appendix 5.5.4). As in the IMPACT trial and other COPD trials used to support marketing, SUMMIT enrolled a population of COPD subjects who were on average 65 years of age, primarily male, and who primarily identified as white. Smoking history and proportion of current versus former smokers were similar across treatment arms.

4.1.4. TORCH: Demographics

There were no clinically meaningful differences between study arms in the collected demographic characteristics of subjects in the TORCH trial (see Table 35, in Appendix 5.6.4). Similar to the IMPACT trial, TORCH enrolled a population of COPD subjects who were on average 65 years of age, primarily male, and who primarily identified as white, similar to other COPD trials used to support marketing. Smoking history and proportion of current versus former smokers were similar across treatment arms.

4.2. Baseline Disease Characteristics and Pre-Study Medication Groups

4.2.1. Baseline Disease Characteristics Across Trials

As shown in Table 5, baseline COPD disease characteristics differed between the IMPACT, SUMMIT, and TORCH trials in clinically important ways. The randomized populations of IMPACT and TORCH had more severe COPD by lung function and symptoms (i.e., as measured by the St. George's Respiratory Questionnaire total score) compared to SUMMIT.

While IMPACT and TORCH show similar baseline disease characteristics in lung function and patient-reported outcomes, all three trials differ substantially regarding exacerbation history. IMPACT enrolled a population with a substantially higher proportion of patients with frequent exacerbations (defined as ≥2 moderate or ≥1 severe AECOPD in the prior year) than both TORCH and SUMMIT (70%, 21%, and 36%, respectively). Since higher numbers of prior AECOPD are associated with higher rates of future AECOPD, this approach to enrich the trial for frequent exacerbators aligned with the IMPACT trial's objective of providing evidence of a difference on ModSev AECOPD endpoints with FF/UMEC/VI versus UMEC/VI and FF/VI, to demonstrate the contribution of both the FF and the UMEC to the FDC with respect to exacerbations. IMPACT also enrolled a comparatively higher proportion of patients with a history of Sev AECOPD (26%). Literature suggests that Sev AECOPD are associated with ACM.

Reviewer's Comment*: The baseline characteristics of subjects in the IMPACT trial indicate a clinically uncontrolled COPD population in terms of lung function, symptoms, and exacerbation history. Compared to the IMPACT trial, the baseline characteristics of subjects in the SUMMIT trial describe a less severe population with better lung function and symptom control, and – most importantly – a lower proportion of patients with frequent exacerbations. TORCH also included a lower proportion of frequent exacerbators compared to the IMPACT trial. These differences are important to note when making comparisons across trials.*

Table 5. Baseline Disease Characteristics Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH

Characteristics	IMPACT	SUMMIT	TORCH
Total	10,355	16,485	6,112
Postbronchodilator FEV1			
N with available data	10,345	16,483	6,111
Mean FEV1%p (SD)	45.5 (14.8)	59.7 (6.1)	44.0 (12.4)
GOLD spirometric severity grade*			
Mild	22 (<1)	8 (<1)	N/A
Moderate	3,719 (36)	16,176 (98)	2,156 (35)
Severe	4,982 (48)	297 (2)	3,019 (49)
Very severe	1,624 (16)	2 (<1)	937 (15)

Characteristics	IMPACT	SUMMIT	TORCH
Moderate AECOPD history**			
N with available data	10,355	16,485	6,112
<2	5,478 (53)	14,906 (90)	4,565 (75)
≥2	4,877 (47)	1,579 (10)	1,547 (25)
Severe AECOPD history**			
N with available data	10,355	16,485	6,112
0	7,684 (74)	14,280 (87)	5,005 (82)
≥1	2,671 (26)	2,205 (13)	1,107 (18)
AECOPD category			
N with available data	10,355	16,485	6,112
<2 moderate and no severe	3,056 (30)	13,057 (79)	3,914 (64)
≥2 moderate or ≥1 severe	7,299 (70)	3,428 (21)	2,198 (36)
SGRQ total score			
N with analyzable data	10,250	4,403	4,951
Mean (SD)	50.6 (16.9)	46.6 (16.0)	49.3 (17.1)

Source: Reviewer. Adapted from CSR and IR Responses of IMPACT, SUMMIT, and TORCH trials. Note: IMPACT and TORCH used ITT population and SUMMIT used ITT-E population. All values are expressed as n (%) unless specified otherwise.
* GOLD spirometric severity grades: Mild = FEV1 ≥80%p; moderate = FEV1 <80%p to ≥50%p; severe = FEV1 <50%p to ≥30%p; very severe = FEV1 <30%
** All enrolled COPD subjects were required to have a history of moderate or severe AECOPD in the prior 12 months.
Abbreviations: %p, percent predicted; AECOPD, acute exacerbation of COPDFEV1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ITT, intention to treat; SGRQ, St. George's Respiratory Questionnaire

4.2.2. Pre-study Medication Groups Across Trials

The higher symptom severity of COPD in the IMPACT trial population is consistent with the pre-study maintenance medication use (Table 6). In IMPACT, 38% of the trial population utilized ICS, LABA, and LAMA triple therapy as COPD maintenance therapy prior to trial enrollment, while 71% of the population was treated with a pre-study regimen that included ICS. In contrast, less than 10% of subjects in SUMMIT utilized pre-study triple therapy regimens, while only 33% were prescribed pre-study ICS-containing regimens. Triple therapy was not widely available or advocated at the time of the TORCH trial, and only one randomized subject had a history of pre-study triple therapy use in that trial. Less than half of the TORCH trial subjects were prescribed pre-study ICS-containing regimens.

When compared to SUMMIT and TORCH, the IMPACT trial included a higher proportion of subjects with pre-study triple therapy and pre-study ICS as part of their COPD maintenance medications prior to enrollment.

Table 6. Pre-study COPD Medication Groups Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH

Medication Groups	IMPACT	SUMMIT	TORCH
Total	10,355	16,485	6,122
Triple therapy*			
Yes	3,970 (38)	1,433 (9)	1 (<1)
No	6,385 (62)	15,052 (91)	6,121 (99)
ICS-containing regimen			
Yes	7,360 (71)	5,486 (33)	2,976 (49)
No	2,995 (29)	10,999 (67)	2,984 (49)
Medication not reported*			
Yes	0	0	152 (2)

Source: Reviewer. Adapted from CSR and IR Responses of IMPACT, SUMMIT, and TORCH trials. Note: IMPACT and TORCH used ITT population and SUMMIT used ITT-E population. All values are expressed as n (%) unless specified otherwise.
* Triple therapy: ICS, LABA, and LAMA-containing regimen
** For the purposes of subgroup analyses, subjects with no pre-study medication reported are included in the "pre-study triple therapy = No" and "pre-study ICS therapy = No" subgroups throughout the review.
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist

4.2.3. IMPACT: Baseline Disease Characteristics and Pre-Study Medication Groups

There were no clinically meaningful differences in the measured baseline disease characteristics between study arms in the IMPACT trial (see Table 7). IMPACT enrolled COPD patients with uncontrolled symptoms (by SGRQ and CAT scores) and frequent exacerbations (i.e., those subjects with ≥2 moderate or ≥1 severe AECOPD in the prior year), despite COPD maintenance treatment.

Table 7. IMPACT: Baseline Disease Characteristics, ITT Population

Characteristics	FF/UMEC/VI	FF/VI	UMEC/VI	Total
Total	4,151	4,134	2,070	10,355
Postbronchodilator FEV1				
N with available data	4,145	4,133	2,069	10,345
Mean FEV1%p (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)
GOLD spirometric severity grade*				
Mild	10 (<1)	8 (<1)	4 (<1)	22 (<1)
Moderate	1,535 (37)	1,455 (35)	729 (35)	3,719 (36)
Severe	1,934 (47)	2,031 (49)	1,017 (49)	4,982 (48)
Very severe	666 (16)	639 (15)	319 (15)	1,624 (16)
Moderate AECOPD history**				
N with available data	4,151	4,134	2,070	10,355
<2	2,184 (53)	2,213 (54)	1,081 (52)	5,478 (53)
≥2	1,967 (47)	1,921 (46)	989 (48)	4,877 (47)
Severe AECOPD history**				
N with available data	4,151	4,134	2,070	10,355
0	3,064 (74)	3,065 (74)	1,555 (75)	7,684 (74)
≥1	1,087 (26)	1,069 (26)	515 (25)	2,671 (26)
AECOPD category				
N with available data	4,151	4,134	2,070	10,355
<2 moderate and no severe	1,198 (29)	1,242 (30)	616 (30)	3,056 (30)
≥2 moderate or ≥1 severe	2,953 (71)	2,892 (70)	1,454 (70)	7,299 (70)

Characteristics	FF/UMEC/VI	FF/VI	UMEC/VI	Total
SGRQ total score				
N with analyzable data	41,08	4,092	2,050	10,250
Mean (SD)	50.8 (16.8)	50.7 (17.0)	50.2 (16.7)	50.6 (16.9)
COPD assessment test score				
N with analyzable data	4142	4124	2061	10,327
Median	20	19	20	20
25-75 percentile	15, 24	15, 24	15, 24	15, 24

Source: Reviewer. Adapted from Applicant's clinical study report and submitted materials for the IMPACT trial.
All values are expressed as n (%) unless specified otherwise.
* GOLD spirometric severity grades: Mild = FEV1 ≥80%p; moderate = FEV1 <80%p to ≥50%p; severe = FEV1 <50%p to ≥30%p; very severe = FEV1 <30%
** All enrolled COPD subjects were required to have a history of moderate or severe AECOPD in the prior 12 months.
Abbreviations: %p, percent predicted; AECOPD, acute exacerbation of COPD; FEV1, forced expiratory volume in one second; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ITT, intention to treat; SGRQ, St. George's Respiratory Questionnaire; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

Pre-study Medication Groups

There were no clinically meaningful differences in baseline (i.e., pre-study) COPD medication between study arms in the IMPACT trial (see Table 8). However, as noted in Section 3.1 and detailed in Section 4.5.2, the trial design and randomization scheme of the IMPACT trial led to the abrupt removal of ICS therapy among subjects with pre-study triple therapy or pre-study ICS therapy who were randomized to the UMEC/VI arm.

***Reviewer's Comment**: It is important to note that subjects with pre-study triple therapy (38% of the enrolled population) could not have added a therapeutic class to their medication regimen by randomization. Randomization of pre-study triple therapy subjects could lead only to removal of one therapeutic class (i.e., ICS removal if randomized to the UMEC/VI arm; LAMA removal if randomized to the FF/VI arm) or the continuation of triple therapy (i.e., if randomized to the FF/UMEC/VI arm). Despite many of the subjects in IMPACT exhibiting uncontrolled COPD and frequent exacerbations on their pre-study medications (e.g., triple therapy), the design of the IMPACT trial led to removal of a therapeutic class in the majority of these pre-study triple therapy subjects.*

***Reviewer's Comment**: The IMPACT trial enrolled a high proportion of subjects with ICS as part of their pre-study maintenance COPD medication regimens (71%). Despite uncontrolled symptoms and frequent exacerbations on pre-study COPD therapy (e.g. indications for ICS use and also a potentially compelling indication for additional therapy), randomization in the IMPACT trial led to ICS removal among those pre-study ICS subjects randomized to the UMEC/VI arm.*

Table 8. IMPACT: Pre-study COPD Medication Groups, ITT Population

Medication Group	FF/UMEC/VI	FF/VI	UMEC/VI	Total
Total	4,151	4,134	2,070	10,355
ICS/LABA/LAMA-containing regimen				
Yes	1,581 (38)	1,563 (38)	826 (40)	3,970 (38)
No	2,570 (62)	2,571 (62)	1,244 (60)	6,385 (62)
ICS-containing regimen				
Yes	2,971 (72)	2,908 (70)	1,481 (72)	7,360 (71)
No	1,180 (28)	1,226 (30)	589 (28)	2,995 (29)

Source: Adapted from Applicant's clinical study report and submitted materials for the IMPACT trial.
All values are expressed as n (%) unless stated otherwise.
Abbreviations: FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ICS, inhaled corticosteroid; ITT, intention to treat; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

4.2.4. SUMMIT: Baseline Disease Characteristics and Pre-Study Medication Groups

There were no clinically significant differences in baseline characteristics between study arms in the SUMMIT trial (see Table 27 in Appendix 5.5.4). In general, SUMMIT randomized a population of moderate patients with moderate COPD by spirometry (mean FEV1 59.7% predicted normal) and additional CV risk factors. In comparison to the IMPACT trial, a minority of patients randomized in the SUMMIT trial experienced frequent AECOPD in the prior year (21%) and the mean baseline SGRQ score was approximately 4 points lower (mean SGRQ score 46.6).

There were no clinically meaningful differences in pre-study COPD medication use between study arms in the SUMMIT trial (see Table 28 in Appendix 5.5.4). However, as discussed in Section 3.2, the trial design and randomization scheme of the SUMMIT trial included a required discontinuation of ICS prior to enrollment in the trial, as well as a run-in period on only short-acting COPD medications. Despite these potential mitigating factors, subjects with pre-study ICS medications randomized to the VI and placebo arms still functionally underwent ICS removal over the course of the study (see Section 4.5.7, below).

4.2.5. TORCH: Baseline Disease Characteristics and Pre-Study Medication Groups

There were no clinically significant differences in baseline characteristics between study arms in the TORCH trial (see Table 36 in Appendix 5.6.4). In general, TORCH randomized a population of patients with moderate-to-very severe COPD by spirometry. In comparison to the IMPACT trial, a minority of patients randomized in the TORCH trial experienced frequent AECOPD in the prior year (i.e., ≥2 moderate or ≥1 severe AECOPD in the prior year).

There were no clinically meaningful differences in pre-study COPD medication use between treatment arms in the TORCH trial (see Table 37 in Appendix 5.6.4). However, as discussed in Section 3.3, the trial design and randomization scheme of the TORCH trial included a run-in period that allowed only short-acting COPD medications. Despite this potential mitigating

factor, subjects with pre-study ICS medications randomized to the SAL and placebo arms still functionally underwent ICS removal over the course of the study (see Section 4.5.7, below).

4.3. Subject Disposition

4.3.1. Disposition Across Trials

As shown in Table 9 and Table 10, the percentage of subjects who completed study drug was higher in IMPACT and SUMMIT than in TORCH. The observed completion rates could be attributable to the longer 3-year duration of TORCH along with other protocol design elements, as opposed to the shorter study durations of IMPACT and SUMMIT (1 year and an average of 1.8 years, respectively).

There was a similar trend in all three studies of treatment-specific differences in study completion, with the study arms with fewer therapeutic modalities (i.e. single and double therapy) displaying lower completion rates. See Table 10, Table 29, and Table 38, below, for disposition data by treatment arm from IMPACT, SUMMIT, and TORCH, respectively.

Table 9. Disposition Across Trials: ITT Population of IMPACT, SUMMIT, and TORCH

Disposition	IMPACT N=10,355	SUMMIT N=16,485	TORCH N=6112
Treatment completion status (ITT population)			
Completed	7,991 (77.2)	12,230 (74.2)	3,769 (61.6)
Prematurely discontinued	2,365 (22.8)	4,255 (265.8)	2,343 (38.3)
Adverse event	760 (32.1)	1,442 (8.7)	1,318 (56.3)
Lack of efficacy	648 (27.4)	299 (1.8)	244 (10.4)
Study completion status (ITT population)			
Completed	9,087 (87.8)	12,230 (74.2)	3,769 (61.7)
Prematurely withdrawn	1,269 (12.3)	4,255 (25.8)	2,343 (38.3)
Vital status follow-up			
Complete vital status follow-up	10,313 (99.6)	16,480 (>99.9)	6111 (>99.9)

Source: Statistical reviewer and Applicant. Note: IMPACT and TORCH used ITT population and SUMMIT used ITT-E population. Percentages for subheadings of "Prematurely Discontinued" and "Prematurely withdrawn" are based upon the total number of subjects who prematurely discontinued and prematurely withdrew, respectively. Not all subcategories are for discontinuation or withdrawal are displayed; see individual trial disposition tables, below.
All values are expressed as n (%) unless specified otherwise.
Abbreviations: ITT: intention to treat, ITT-E: intention to treat, efficacy; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

4.3.2. IMPACT: Disposition

The reader is referred to the Agency's previous review of the IMPACT study for details and interpretation of subject disposition. The Agency's statistical review for the original submission noted a difference in proportions of patients who discontinued or withdrew when comparing FF/UMEC/VI to the FF/VI and UMEC/VI arms, and also noted that a Kaplan-Meier plot reflecting the accumulating difference in percentages of treatment discontinuation between the

treatment curves showed clear separation between arms. A table of subject disposition is included below (see Table 10).

Table 10. IMPACT: Subject Disposition, ITT Population

Disposition	FF/UMEC/VI	FF/VI	UMEC/VI	Total
No. of subjects, N	4,151	4,134	2,070	10,355
Treatment completion status				
Completed	**3,393 (81.7)**	**3,094 (74.8)**	**1,504 (72.7)**	**7,991 (77.2)**
Prematurely discontinued	**758 (18.3)**	**1,040 (25.2)**	**567 (27.4)**	**2,365 (22.8)**
Adverse event	249 (32.8)	325 (31.3)	186 (32.9)	760 (32.1)
Decision by subject or proxy	250 (33)	296 (28.5)	153 (27)	699 (29.6)
Investigator discretion	33 (4.4)	36 (3.5)	15 (2.7)	84 ((3.6)
Lack of efficacy	163 (21.5)	313 (30.1)	172 (30.3)	648 (27.4)
Lost to follow-up	21 (2.8)	25 (2.4)	14 (2.5)	60 (2.5)
Protocol deviation	32 (4.2)	41 (3.9)	19 (3.4)	92 (3.9)
Study closed/terminated	5 (0.7)	2 (0.2)	5 (0.9)	12 (0.5)
Reached stopping criteria	4 (0.5)	1 (0.1)	2 (0.4)	7 (0.3)
Unknown	1 (0.1)	1 (0.1)	0	2 (0.1)
Study completion status				
Completed	**3,714 (89.5)**	**3,598 (87.1)**	**1,775 (85.7)**	**9,087 (87.8)**
Prematurely withdrawn	**437 (10.5)**	**537 (13.0)**	**295 (14.3)**	**1,269 (12.3)**
Adverse event	162 (37.0)	180 (33.5)	111 (37.6)	453 (35.7)
Investigator discretion	48 (11.0)	58 (10.8)	28 (9.5)	134 (10.6)
Lost to follow-up	30 (6.9)	36 (6.7)	22 (7.5)	88 (6.9)
Study closed/terminated	5 (1.1)	2 (<1)	4 (1.4)	11 (<1)
Unknown	1 (<1)	0	0	1 (<1)
Withdrew consent	192 (43.8)	261 (48.6)	130 (44.1)	583 (45.9)

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\disp.sas from data submitted for original submission. Percentages for subheadings of "Prematurely Discontinued" and "Prematurely withdrawn" are based upon the total number of subjects who prematurely discontinued and prematurely withdrew, respectively.
All values are expressed as n (%) unless specified otherwise.
Abbreviations: FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

Due to concerns that the analyses of on-treatment data (ITT) and of on- and off-treatment data (ITT+VS) – with 2153 (20.8%) and 574 (5.5%) patients with unconfirmed vital status, respectively – could be influenced by bias due to data missing not at random, the Agency requested additional analyses (ITT+VS+VSFU) that included additional vital status ascertainment in patients who had withdrawn from the study (see Section 3.1.7 and Table 11). The number of patients with unconfirmed vital status through one year was greatly reduced, to 42 (0.4%), in the ITT+VS+VSFU analysis (Table 11). These analyses included all vital status follow-up and captured considerably more deaths than analyses including the ITT and ITT+VS data only.

Reviewer's comment: *As discussed above, with considerably less missing data in the ITT+VS+VSFU analyses, these analyses are considered more reliable and are the focus of the analyses presented below. Missing data are not considered a critical issue in the ITT+VS+VSFU analyses, with only 0.4% of patients not having complete follow-up for mortality through one year.*

Table 11. IMPACT: Follow-up for Mortality and Number of Deaths

Category	FF/UMEC/VI	FF/VI	UMEC/VI	Total
No. of subjects, N	**4,151**	**4,134**	**2,070**	**10,355**
Complete follow-up for mortality*				
On-treatment follow-up (ITT)	3,475 (87.7)	3,166 (76.6)	1,561 (74.4)	8,202 (79.2)
On-study follow-up (ITT+VS)	3,960 (95.4)	3,886 (94.0)	1,935 (93.5)	9,781 (94.5)
All vital status follow-up (ITT+VS+VSFU)	4,142 (99.8)	4,116 (99.6)	2,055 (99.3)	10,313 (99.6)
Total deaths at 1 year				
On-treatment follow-up (ITT)	50 (1.2)	49 (1.2)	39 (1.9)	138 (1.3)
On-study follow-up (ITT+VS)	89 (2.1)	97 (2.3)	60 (2.9)	246 (2.4)
All vital status follow-up (ITT+VS+VSFU)	98 (2.4)	109 (2.6)	66 (3.2)	273 (2.6)

Source: Statistical reviewer
All values are expressed as n (%) unless specified otherwise.
* Complete follow-up for mortality included subjects who died + subjects confirmed alive at 1 year.
Abbreviations: CI, confidence interval; FF/UMEC/VI, fluticasone furoate 100 µg /umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg /vilanterol 25 µg; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg /vilanterol 25 µg; VS, end of study vital status; VSFU, vital status follow-up

4.3.3. SUMMIT: Disposition

SUMMIT was an event-driven trial, and subjects participated in a variable length randomized treatment period depending on whether they enrolled earlier or later in the total time course of the trial. The maximum time in the trial was 4 years, while the average time in the trial was 1.8 years. The disposition of subjects over this variable time period suggests a potential trend towards differential rates of completion by treatment arm (see Table 29 in Appendix 5.5.4), with subjects in the FF/VI arm exhibiting the highest treatment completion rate (77%), followed by VI (75%), FF (74%), and placebo (71%). More than 99% of randomized subjects in SUMMIT had complete follow-up for mortality.

4.3.4. TORCH: Disposition

Subjects in the FP/SAL arm exhibited the highest treatment completion rate (66%), followed by SAL (63%), FP (62%), and placebo (56%). For more disposition information in the TORCH trial, see Table 38 in Appendix 5.6.4). More than 98% of randomized subjects in TORCH had complete follow-up for mortality.

4.4. Analyses of All-cause Mortality

The Agency examined the submitted exploratory analysis of ACM for the IMPACT trial as stand-alone data, as well as in the context of additional ACM data provided by the previous COPD ACM trials TORCH and SUMMIT. As described above, IMPACT utilized a partial factorial design and evaluated mortality over the course of 52 weeks. IMPACT provides data on the efficacy of ICS on ACM through its FF/UMEC/VI versus UMEC/VI comparison. Analyses of ACM for the IMPACT trial are presented in Section 4.4.1.

Review of IMPACT ACM results revealed several statistical and clinical issues with the data and their interpretation. Due to these uncertainties, the Agency examined additional ACM data

from the SUMMIT and TORCH trials to provide supportive evidence to better evaluate the efficacy of ICS on COPD mortality. As described in Section 3.2, the SUMMIT trial utilized a full factorial design and evaluated mortality over a variable treatment period based on an event-driven design. SUMMIT provides data on the efficacy of ICS on ACM through its FF/VI versus VI comparison as well as its FF versus placebo comparison. Analyses of ACM for the SUMMIT trial are presented in Section 4.4.2. As described in Section 3.3, the TORCH trial utilized a full factorial design and evaluated mortality over three years. TORCH provides data on the efficacy of ICS on ACM through its FP/SAL versus SAL comparison as well as its FP versus placebo comparison. Analyses of ACM for the TORCH trial are presented in Section 4.4.3.

The evidence for the efficacy of ICS on ACM in COPD from IMPACT, SUMMIT, and TORCH, and a summary of additional uncertainties in the interpretation is provided in Section 4.4.4.

4.4.1. IMPACT: All-cause Mortality

The focus of the Advisory Committee Meeting is the analysis of ACM data at 52 weeks from the IMPACT trial among subjects administered FF/UMEC/VI compared to UMEC/VI. This comparison of ACM between FF/UMEC/VI and UMEC/VI provides data to inform the contribution of FF to the fixed-dose combination. Additional data regarding comparison to the FF/VI arm (assessing the contribution of UMEC) are also presented for completeness.

IMPACT ACM: Analyses at 52 Weeks

The results of the exploratory ACM analysis of IMPACT including all available vital status follow-up (ITT+VS+VSFU) are presented in Table 12, below. In this table, the FF/UMEC/VI versus UMEC/VI comparison results appear in bold text. The same data are presented visually in Figure 4 below.

Table 12. IMPACT: All-cause Mortality Results at 52 Weeks (ITT+VS+VSFU)

Category	FF/UMEC/VI N=4,151	FF/VI N=4,134	UMEC/VI N=2,070
Subjects with event, n (%)	98 (2.4)	109 (2.6)	66 (3.2)
ACM analysis of FF/UMEC/VI vs. comp			
HR for ACM[1]		0.89	**0.72**
95% CI		0.68, 1.17	**0.53, 0.99**
p-value (Cox PH model – main)		0.387	**0.042**
p-value (Log-rank test -supplemental)		0.405	0.048

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_primary.sas. [1]These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. Cox model includes age and gender as covariates. Comparisons in **bold text** provide data to inform the contribution of FF on ACM endpoints as part of the FF/UMEC/VI FDC.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; comp, comparator; FF/UMEC/VI, fluticasone furoate 100 µg /umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg /vilanterol 25 µg; HR, hazard ratio; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg /vilanterol 25 µg; VS, end of study vital status; VSFU, vital status follow-up

Based on all available vital-status follow-up, 273 subjects died during the 52-week duration of the IMPACT trial, with 2.4% mortality among subjects administered FF/UMEC/VI, compared to 3.2% among subjects administered UMEC/VI. The exploratory Cox PH analysis of the ACM data

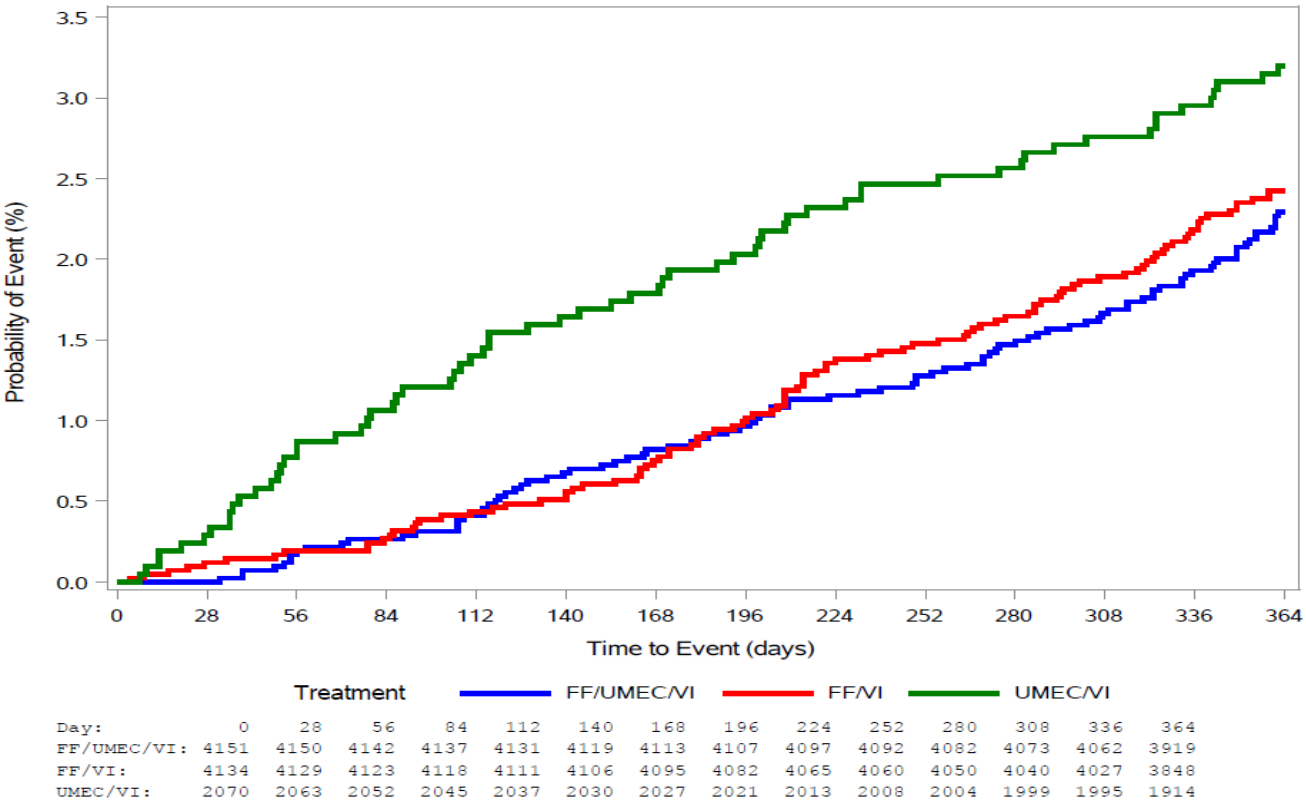
yields a hazard ratio (HR) for ACM of 0.72 (95% CI 0.53 to 0.99) comparing FF/UMEC/VI with UMEC/VI, with a nominal p-value of 0.042.

Reviewer's Comment: *The nominal p-value for the FF/UMEC/VI versus UMEC/VI ACM comparison of 0.042 is close to the typical 2-sided significance threshold of 0.05. However, as noted above, this analysis was one of many exploratory analyses not included in the multiple testing strategy to control Type I error, such that the results are not considered statistically significant. The estimate, CI, and p-value from such an exploratory analysis are difficult to interpret and the results may be subject to substantial bias.*

The ACM data are displayed as Kaplan-Meier curves in Figure 4, below. Visualization of the ACM data from IMPACT shows an unexpected trend: the separation between the curves (i.e., the increase in mortality incidence on UMEC/VI compared to FF/UMEC/VI and FF/VI) is primarily driven by events within the first ~90 days.

Reviewer's Comment*: This early increased number of deaths in the UMEC/VI arm leads to an apparent early division of the UMEC/VI curve from the FF/VI and FF/UMEC/VI curves over the first ~90 days of the trial. However, after this initial apparent division, the curves appear to follow a more parallel course. While the interpretation of these curves at different timepoints was not a prespecified analysis and should be approached with caution, this trend may suggest that the event rates across treatment arms were similar after this initial period of divergence.*

Figure 4. IMPACT: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Day:	0	28	56	84	112	140	168	196	224	252	280	308	336	364
FF/UMEC/VI:	4151	4150	4142	4137	4131	4119	4113	4107	4097	4092	4082	4073	4062	3919
FF/VI:	4134	4129	4123	4118	4111	4106	4095	4082	4065	4060	4050	4040	4027	3848
UMEC/VI:	2070	2063	2052	2045	2037	2030	2027	2021	2013	2008	2004	1999	1995	1914

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_kmplot.sas. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FF/UMEC/VI: fluticasone furoate 100 µg/ umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

IMPACT ACM: Exploratory Analyses at Other Timepoints

In order to further examine this visual trend of early mortality in the UMEC/VI arm using available data, the Agency requested analyses of ACM at earlier timepoints in the IMPACT trial. These data, displayed in Table 13 below, suggest a high early event rate, reinforcing the visual trend suggested by the Kaplan-Meier curve. While the HR for ACM comparing FF/UMEC/VI to UMEC/VI was not calculable at Day 30, already 0.3% of subjects in the UMEC/VI arm had died, compared to 0% of subjects in the FF/UMEC/VI arm and 0.1% of the FF/VI arm. By the Day 60 timepoint, 0.9% of subjects in the UMEC/VI arm had died, compared to 0.2% of the FF/UMEC/VI arm, yielding an observed HR for ACM in the FF/UMEC/VI versus UMEC/VI comparison of 0.25 (95% CI of 0.11 to 0.55). By the Day 90 timepoint, 1.2% of subjects in the UMEC/VI arm had died, compared to 0.3% in the FF/UMEC/VI arm, yielding an observed HR for ACM in the FF/UMEC/VI versus UMEC/VI comparison of 0.24 (95% CI of 0.12 to 0.47).

***Reviewer's Comment**: While these analyses were exploratory and should be interpreted with caution, they suggest a potentially alarming trend of early mortality events in the UMEC/VI arm. In the comparison of FF/UMEC/VI versus*

UMEC/VI, this early mortality trend in the UMEC/VI arm led to observed results suggesting a peak difference between treatment arms around 90 days. On initial examination, these data might imply an effect on mortality attributable to the ICS component within 90 days. Such an early mortality signal is unexpected and not consistent with previous COPD trials that failed to demonstrate an ACM difference attributable to ICS over trial durations of 3 years or more, and the same trials have not supported an early mortality benefit with ICS (see Section 4.4.4). Potential factors which may have contributed to these observed trends are discussed in Section 4.5.2 Pre-study Therapy and ICS Removal in IMPACT and Section 4.6.3 Efficacy Timeframe in IMPACT. In contrast, the comparison of the FF/UMEC/VI versus FF/VI (i.e., treatment arms that both include an ICS component) showed no marked early trend in mortality events.

In exploratory, post-hoc analyses excluding this initial ~90-day period of risk and including only mortality follow-up and events after Day 90 (see Table 13 and Figure 5), the proportion of subjects who died in the FF/UMEC/VI and UMEC/VI arms are 2.1% and 2.0%, respectively. These analyses condition on the post-randomization variable of surviving to Day 90, so may be subject to bias, but are intended to help explore the time course of the separation in survival curves. The comparison of events after Day 90 translate to a hazard ratio of 1.02 (95% CI 0.7 to 1.48) for the comparison of FF/UMEC/VI to UMEC/VI, potentially suggesting that the ICS component of FF/UMEC/VI did not show efficacy on ACM after this initial ~90-day period. Alternatively, these same data may imply that the ACM difference observed between FF/UMEC/VI and UMEC/VI (Table 12) may have been driven primarily by data from the initial ~90-day period.

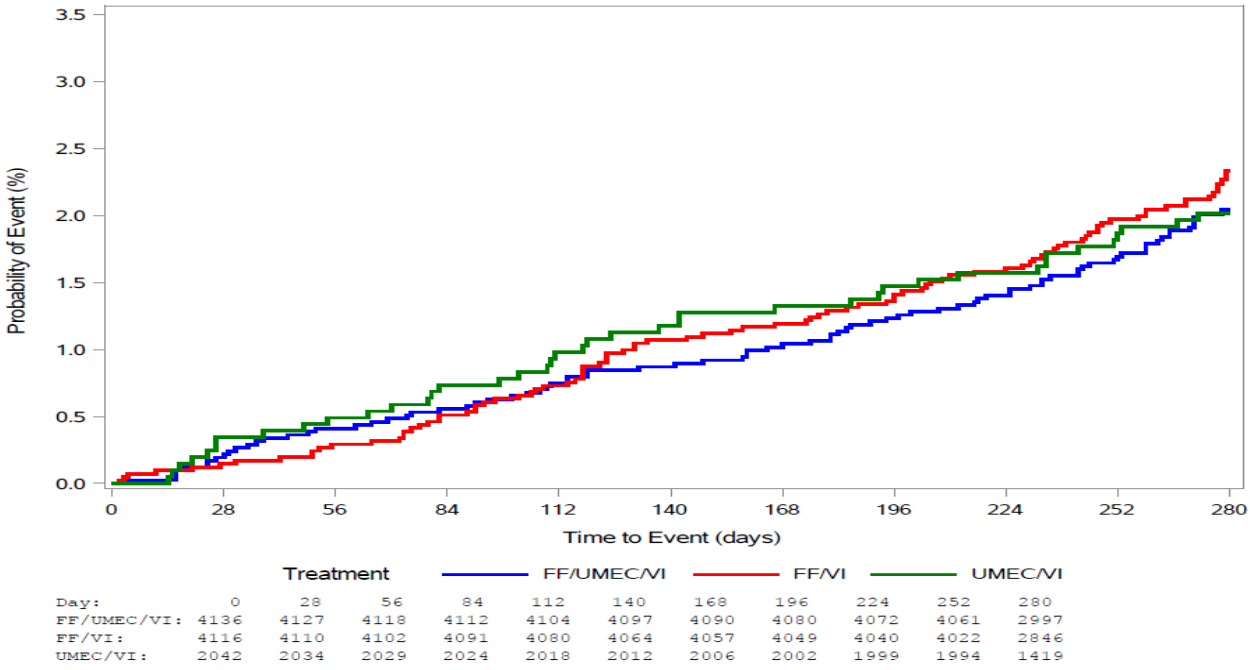
***Reviewer's Comment**: Taken together, these exploratory analyses suggest that initial mortality events in the UMEC/VI arm drove the observed mortality difference at Week 52. In addition, given the exploratory results from the analysis "after Day 90", it is uncertain whether the data support a sustained effect on survival in the comparison of FF/UMEC/VI versus UMEC/VI after this initial 90-day period. There are multiple possible explanations for the observed hazard ratio of 1.02 for the FF/UMEC/VI versus UMEC/VI comparison "after Day 90." These exploratory results could simply be due to chance, or they could represent a "healthy survivor" effect among the subjects who survived past Day 90. Further, examining this trend in the context of the high early event rate of the ACM data and IMPACT's study design may also suggest an early risk period for mortality for subjects in the UMEC/VI arm, rather than an early benefit in the two ICS-containing arms. The possibility of an early risk period due to ICS removal effects is discussed further in Sections 4.5.3, 4.5.4, 4.5.5, and 4.5.6.*

Table 13. IMPACT: All-cause Mortality Results at Various Timepoints (ITT+VS+VSFU)

Timepoint	FF/UMEC/VI N=4,151	FF/VI N=4,134	UMEC/VI N=2,070
Day 30			
Subjects with event at day 30, n (%)	0	5 (0.1)	7 (0.3)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		N/A	**N/A**
Day 60			
Subjects with event at day 60, n(%)	9 (0.2)	8 (0.2)	18 (0.9)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		1.12 (0.43, 2.90)	**0.25 (0.11, 0.55)**
Day 90			
Subjects with event at day 90, n (%)	12 (0.3)	13 (0.3)	25 (1.2)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		0.92 (0.42, 2.01)	**0.24 (0.12, 0.47)**
After day 90 (excluding first 90 days)			
Subjects with available data after day 90, N	4,135	4,116	2,042
Subjects with event after day 90, n (%)	86 (2.1)	96 (2.3)	41 (2.0)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		0.88 (0.66, 1.18)	**1.02 (0.7, 1.48)**

Source: Statistical reviewer. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints as part of the FF/UMEC/VI FDC.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; HR, hazard ratio; ITT, intention to treat; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; N/A, not applicable; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg, VS, end of study vital status; VSFU, vital status follow-up

Figure 5. IMPACT: Probability of All-cause Mortality after Day 90 by Treatment Arm (ITT+VS+VSFU)



Source: Statistical reviewer. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FF/UMEC/VI: fluticasone furoate 100 µg /umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg /vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg /vilanterol 25 µg

4.4.2. SUMMIT: All-cause Mortality

SUMMIT ACM: Analyses at Common End Date

Based on available data and vital-status follow-up, 1037 subjects died during the course of the SUMMIT trial (i.e., from randomization to Common End Date). As shown in Table 14, ACM events occurred in 6% of subjects in the FF/VI arm, 6.1% of subjects in the FF arm, 6.4% of subjects in the VI arm, and 6.7% of subjects in the placebo arm. The SUMMIT trial failed to demonstrate a statistically significant difference in the time-to-event analysis of ACM among subjects administered FF/VI versus VI (HR 0.91, 95% CI 0.77 to 1.09). Similarly, the FF versus placebo comparison failed to demonstrate a statistically significant effect of FF on ACM at the Common End Date (HR 0.91, 95% CI 0.77 to 1.08). A visualization of ACM in SUMMIT to the CED is provided in Figure 6.

***Reviewer's Comment**: In comparison to IMPACT, the SUMMIT trial failed to show a statistically significant difference in the risk of ACM for both the FF/VI versus VI comparison as well as the FF versus placebo comparison, both of which provide data to inform the efficacy and safety of FF on ACM in COPD. The SUMMIT trial was longer in duration, had a higher number of mortality events, and therefore greater statistical power to detect a difference in ACM attributable to ICS. In*

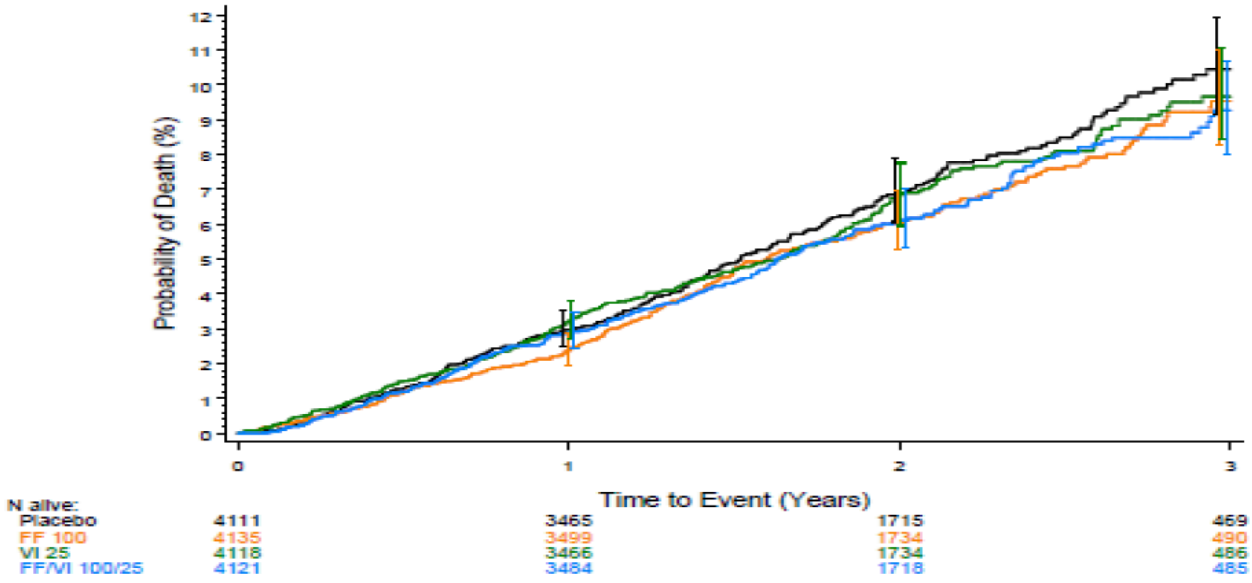
addition, the SUMMIT trial's primary comparison of FF/VI versus placebo failed to demonstrate a statistically significant difference on the risk of ACM at the CED.

Table 14. SUMMIT: All-cause Mortality Results at Common End Date, ITT-E Population With Vital Status Follow-up, Including Both On- and Off-treatment Data

Category Analysis	FF/VI N=4,121	FF N=4,135	VI N=4,118	Pbo N=4,111
Number of subjects with event, n (%)	246 (6.0)	251 (6.1)	265 (6.4)	275 (6.7)
ACM analysis of FF/VI vs. comparator				
ACM HR			**0.91**	0.88
95% CI			**0.77, 1.09**	0.74, 1.04
p-value			**0.30**	0.14
ACM analysis of FF vs. comparator				
ACM HR				**0.91**
95% CI				**0.77, 1.08**
p-value				**0.28**

Source: Adapted from Applicant's submitted materials
These analyses incorporate on- and off-treatment vital status data from the SUMMIT study and available vital status follow-up data for subjects who withdrew from the study.
Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; FF, fluticasone furoate 100 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo: placebo; VI, vilanterol 25 µg

Figure 6. SUMMIT: Probability of All-cause Mortality through Common End Date by Treatment Arm (ITT-E)



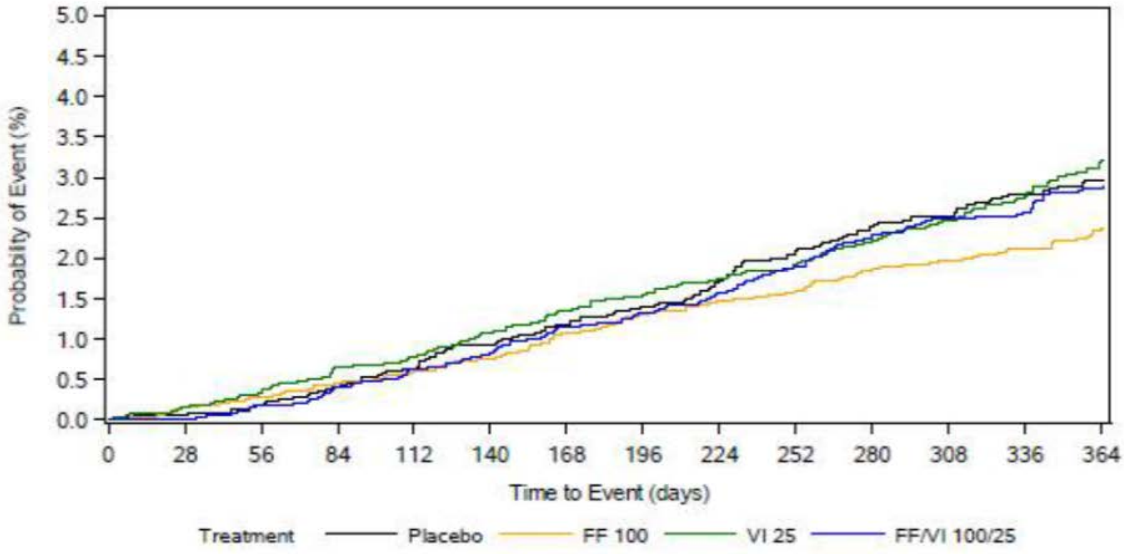
Source: Figure 2.002
Source: Applicant
Note: The SUMMIT trial was an event-driven trial, so subjects were enrolled for differing amounts of time. The common end date represents the trial end date at which the event-driven goals were met for the trial. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT-E: intention-to-treat efficacy population; FF/VI: fluticasone furoate 100mcg /vilanterol 25mcg, FF/VI: fluticasone furoate 100mcg; VI: vilanterol 25mcg

SUMMIT ACM: Analyses at 52 Weeks

Examination of the SUMMIT data up to the 52-week timepoint (i.e., the duration of the IMPACT trial) does not suggest an early signal for mortality events in the overall analysis by Day 90, as shown in Figure 7. However, analysis of the Day 90 data by pre-study ICS use in Appendix 5.5.5 may suggest an early risk period among those subjects who experienced ICS removal events. While additional discussion of this phenomenon is provided in Sections 4.5.7 and 4.6.3, it is notable that the SUMMIT trial included a lower proportion of subjects with pre-study ICS-containing COPD maintenance medications, a lower proportion of enrolled subjects with frequent exacerbations in the previous year, and the SUMMIT trial included a population with markers for lower COPD severity at baseline compared to IMPACT. In addition, the SUMMIT trial included a pre-enrollment requirement for removal of pre-study ICS and LABA medications as well as a run-in on short-acting medications alone.

Reviewer's Comment*: SUMMIT did not exhibit separation in trial arms by Day 90 in the overall analysis including all subjects. This lack of differential early events could be due to SUMMIT's better controlled, less severe COPD population. It is worth noting, however, that the pre-enrollment and run-in periods of the SUMMIT trial required removal of ICS from the COPD maintenance medication regimen of all patients. Subjects with an AECOPD or death during this time period were not randomized. This pre-randomization medication removal may have prevented those subjects most vulnerable to ICS removal effects from being randomized.*

Figure 7. SUMMIT: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT-E Including On- and Off-treatment Data)



Number Alive [1]														
Placebo	4111	4109	4104	4093	4083	4070	4060	4051	4037	4022	4010	4005	3712	3465
FF 100	4135	4128	4123	4116	4110	4104	4090	4081	4074	4069	4058	4054	3760	3502
VI 25	4118	4112	4102	4091	4086	4074	4062	4054	4046	4039	4027	4016	3722	3468
FF/VI 100/25	4121	4121	4114	4104	4095	4087	4074	4066	4056	4043	4027	4018	3744	3487

Source: Applicant
Note: The SUMMIT trial was an event-driven trial, so subjects were enrolled for differing amounts of time. The common end date represents the trial end date at which the event-driven goals were met for the trial. The data presented in this graph represent ACM events at the 52-week timepoint. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT-E: intention to treat efficacy; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg

4.4.3. TORCH: All-cause Mortality

TORCH ACM: Analysis at 156 Weeks

Based on available data and vital-status follow-up, 875 subjects died during the course of the TORCH trial (i.e., from randomization to 156 weeks). As shown in Table 15, ACM events occurred in 12.6% of subjects in the FP/SAL arm, 16.0% of subjects in the FP arm, 13.5% of subjects in the SAL arm, and 15.2% of subjects in the placebo arm. The TORCH trial failed to demonstrate a statistically significant difference in the time-to-event analysis of ACM among subjects administered FP/SAL versus SAL (HR 0.95, 95% CI 0.78 to 1.15). Similarly, the FP versus placebo comparison failed to demonstrate a statistically significant effect of FP on ACM at the Common End Date (HR 1.06, 95% CI 0.88 to 1.26). A visualization of ACM in TORCH to Week 156 is provided in Figure 8.

***Reviewer's Comment**: In comparison to IMPACT, the TORCH trial failed to show a statistically significant difference in the risk of ACM for both the FP/SAL versus SAL comparison as well as the FP versus placebo comparison, both of which*

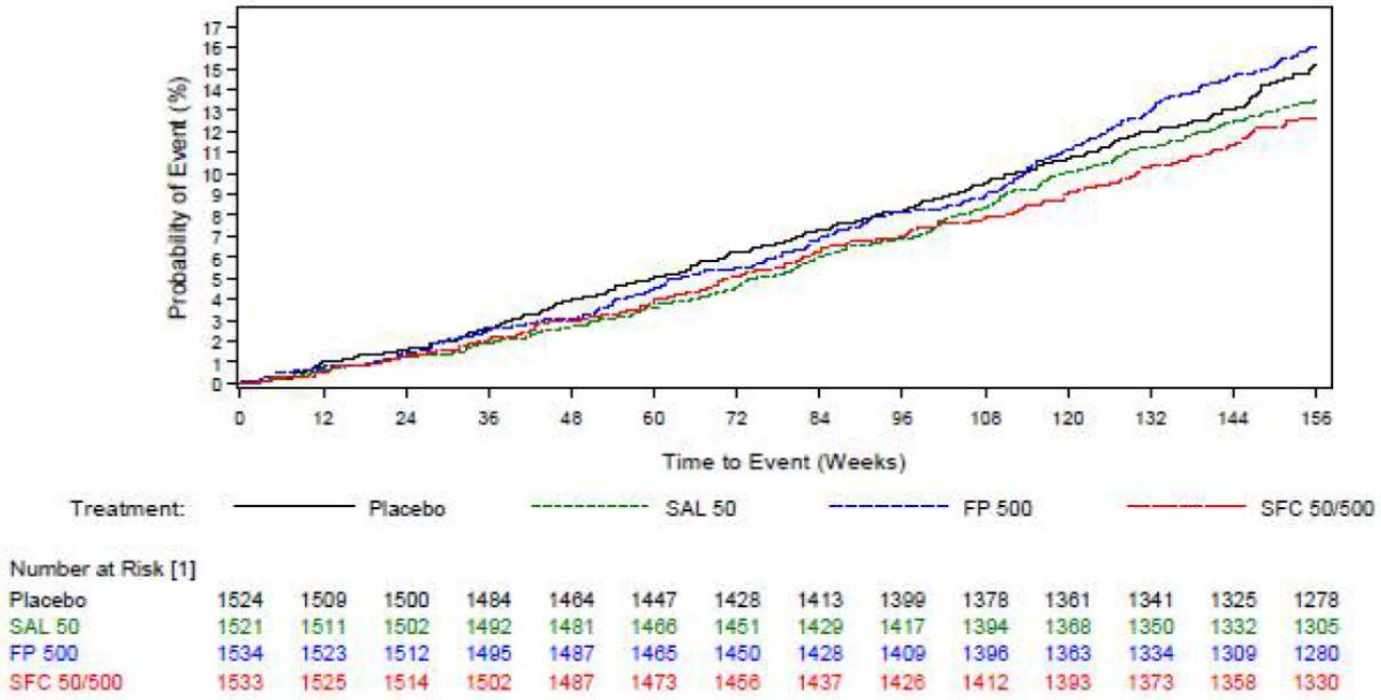
provide data to inform the contribution of fluticasone to reduction of ACM in COPD. Like SUMMIT, TORCH had a longer treatment duration than IMPACT and higher number of deaths, and therefore more statistical power to detect a difference in ACM endpoints attributable to ICS. In addition, the TORCH trial's primary comparison of FP/SAL versus placebo failed to demonstrate a statistically significant difference in the risk of ACM at 156 weeks.

Table 15. TORCH: All-cause Mortality Results at Week 156, ITT population With Vital Status Follow-up, Including Both On- and Off-treatment Data

Category **Analysis**	**FP/SAL** **N=1,533**	**FP** **N=1,534**	**SAL** **N=1,521**	**Pbo** **N=1,524**
Subjects with event, n (%)	193 (12.6)	246 (16.0)	205 (13.5)	231 (15.2)
ACM analysis of FP/SAL vs. comparator				
ACM HR			**0.95**	0.81
95% CI			**0.78, 1.15**	0.67, 0.98
p-value			**0.58**	0.052*
ACM analysis of FP vs. comparator				
ACM HR				**1.06**
95% CI				**0.88, 1.26**
p-value				**0.55**

Source: Applicant
These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold** text provide data to inform the efficacy and safety of FF on ACM endpoints. Not all trial comparisons are presented in this table.
*This p-value refers to the adjusted comparison after accounting for multiplicity and interim analyses. Only the primary comparison was adjusted because interim analyses were performed. Unadjusted p-value (using log-rank primary analysis model adjusting for smoking status): 0.04. P-value from Cox PH model, an unadjusted supplementary analysis was 0.03.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FP, fluticasone propionate 500 µg; FP/SAL, fluticasone propionate 500 µg / salmeterol 50 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo, placebo; SAL, salmeterol 50 µg

Figure 8. TORCH: Probability of All-cause Mortality over 156 Weeks by Treatment Arm (ITT Including Both On- and Off-treatment Data)



Number at Risk [1]														
Placebo	1524	1509	1500	1484	1464	1447	1428	1413	1399	1378	1361	1341	1325	1278
SAL 50	1521	1511	1502	1492	1481	1466	1451	1429	1417	1394	1368	1350	1332	1305
FP 500	1534	1523	1512	1495	1487	1465	1450	1428	1409	1396	1363	1334	1309	1280
SFC 50/500	1533	1525	1514	1502	1487	1473	1456	1437	1426	1412	1393	1373	1358	1330

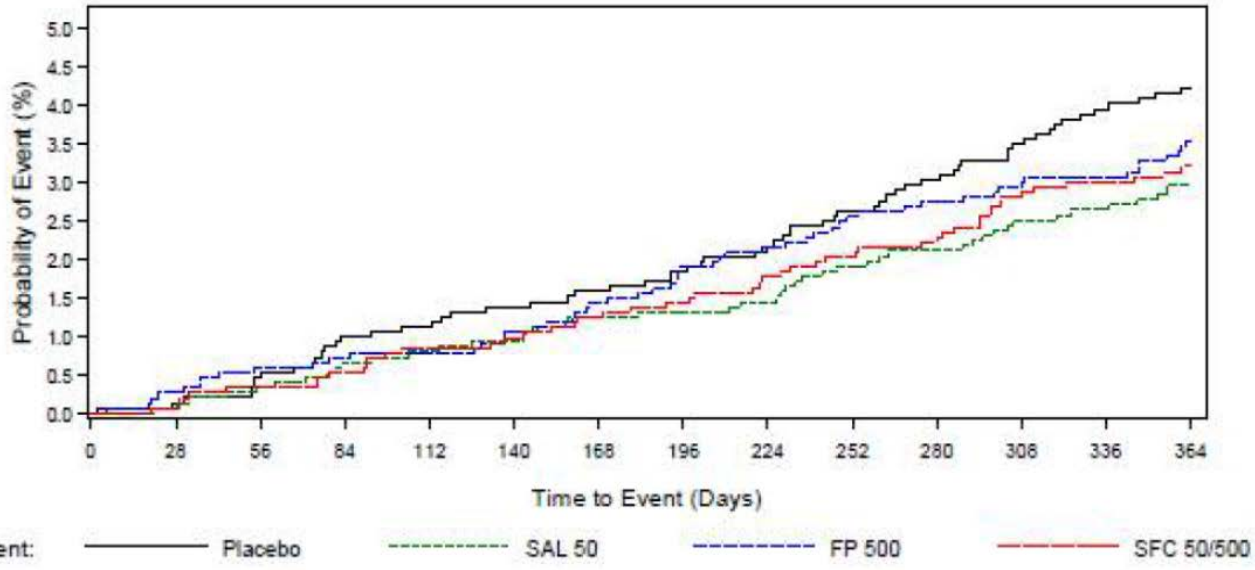
Source: Applicant
These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study.
ITT-E: intention to treat, efficacy; CI: confidence interval; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo

TORCH ACM: Analyses at 52 Weeks

Examination of the TORCH data up to the 52-week timepoint (i.e., the duration of the IMPACT trial) does not suggest an early signal for mortality events by Day 90, as shown in Figure 9, although the curves may suggest an increased event rate in the placebo arm compared to the active treatment arms at that timepoint. However, exploratory analyses of the Day 90 data by pre-study ICS use (see Appendix 5.6.5) may suggest an early risk period for those subjects experiencing ICS removal events. While additional discussion of the efficacy timeframe phenomenon is provided in Sections 4.5.7 and 4.6.3, it is notable that the TORCH trial included a lower proportion of subjects with pre-study ICS-containing COPD maintenance medications and a lower proportion of enrolled subjects with frequent exacerbations in the previous year compared to IMPACT. In addition, the TORCH trial included a run-in on short-acting medications alone that required removal of pre-study ICS and LABA medications.

***Reviewer's Comment**: The run-in period of the TORCH trial required removal of ICS from the COPD maintenance medication regimen of all enrolled patients. Subjects with an AECOPD or death during this time period were not randomized. While intended to standardize treatments prior to randomization, this run-in design may have excluded those COPD subjects most vulnerable to ICS removal effects from enrollment in the TORCH trial.*

Figure 9. TORCH: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT Including On- and Off-treatment Data)



Number Alive [1]														
Placebo	1524	1522	1516	1509	1507	1503	1500	1496	1491	1484	1478	1471	1464	1460
SAL 50	1521	1519	1516	1511	1509	1507	1502	1501	1499	1492	1489	1483	1481	1476
FP 500	1534	1530	1525	1523	1522	1518	1512	1505	1501	1495	1492	1488	1487	1480
SFC 50/500	1533	1532	1528	1525	1520	1518	1514	1511	1506	1502	1498	1489	1487	1484

Source: Applicant
These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study.
ITT-E: intention to treat, efficacy; CI: confidence interval; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo

4.4.4. All-cause Mortality Across Trials

Both SUMMIT and TORCH were designed to examine ACM as a primary efficacy endpoint using a factorial design over the course of multiple years. Both examined ACM over a longer duration than IMPACT, both included a higher number of mortality events (193-275 events per treatment arm, as compared to 66-109 events per treatment arm in IMPACT, or roughly three times the statistical information) to inform the determinations of efficacy, and both failed to achieve a statistically significant result in their primary analysis of ACM, as well as in analyses that isolated the ICS effect. These mortality results from IMPACT, SUMMIT, and TORCH are presented in Table 16 below, displaying treatment comparisons that focus on the effect of ICS.

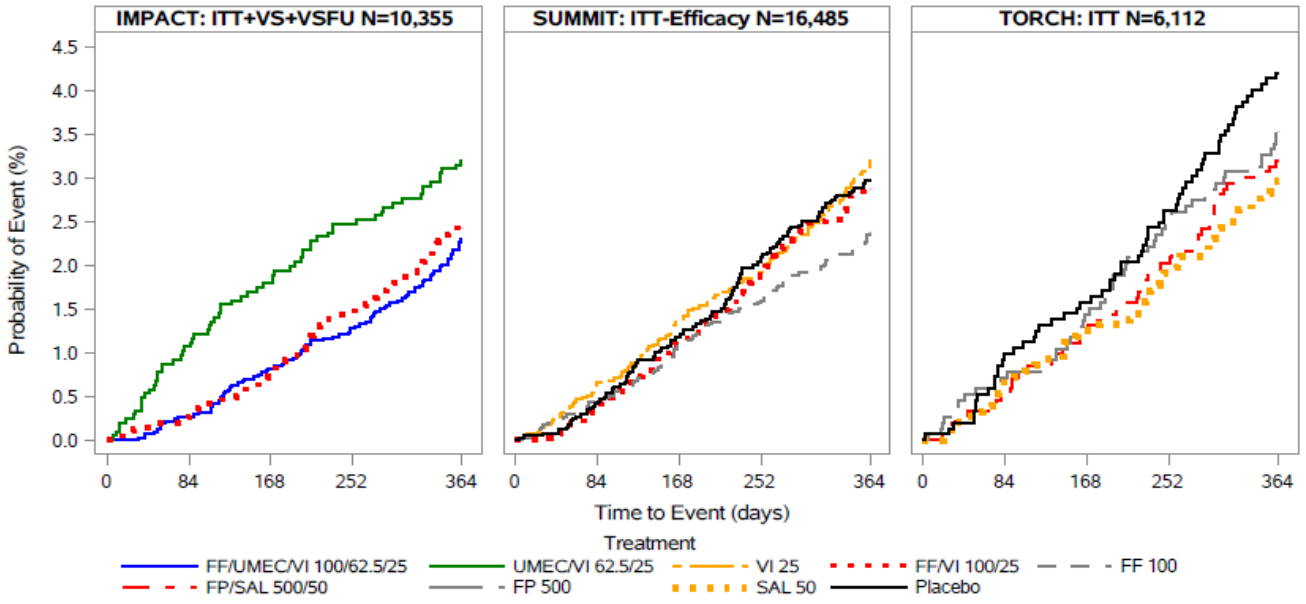
Table 16. All-cause Mortality Across Trials: Pairwise ICS Treatment Comparisons on ACM in IMPACT, SUMMIT and TORCH

	IMPACT N=10,355	SUMMIT N=16,485		TORCH N=6,112	
Category	FF/UMEC/VI vs. UMEC/VI	FF/VI vs. VI	FF vs. Pbo	FP/SAL vs. SAL	FP vs. Pbo
Patients in ICS comparison	6,221	8,239	8,246	3,054	3,057
Mortality events in comparison	164	511	526	398	477
ACM analyses					
Hazard ratio	0.72	0.91	0.91	0.95	1.06
95% CI	0.53 to 0.99	0.77 to 1.09	0.77 to 1.08	0.78 to 1.15	0.88 to 1.25

Source: Reviewer, adapted from Applicant's submitted materials.
Note: Values are based on the ITT-E population for SUMMIT, the ITT population for TORCH, and the ITT+VS+VSFU population for IMPACT, isolating only those subjects in the corresponding treatment arms that isolate the contribution of the ICS component. Data presented are from each study's analysis at study end: IMPACT's analysis at 52 weeks, SUMMIT's analysis at the CED, with a median duration of 1.8 years, and TORCH's analysis at 156 weeks.
Abbreviations: ACM, all-cause mortality; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; VI: vilanterol 25 µg; FF: fluticasone furoate 100 µg; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo CI: confidence interval; CED = common end date;

Given the early ACM events observed in IMPACT, in addition to evaluating the primary efficacy analysis from TORCH and SUMMIT, the Agency also requested efficacy analyses conducted at the 52-week timepoint for TORCH and SUMMIT for comparison of early ACM trends. Kaplan-Meier ACM curves over 52 weeks for IMPACT, SUMMIT, and TORCH are displayed in Figure 10. This 52-week timeframe represents the entire duration of the IMPACT study and the first year of the SUMMIT and TORCH studies.

Figure 10. All-cause Mortality Across Trials: Probability of All-cause Mortality over 52 Weeks by Treatment Arm in IMPACT, SUMMIT, and TORCH (Including On- and Off-treatment Data)



Source: Reviewer program M:\NDA 209482\Analysis\ALL\reviewer programs\kmfig.sas
All data and treatment arms from each study are used in the analysis; plots are truncated at Day 364.

Abbreviations: ITT-E: intention to treat, efficacy; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; VI: vilanterol 25 µg; FF: fluticasone furoate 100 µg; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo CI: confidence interval; CED = common end date

While formal cross-study comparisons should be approached with caution, descriptively, the early division in the Kaplan-Meier curves in the IMPACT trial is notably different than the trends observed in both SUMMIT and TORCH.

***Reviewer's Comment**: The UMEC/VI arm of the IMPACT trial shows an abrupt upswing (i.e., higher probability of mortality events) within the initial ~90 days compared to the FF/UMEC/VI and FF/VI curves, suggesting an unexpected difference in the probability of an ACM event within the first 90 days. This trend of early division of the study arms is not observed among the study arms in the TORCH or SUMMIT trials.*

4.5. Analyses by Pre-study Medication Subgroup

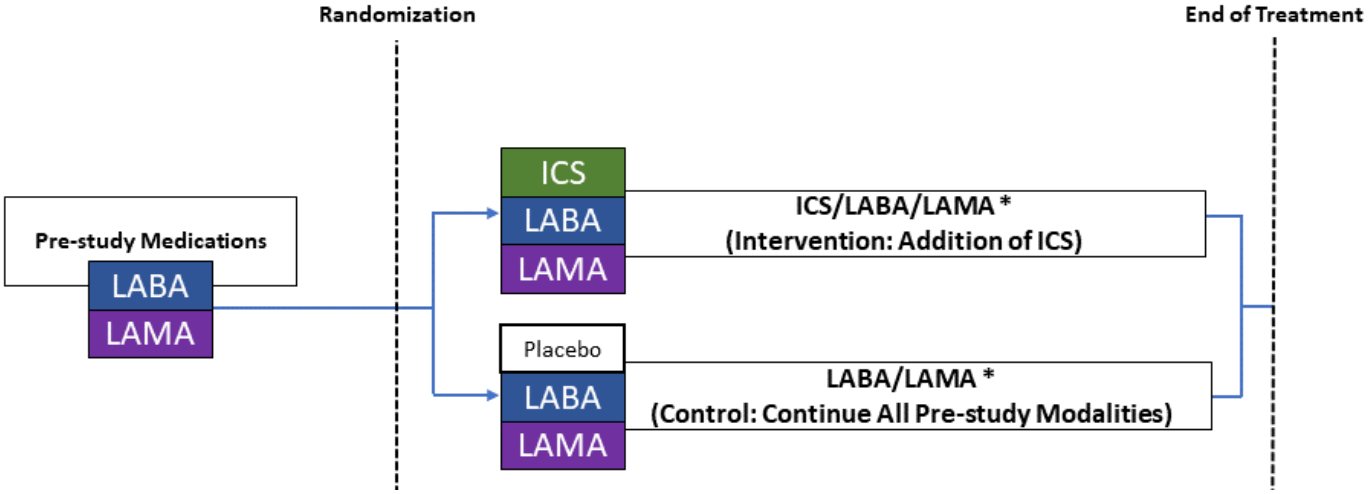
Based on IMPACT's trial design choices that allowed ICS removal at randomization among subjects with pre-study ICS, extant literature suggesting harmful effects of ICS removal, and the early timeframe of the observed ACM signal in survival curves between the FF/UMEC/VI and UMEC/VI treatment arms (see Table 13 and Figure 4), a concern evolved that pre-study ICS status could affect the interpretation of the ACM results through ICS removal effects. To evaluate whether ICS removal played a role in the observed mortality results, the Agency requested exploratory subgroup analyses of IMPACT by pre-study medication. Based on the results of these subgroup analyses, the Agency requested additional pre-study medication subgroup analyses of SUMMIT and TORCH. Additionally, the Agency examined extant literature on COPD trial methodology and randomized ICS removal as well as applicable COPD practice guidelines to provide additional context for the pre-study medication subgroup analyses.

In presenting the review of these data, the Agency first provides a conceptual framework for interpreting the pre-study medication subgroup analyses based on literature discussing methodological issues in COPD trial design, followed by application of these principles to the IMPACT trial. Next, the Agency presents the results of the pre-study medication subgroup analyses of ACM, focusing on the results of IMPACT's pre-study ICS subgroup analyses presented in 4.5.4. Following the presentation of these subgroup results, selected meeting minutes from IMPACT's IDMC are presented for context regarding the interpretation of early mortality events during the course of the trial. Pre-study ICS subgroup analyses of severe AECOPD in IMPACT are presented next, since severe AECOPD events are associated with mortality in COPD. After the presentation of IMPACT's pre-study medication subgroups, analogous pre-study ICS subgroup data for the ACM endpoints are provided for both SUMMIT and TORCH. Finally, a summary of relevant studies and trials of ICS removal in the COPD literature is provided along with a discussion of international guidelines regarding ICS removal in COPD.

4.5.1. ICS Removal as an Intervention in COPD Trial Design

Conceptually, trials seeking to show a mortality benefit of a treatment may recruit subjects with a common set of pre-study maintenance medications and randomize these subjects to the addition of a blinded investigational drug (e.g., an ICS) versus blinded placebo to examine all-cause mortality events over an appropriate period of time. Importantly, the pre-study maintenance medications used by enrolled patients generally do not include the investigational drug or the same drug class. Stated plainly, the study subjects are naïve to the study drug prior to entering the trial. In a randomized addition study design, the comparison of all-cause mortality events between the investigational drug arm (i.e., the intervention) and the placebo arm (i.e., the control) forms the evidence base for an efficacy claim of improved mortality, and this evidence base informs the potential benefit of the addition of the investigational drug in clinical practice. A schematic of this randomized addition trial design is provided in Figure 11, below.

Figure 11. Conceptual Trial Design Schematic for Randomized Addition of ICS Medication

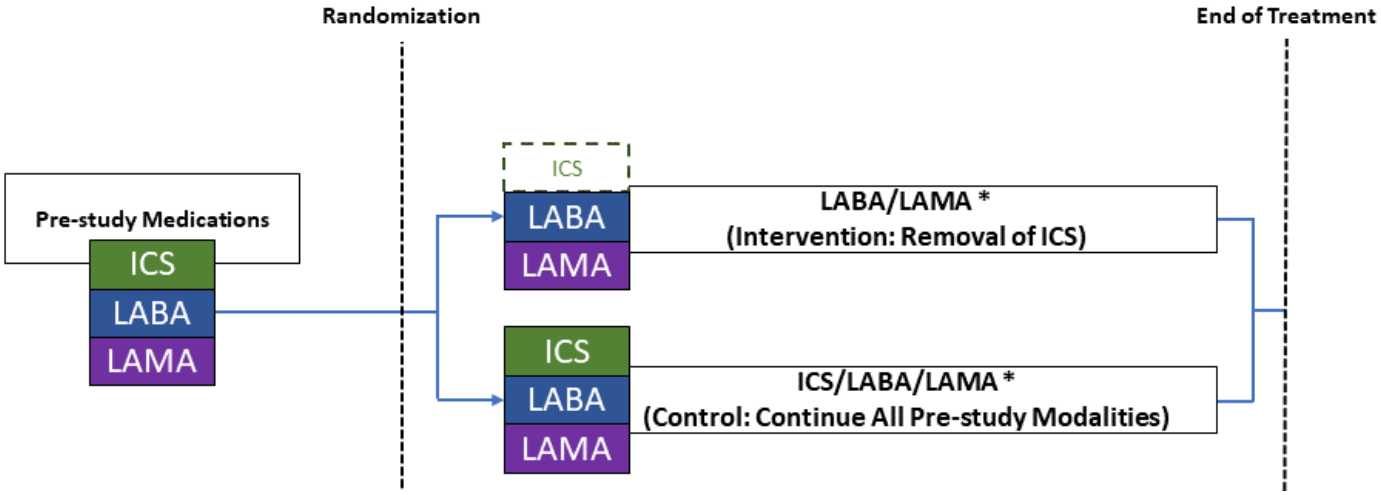


Source: Reviewer.
*the comparison of these two treatment arms isolates the effect of the ICS component
Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

While infrequently utilized for mortality trials, another potential trial design involves randomized removal (i.e., randomized withdrawal) of a medication compared to continuation of the drug. Randomized removal trials recruit subjects with a common set of pre-study maintenance medications and randomize these subjects to the blinded removal of an investigational drug (e.g., an ICS) versus blinded continuation of the drug. Importantly, a randomized removal trial generally does not include subjects who are naïve to the drug removed. In this study design, the comparison of the endpoint between the drug removal arm (i.e., the intervention) and the drug continuation arm (i.e., the control) forms the evidence base for an efficacy or safety claim, informing the potential benefit or risk of the removal of the investigational drug in clinical practice. A schematic of this randomized removal trial design is provided in Figure 12 below.

Reviewer's Comment: *A randomized removal trial that seeks to use drug removal data to provide supportive evidence of efficacy would generally be conducted in a subset of well-controlled patients in whom a decision of medication removal might be clinically reasonable. Generally, such randomized removal trials would not be conducted in a patient population exhibiting poor disease control – especially for medications that might be predicted to exhibit an acute withdrawal effect – because data on drug removal as an intervention in this situation would be of unclear clinical significance to the drug's efficacy assessment.*

Figure 12. Conceptual Trial Design Schematic for Randomized Removal of ICS Medication



Source: Reviewer
A dashed outline indicates removal of the drug class at randomization.
*the comparison of these two treatment arms isolates the effect of the ICS component.
ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

The design of the IMPACT trial, however, is more complicated than these examples, and combines the concepts of ICS addition and ICS removal. The IMPACT trial recruited subjects with any pre-study COPD maintenance medication regimen. In practice, this design led to an enrolled population in which 38% reported pre-study triple therapy with ICS, LABA, and LAMA medications, and 71% reported any pre-study ICS medication as part of their maintenance regimen. The run-in period of the IMPACT trial mandated continuation of these pre-study medications. The partial factorial design of the IMPACT trial then randomized these subjects to two ICS-containing arms and one arm that did not contain an ICS component.

Since patients were recruited into the IMPACT trial with any pre-study medication, some of the subjects were already receiving some or all drug classes (i.e., ICS) included in the IMPACT trial's study arms, while others were naïve to the drug class. Depending on pre-study therapy, this design choice created distinct subgroups of the IMPACT population in which the clinical interpretation of the results is uncertain. These subgroups are exploratory, but important to consider when interpreting the ACM results. The subgroups are:

1) Subjects with pre-study triple therapy (i.e., ICS, LABA, and LAMA), in which randomization to ICS/LABA or LABA/LAMA arms could represent randomized removal of a therapeutic drug class (i.e., ICS removal or LAMA-removal) compared to continuation of triple therapy.

2) Subjects with pre-study ICS, in which randomization to LABA/LAMA could represent removal of a therapeutic drug class (i.e., ICS removal) compared to continuation of ICS, in addition to other trial interventions. This subgroup of subjects made up 71% of the IMPACT trial.

These pre-study medication subgroups dictated separate and discrete clinical trial courses for patients in each subgroup. One subgroup had new therapeutic modalities added by randomization, while the other had therapeutic modalities removed by randomization. It is unclear whether data from these two different interventions (i.e., removal versus addition of therapeutic modalities) can address the same clinical question.

Because of these two clinically distinct subgroups and clinical scenarios of therapy removal versus therapy addition, there is uncertainty about whether a comparison of mortality events between arms without accounting for pre-study therapy is appropriate. The Applicant's all-cause mortality claim relies on the efficacy of the ICS component in the context of TRELEGY ELLIPTA therapy versus UMEC/VI therapy. However, the ACM claim does not account for these different subgroups of patients and the different clinical interventions in each. Nor does the analysis account for whether the observed result was due to benefit from the addition of a therapy or due to harm in a subgroup where the therapy was removed. Given TRELEGY ELLIPTA's proposed claim of benefit of the ICS component on ACM, the Agency considered subgroups based on pre-study therapy with or without ICS in order to better understand these data.

These methodological concerns related to pre-study therapy in COPD trials are not new, and multiple authors have described the challenges in interpreting results from such trials. In a critique of contemporaneous COPD trials – including the TORCH trial – in 2008, Suissa and colleagues[50] described a subgroup approach to interpret data from trials in which subjects were randomized to therapy choices that included the same modalities used prior to randomization (i.e., an ICS trial including pre-study ICS therapy). A quote from the article by Suissa and colleagues states:

> *The single most important methodological concern is the rather unique situation in COPD of randomising some patients who were already being treated with ICSs before randomisation, to treatment with ICSs after randomisation. In actuality, this unusual situation creates two types of comparison. Among the patients who did not previously use ICSs (ICS-naïve), the randomisation leads to a comparison of patients initiating treatment with ICS with similar patients who do not. Among previous users of ICSs, however,*

> *the randomisation will lead to a comparison of patients who continue ICS use with patients who stop their use of ICS. Thus, combining previous users with nonusers in the trials leads to a mixture of the true effect of ICSs (in ICS-naïve patients) with the effect of suddenly interrupting ICSs (previous ICS users).*

The authors state that – in regular users of pre-study ICS – randomization provides a comparison of ICS removal versus ICS continuation. It should be highlighted that the ICS continuation arm acts as the control arm in this interpretation, while the ICS removal arm represents the experimental intervention. Only among subjects without pre-study ICS (i.e., ICS-naïve subjects) can randomization lead to the standard comparison of subjects initiating ICS therapy versus subjects who do not.

Reviewer's Comment*: The subgroup approach to interpretation suggested by Suissa and colleagues is applicable to the IMPACT trial's pre-study triple therapy and pre-study ICS populations, and is discussed in detail in Section 4.5.3 IMPACT: All-cause Mortality and Pre-study Triple Therapy and Section 4.5.4 IMPACT: All-cause Mortality and Pre-study ICS, below. Whether the subgroup interpretation creates uncertainty in the ACM results merits discussion with the Advisory Committee.*

Importantly, the 2008 article by Suissa and colleagues went on to compare AECOPD outcome results among the subgroups of randomized subjects with pre-study ICS and those without. The authors noted that the observed effects for time-to-first AECOPD in each subgroup were different both in magnitude and direction of effect. In the same article, the authors provided an analysis of previous COPD trials with similar methodologic issues regarding pre-study ICS use and ICS removal. Notably, using a generalized linear model including a logarithmic transform of the rate ratio, this analysis described a linear correlation between the proportion of patients with pre-study ICS in a study and the rate ratio of the result.

Reviewer's Comment*: In essence, this additional analysis by Suissa and colleagues described an association between studies enrolling higher proportions of pre-study ICS users and higher effect sizes in their overall analyses of AECOPD comparing ICS versus placebo arms, among the prior COPD trials examined. While this association between higher rates of pre-study ICS use and higher effect sizes is provocative, Suissa and colleagues' analysis was based on AECOPD endpoints. ACM endpoints were not examined in this publication, and whether a similar association could exist between proportion of subjects with pre-study ICS therapy and observed risk of ACM in trials that may include ICS removal as part of randomized treatment has not been studied. However, it is worth noting that IMPACT randomized a higher proportion of subjects with pre-study ICS than both SUMMIT and TORCH.*

Suissa applied a similar argument to all-cause mortality endpoints in a commentary[65] following

the INSPIRE[66] trial by Wedzicha and colleagues, as well as in a commentary prior to publication of the SUMMIT trial[67]. In the INSPIRE comment, Suissa noted that the same issue of pre-study ICS complicated the observed mortality result, because randomization led to the creation of pre-study ICS and ICS-naïve subgroups that could be described as testing the effects of ICS removal and ICS continuation, respectively, on all-cause mortality. It is notable that Suissa concluded that the mortality data from INSPIRE were uninterpretable for that reason.

Other authors have commented on the same phenomenon of pre-study ICS therapy and the need for subgroup analyses. In an article published in 2009[51] entitled "Methods for therapeutic trials in COPD: lessons from the TORCH trial", investigators from the TORCH trial acknowledged the methodological issue of pre-study ICS in the TORCH trial, noting that it was important to evaluate whether effects observed for ICS therapy were due to steroid withdrawal (i.e., ICS removal). In subgroup analyses of TORCH data, the investigators showed that patients with pre-study ICS use had higher rates of AECOPD after randomization compared to those without pre-study ICS. However, these TORCH investigators did not explicitly endorse the interpretation that these data represented the effect of ICS removal compared to ICS continuation.

Reviewer's Comment*: Importantly, this subgroup interpretation of the data raises a fundamental question for the IMPACT data: can data that may suggest harm on ACM endpoints as a result of medication removal be used to provide substantial evidence of efficacy and benefit on ACM endpoints for that medication? Given that an efficacy claim for fluticasone furoate on ACM endpoints may be interpreted by healthcare providers to support the addition of fluticasone furoate to the regimen of an ICS-naïve COPD patient, are ICS removal data appropriate and adequate to support the proposed indication? Whether data that may demonstrate a mortality risk after ICS removal among symptomatically uncontrolled patients with COPD can be used to support a claim of mortality benefit for the addition of ICS in any patient with COPD is unclear, and merits discussion with the Advisory Committee.*

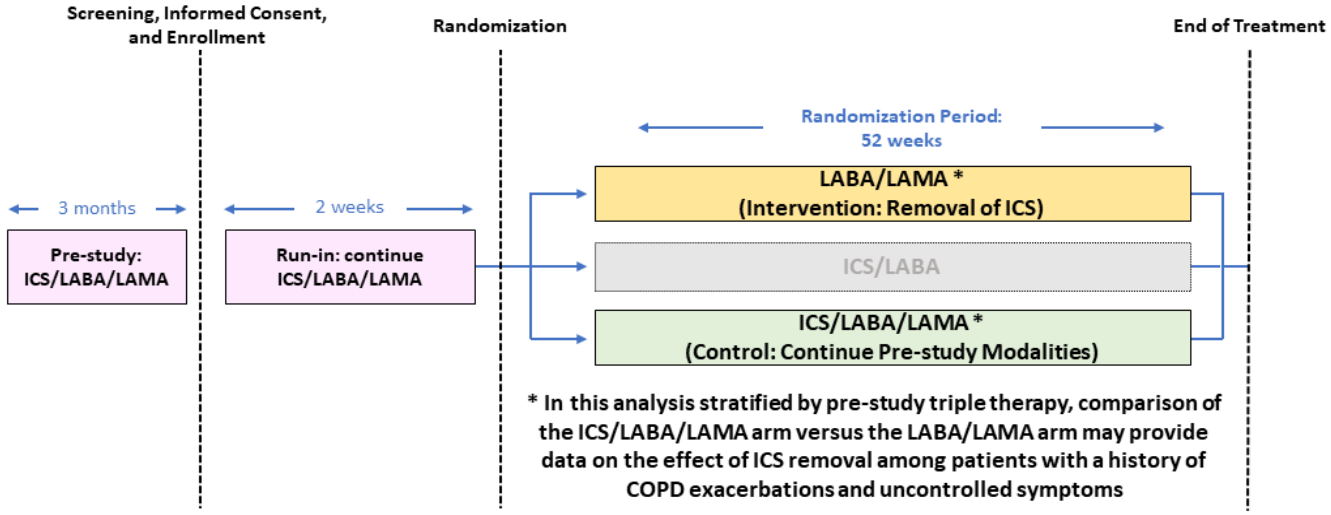
4.5.2. Pre-study Therapy and ICS Removal in IMPACT

The primary objective of the IMPACT trial was to demonstrate superiority on the rate of ModSev AECOPD of the ICS/LAMA/LABA, TRELEGY ELLIPTA, compared to two of its dual combination component products – regardless of the COPD maintenance medications they were prescribed prior to the study – among uncontrolled symptomatic COPD patients with a history of AECOPD in the prior year. However, among subjects who received pre-study COPD maintenance with ICS/LABA/LAMA (pre-study triple therapy) or with an ICS-containing regimen (pre-study ICS), the application of this study design led to a protocol-mandated abrupt removal of ICS as a therapeutic modality of COPD treatment among this vulnerable group of symptomatic patients with a prior history of AECOPD.

If the ACM analyses are examined with respect to pre-study medication subgroups using the concepts suggested by Suissa and colleagues[50], the interpretation of the effect changes. Since

subjects with pre-study triple therapy comprised 38% of the randomized population, these subjects provided a substantial amount of the trial's mortality data. The IMPACT trial randomized subjects prescribed pre-study triple therapy to either continue ICS/LABA/LAMA or to have a therapeutic modality taken away at randomization, if randomized to the ICS/LABA or LABA/LAMA arms. Moreover, the clinical intervention among subjects with pre-study triple therapy randomized to the LAMA/LABA arm was to abruptly remove ICS from the COPD regimen of these symptomatic patients with a prior history of AECOPD without a washout or medication taper period; no drugs were added by randomization for additional control of their symptoms. This concept is illustrated in Figure 13 below. Since the focus of this application was on the ICS/LABA/LAMA versus LABA/LAMA comparison and the contribution of the ICS, the focus of the discussion is limited to that comparison.

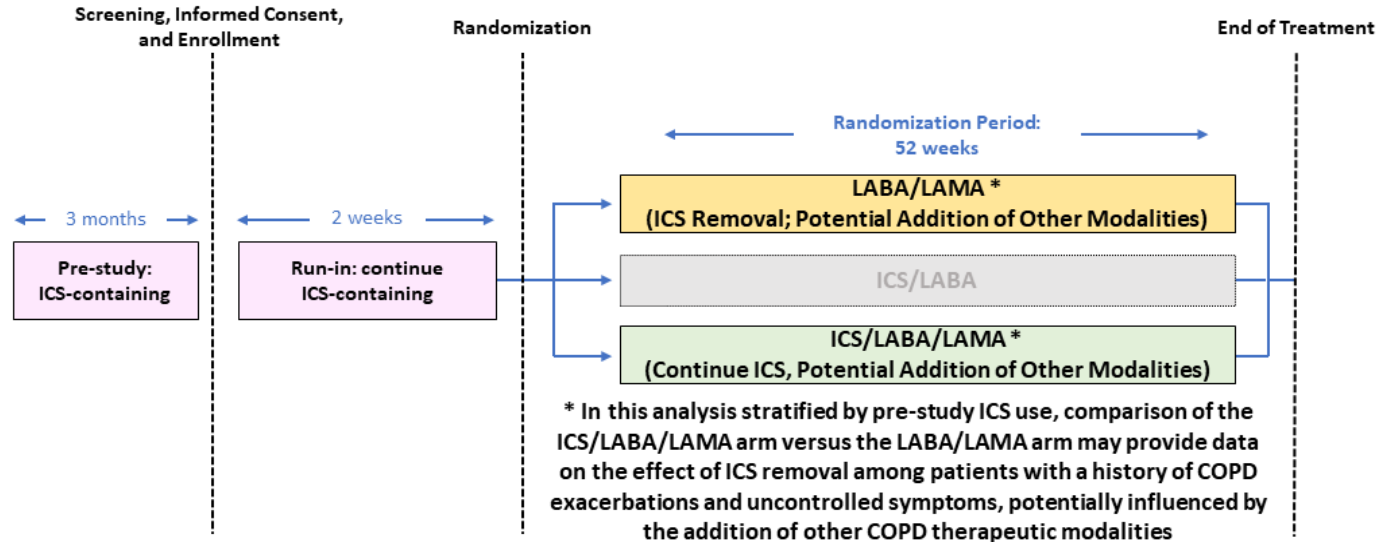
Figure 13. IMPACT: Study Schematic for Subgroup Receiving Pre-study Triple Therapy



Source: Reviewer
Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist

Randomization imposed a similar ICS removal scenario among those subjects prescribed pre-study ICS-containing regimens (e.g., primarily patients with pre-study ICS/LABA or ICS/LABA/LAMA). These pre-study ICS subjects comprised 71% of the randomized population. Functionally, the IMPACT trial randomized subjects with pre-study ICS to ICS removal or ICS continuation. The clinical intervention among subjects with ICS-containing pre-study regimens who were randomized to the LABA/LAMA arm involved abrupt removal of ICS from their COPD regimen. The potential for the addition of LAMA did also exist in this subgroup comparison; however, relying solely on the ICS/LABA/LAMA versus LABA/LAMA comparison allows us to isolate the contribution of the ICS, since LAMA addition would occur equally in both arms due to randomization. This concept is illustrated in Figure 14 below.

Figure 14. IMPACT: Study Schematic for Subgroup Receiving Pre-study ICS



Source: Reviewer
Abbreviations: ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist

As described above, and as shown in Table 8, approximately 71% of the subjects enrolled in the IMPACT trial received pre-study ICS-containing regimens, while 38% of the enrolled subjects received pre-study triple therapy. In order to further assess the influence of pre-study ICS therapy on the results of the IMPACT trial, the Agency requested exploratory, subgroup analyses of ACM data by the presence/absence of pre-study triple therapy, as well as by the presence/absence of pre-study ICS therapy.

Reviewer's Comment*: If the uncertainties surrounding ICS removal influence the clinical interpretation of the all-cause mortality results of IMPACT, a large proportion of the all-cause mortality data would be affected. Whether the uncertainty related to pre-study medications and the potential effect of ICS removal limit interpretation of IMPACT's all-cause mortality data for TRELEGY ELLIPTA's proposed mortality claim is discussed further below. This topic merits discussion by the Advisory Committee.*

As demonstrated, subjects in IMPACT may have been randomized to an intervention of ICS removal due to their pre-study medication regimen. While randomized removal trial designs can be acceptable tools in the evaluation of drugs, they are generally performed in settings of clinical equipoise where there are questions regarding the added utility of a drug, and where subjects are otherwise clinically stable. In contrast, 71% of subjects in the IMPACT trial exhibited frequent exacerbations in the prior year – most despite being prescribed FDA-approved therapies – while almost all subjects had moderate-to-severe COPD by spirometry and elevated symptom scores at baseline. While practice guidelines have not provided strict criteria to guide medication removal in COPD, the removal of therapeutic medication modalities among COPD patients who continue to experience AECOPD despite multiple effective medications would generally not be considered in clinical practice.

***Reviewer's Comment**: It is worth noting that clinical decision-making for patients with this severity of symptomatic COPD in normal practice focuses on adding medications for better AECOPD control and generally would not include medication removal. While COPD guidelines have not relied on strictly defined "step-up" approaches to symptomatic management, Global Initiative for Chronic Obstructive Lung Disease (GOLD) clinical guidelines from 2013 onward suggest that symptomatic COPD patients with a history of exacerbations in the previous year – as required by enrollment criteria – could benefit from additional modalities of COPD maintenance medications. The IMPACT protocol cites these guidelines, acknowledges the potential additive effect of therapeutic modalities, and acknowledges that the "withdrawal of ICS has also led to exacerbations in some patients."*

Finally, the Division acknowledges that clinical changes other than ICS removal or ICS continuation may have occurred in IMPACT's pre-study medication subgroups at randomization. For example, changes in adherence compared to pre-study adherence patterns may have influenced results. In addition, changes from one particular pre-study active ingredient within a drug class to the Applicant's study drug of the same class (i.e., one LAMA to another) may have occurred as a result of randomization. However, in both of these cases, these clinical changes would not be predicted to differentially affect one trial arm over another in a clinically meaningful way due to randomization. In contrast, the uncertainty regarding ICS removal would affect only the UMEC/VI arm of the trial, the arm that exhibited a higher mortality rate in the first ~90 days.

4.5.3. IMPACT: All-cause Mortality and Pre-study Triple Therapy

When examined by pre-study triple therapy subgroup, there is uncertainty in the interpretation of the all-cause mortality results from the IMPACT trial. As shown in Figure 15 below, subjects with pre-study triple therapy who had ICS removed (i.e., those randomized to UMEC/VI; left panel, green arm) showed increased mortality compared to those who remained on triple therapy (i.e., those randomized to FF/UMEC/VI; left panel, blue arm). While the UMEC/VI and FF/UMEC/VI curves also showed separation in the subgroup of subjects without pre-study triple therapy (i.e., right panel), this latter subgroup still contained subjects whose pre-study medication regimen included ICS, and these results should be interpreted with caution.

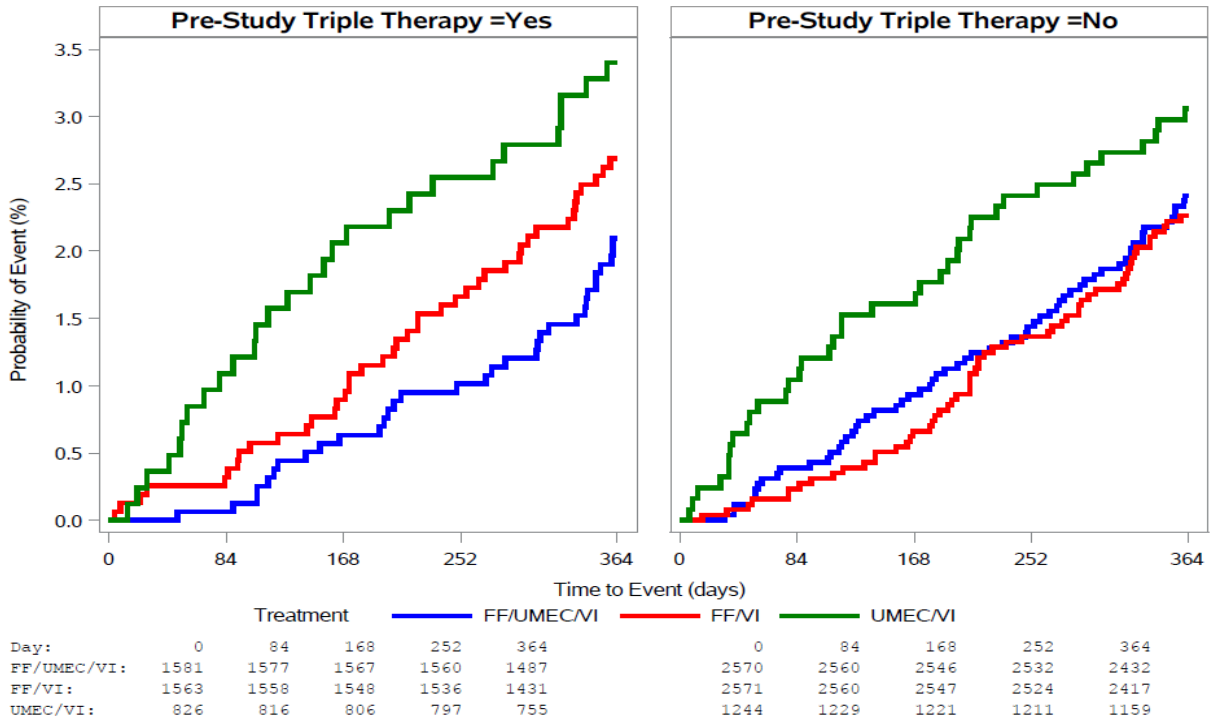
To more clearly isolate the potential role of ICS removal on the results, the Agency requested subgroup analyses by pre-study ICS therapy. See Section 4.5.4 for additional exploration of the potential effect of ICS removal through subgroup analyses by pre-study ICS.

When the data are examined with respect to pre-study therapy subgroup in Figure 15, the analysis of ACM comparing FF/UMEC/VI versus UMEC/VI among the pre-study triple therapy subgroup (i.e., left panel) could be interpreted as showing the effect of abrupt randomization-mandated removal of ICS among subjects with symptomatically uncontrolled COPD and

frequent exacerbations, compared to continuation of triple therapy. Under this subgroup interpretation in the Pre-Study Triple Therapy = Yes panel, the ICS removal intervention arm (i.e., UMEC/VI, the green curve) experienced higher early and total probabilities of death events compared to the ICS continuation control arm (i.e., FF/UMEC/VI, the blue curve). While the data in the left graph may suggest an effect related to ICS removal, they do not give a full picture of a potential effect of ICS removal, since the subgroup pictured in the right graph (Pre-Study Triple therapy = No) still included subjects with pre-study ICS.

***Reviewer's Comment**: Data from the pre-study triple therapy subgroup may suggest that ICS removal led to increased deaths in the UMEC/VI arm, since patients on pre-study triple therapy randomized to UMEC/VI experienced an intervention of ICS removal at randomization.*

Figure 15. IMPACT: Pre-study Triple Therapy Subgroups: Probability of All-cause Mortality Over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Day:	0	84	168	252	364	0	84	168	252	364
FF/UMEC/VI:	1581	1577	1567	1560	1487	2570	2560	2546	2532	2432
FF/VI:	1563	1558	1548	1536	1431	2571	2560	2547	2524	2417
UMEC/VI:	826	816	806	797	755	1244	1229	1221	1211	1159

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_kmplot_triple.sas. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT: intention-to-treat; VS: end of study vital status; VSFU: vital status follow-up; Triple therapy at Screening = Yes: subjects with pre-study ICS, LABA, and LAMA therapy; Triple therapy at Screening = No: subjects without pre-study ICS, LABA, and LAMA therapy; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg

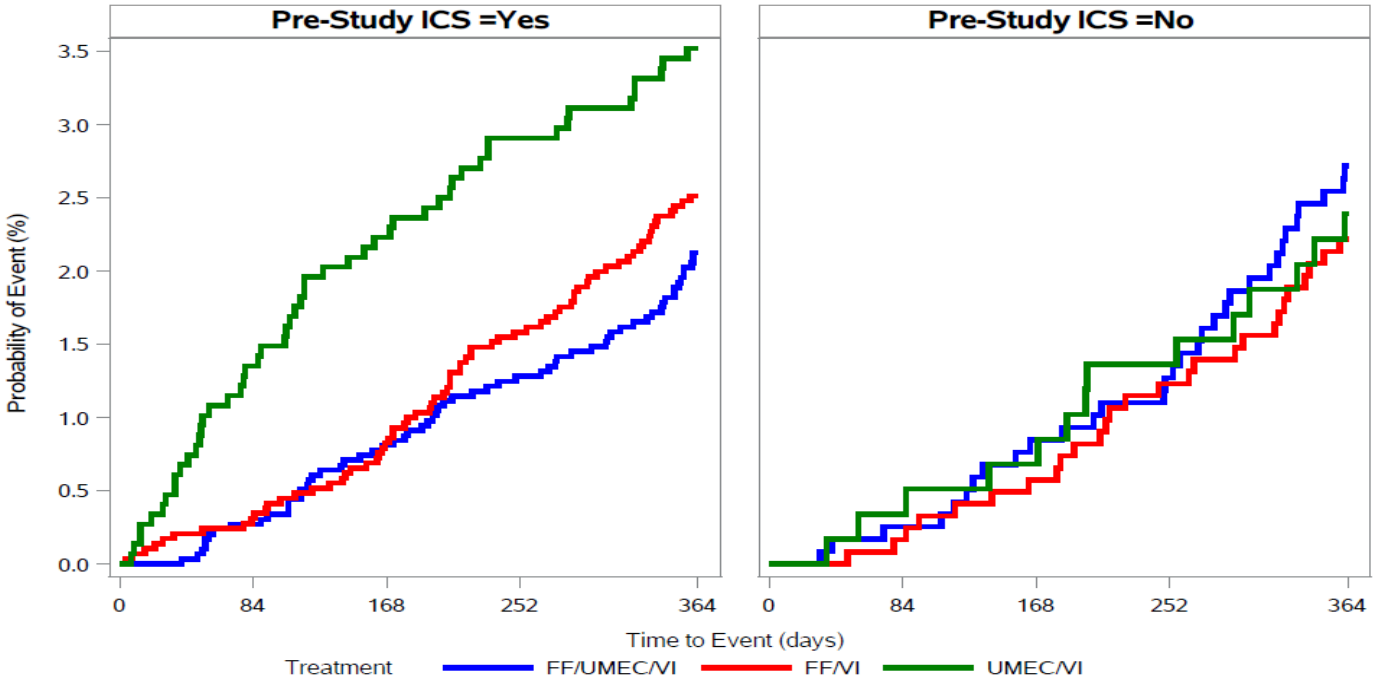
4.5.4. IMPACT: All-cause Mortality and Pre-study ICS

While the data in the pre-study triple therapy subgroup may suggest an effect related to ICS removal, they do not give a full picture of the potential effect of ICS removal in IMPACT, since the "pre-study triple therapy = no" subgroup still included subjects treated with pre-study ICS (e.g., patients treated with ICS/LABA pre-study). Therefore, we examined the data using pre-study ICS and ICS-naïve subgroups. Examinations by pre-study ICS subgroup reinforce the uncertainty in the interpretation of the all-cause mortality results from the IMPACT trial. The Kaplan-Meier curves for the subgroup of subjects with pre-study ICS and the subgroup without pre-study ICS differ strikingly in character and interpretation (see Figure 16 below).

When the IMPACT data are examined with respect to pre-study ICS subgroups, the analysis of ACM comparing FF/UMEC/VI versus UMEC/VI among subjects with pre-study ICS (i.e., Figure 16; left panel) shows a higher early and total probability of death events in the UMEC/VI arm. Based on the study design, mortality results in the UMEC/VI arm of the pre-study ICS subgroup could be attributed to the abrupt randomization-mandated ICS removal (i.e., intervention) in the UMEC/VI arm compared to continuation of ICS therapy (i.e., control) in the FF/UMEC/VI arm among subjects with uncontrolled COPD and a history of frequent exacerbations.

In contrast, an early mortality signal is not observed in any arm of the right panel, which presents the data for the ICS-naïve subgroup who were not at risk of ICS removal, and for whom ICS was added in the FF/UMEC/VI treatment arm Notably, these same ICS-naïve subgroup data do not suggest a mortality difference for the FF/UMEC/VI versus UMEC/VI comparison.

Figure 16. IMPACT: Pre-study ICS Subgroups: Probability of All-cause Mortality Over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Day:	0	84	168	252	364	0	84	168	252	364
FF/UMEC/VI:	2971	2960	2943	2927	2812	1180	1177	1170	1165	1107
FF/VI:	2908	2898	2882	2858	2709	1226	1220	1213	1202	1139
UMEC/VI:	1481	1460	1444	1429	1363	589	585	583	579	551

Source: Statistical reviewer, Analysis\IMPACT\reviewer programs\acm_vsfu_kmplot_ics.sas. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT: intention-to-treat; VS: end of study vital status; VSFU: vital status follow-up; Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-Study ICS = No: subjects without pre-study ICS-containing therapy; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg /vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg /vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg

***Reviewer's Comment**: Data from the left panel may suggest that a randomized intervention of ICS removal among subjects with pre-study ICS led to increased deaths in the UMEC/VI arm. Data from the right panel, while underpowered to detect a difference in ACM, suggest that an effect on ACM in IMPACT was not observed for ICS addition in ICS-naïve subjects.*

IMPACT ACM: Exploratory Analyses including pre-study ICS as an interaction term

As part of data exploration surrounding ICS removal as an intervention in IMPACT, the additional terms of pre-study ICS status and a pre-study ICS status by treatment interaction were added to the main analysis model that included treatment and covariates of age and gender. This post hoc analysis evaluating a possible interaction between treatment and pre-study ICS status suggested that the treatment effect might differ according to this baseline factor (p-value of 0.08 for interaction of pre-study ICS with pairwise comparison of FF/UMEC/VI versus UMEC/VI).

Reviewer's Comment: *These results, while exploratory in nature, suggest that the overall population ACM results may be difficult to interpret, and that it may be more appropriate to consider the subgroup analyses by pre-study ICS.*

Additional Analyses in the Pre-study ICS Subgroup

As shown in Figure 16 and detailed in Table 17, subjects with pre-study ICS-containing therapy who had ICS removed (i.e., those with pre-study ICS randomized to UMEC/VI) showed increased mortality compared to those who remained on ICS-containing therapies (i.e., those randomized to FF/UMEC/VI).

Following the paradigm in Figure 14, the pre-study ICS subgroup analysis of ACM comparing UMEC/VI (i.e. ICS removal) to FF/UMEC/VI (i.e., ICS continuation) could be interpreted as showing the effect of abrupt removal of ICS among subjects with symptomatically uncontrolled COPD and a history of frequent exacerbations. Supported by the suggestion of a potential treatment by pre-study ICS interaction term, and as described from a clinical perspective in Section 4.5.2, one could then view these pre-study ICS subgroup results as the results of an ICS removal trial design (see Section 4.5.8 ICS Removal in COPD). If this approach is accepted, the hazard ratio of the result is more appropriately "flipped" to the UMEC/VI versus FF/UMEC/VI orientation, considering the FF/UMEC/VI arm as active control in comparison to UMEC/VI as the ICS removal intervention. Both methods of hazard ratio calculation are presented in Table 17.

Under this "flipped" interpretation that describes the potential effects of ICS removal, subjects with pre-study ICS randomized to UMEC/VI (i.e., ICS removal) demonstrated a hazard ratio for death of 5.0 (95% CI 2.27 to 11.11) compared to those randomized to FF/UMEC/VI (i.e., ICS continuation) at Day 90. If the entire 52-Week course of the IMPACT trial is examined using this "flipped" interpretation, subjects with pre-study ICS randomized to UMEC/VI and ICS removal demonstrated a hazard ratio for death of 1.64 (95% CI 1.15 to 2.38) compared to those randomized to FF/UMEC/VI and ICS continuation.

Reviewer's Comment*: The IMPACT trial's "flipped" ACM results could be interpreted as showing a clinically significant effect on mortality of abrupt randomization-mandated removal of ICS among subjects with uncontrolled COPD and a history of frequent exacerbations, compared to continuation of ICS therapy. These are exploratory analyses where the 90-day time period of evaluation was in part data-driven and therefore may be subject to bias, and there is considerable uncertainty around the estimates due to the small numbers of events. Nevertheless, the results are striking, with a point estimate that would suggest a potentially clinically significant, five-fold increased risk of mortality attributable to ICS removal in this COPD patient population from baseline to Day 90. This interpretation would also suggest that the difference due to ICS removal persisted at Week 52.*

Table 17. IMPACT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Various Timepoints (ITT+VS+VSFU)

Timepoint Analysis	FF/UMEC/VI N=2,971	FF/VI N=2,908	UMEC/VI N=1,481
Week 52			
Number of subjects with event, n (%)	65 (2.2)	79 (2.7)	52 (3.5)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		0.80 (0.57, 1.11)	0.61 (0.42, 0.87)
ACM HR (95% CI, comparator vs. FF/UMEC/VI)		1.25 (0.90, 1.75)	**1.64 (1.15, 2.38)**
Day 90			
Subjects with event at day 90, n (%)	9 (0.3)	10 (0.3)	22 (1.5)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		0.88 (0.36, 2.16)	0.20 (0.09, 0.44)
ACM HR (95% CI, comparator vs FF/UMEC/VI)		1.14 (0.46, 2.78)	**5.00 (2.27, 11.11)**
After day 90 (excluding first 90 days)			
Subjects with available data after day 90	2,933	2,856	1,435
Subjects with event after day 90, n (%)	49 (1.7)	51 (2.1)	26 (1.8)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		0.77 (0.53, 1,12)	0.90 (0.56, 1.44)
ACM HR (95% CI, comparator vs. FF/UMEC/VI)		1.30 (0.89, 1.89)	**1.11 (0.69, 1.79)**

Source: Applicant submitted materials and Division statistical reviewer analyses. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints as part of the FF/UMEC/VI FDC; these **bold text** comparisons are based on the "UMEC/VI vs. FF/UMEC/VI" comparison orientation that may capture the effect of ICS removal, described above the table.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA
Abbreviations: ACM, all-cause mortality; CI, confidence interval. FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; HR, hazard ratio; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg; VSFU, vital status follow-up

As shown in the table, the mortality rate within the first 90 days is markedly higher in the UMEC/VI arm (i.e., where ICS was removed) compared to both the FF/UMEC/VI arm and the FF/VI arm (i.e., arms where ICS was continued), as is the hazard ratio at that timepoint. This analysis showing a potential early mortality signal for ICS removal reinforces the trend of early mortality for the UMEC/VI arm observed in Figure 16.

Reviewer's Comment*: These unexpected early mortality differences observed primarily in the pre-study ICS subgroup create uncertainty in using these ACM results to support a benefit claim attributable to the FF component, given that subjects in this subgroup were not ICS-naïve. The results could instead be interpreted to demonstrate potentially early and persistent harmful effects of ICS removal on mortality among a population of symptomatic COPD subjects who continued to exhibit frequent exacerbations despite previous maintenance ICS treatment. This potential safety signal for mortality warrants discussion by the Advisory Committee.*

Analyses in the ICS-naïve Subgroup

Data suggesting lower mortality among those subjects without pre-study ICS-containing medications (i.e., ICS-naïve subjects) that were randomized to FF/UMEC/VI compared to UMEC/VI (i.e. those subjects who had an ICS added) would increase confidence in the claim of a benefit of the addition of ICS on ACM, which is the clinically relevant question. However, these subgroup analyses among ICS-naïve subjects do not suggest a beneficial trend on mortality (see Figure 16, right panel, and Table 18).

***Reviewer's comment**: The exploratory subgroup comparison of ICS-naïve subjects randomized to FF/UMEC/VI compared to UMEC/VI in IMPACT is limited in power and should be interpreted with caution. Despite these limitations, these data do not provide support to a claim of ICS efficacy on ACM over 52 weeks. While the point estimate for the Day 90 data trends in the direction of benefit, the confidence intervals are wide, and this potential early signal is not present by the Week 52 timepoint.*

Table 18. IMPACT: Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Various Timepoints (ITT+VS+VSFU)

Timepoint Analysis	FF/UMEC/VI N=1,180	FF/VI N=1,226	UMEC/VI N=589
Week 52			
Subjects with event, n (%)	33 (2.8)	30 (2.5)	14 (2.4)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		1.13 (0.69, 1.86)	**1.16 (0.62, 2.16)**
Day 90			
Subjects with event at day 90, n (%)	3 (0.3)	3 (0.2)	3 (0.5)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		1.03 (0.21, 5.10)	**0.50 (0.10, 2.50)**
After day 90 (excluding first 90 days)			
Subjects with available data after day 90	1,164	1,203	578
Subjects with event after day 90, n (%)	28 (2.4)	23 (1.9)	10 (1.7)
ACM HR (95% CI, FF/UMEC/VI vs. comparator)			**1.35 (0.66, 2.78)**

Source: Applicant submitted materials and Division statistical reviewer analyses. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints as part of the FF/UMEC/VI FDC.
Pre-study ICS = No: subjects without prestudy ICS-containing therapy;
Abbreviations: ACM, all-cause mortality; CI, confidence interval; comp, comparator; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; HR, hazard ratio; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg; VSFU, vital status follow-up

Baseline Characteristics by Pre-Study ICS Subgroup

Baseline characteristics examined by pre-study ICS subgroup are presented in Table 19 and Table 20, below. This subgroup analysis reveals that the subgroup prescribed pre-study ICS exhibited numeric differences in both FEV1 and the proportion of subjects experiencing frequent exacerbations in the previous year. However, if the pre-study ICS interpretation paradigm of Suissa and colleagues[50] is accepted, the clinical interpretations of the data in each subgroup are fundamentally different, and each subgroup analysis stands alone. The results of

adding the pre-study ICS by treatment interaction term to the statistical model support that this pre-study ICS subgroup interpretation may be more appropriate. Since each subgroup provides data on a different clinical question – and since only within-subgroup comparisons were used for the subgroup analyses presented above – differences in baseline characteristics alone between these subgroups likely do not adequately explain the between-subgroup difference in mortality risk observed, nor do they provide justification for combining the data to simply interpret the overall result.

***Reviewer's Comment**: Markers of COPD control and severity are numerically increased among the subgroup of subjects with pre-study ICS compared to the ICS-naïve subgroup. However, these between-subgroup differences do not influence the interpretation of within-subgroup comparisons. The ICS removal concerns described above are based purely on within-subgroup comparisons, where severity and exacerbation frequency would be comparable across study arms. Indeed, the within-subgroup pre-study ICS comparison highlights the fact that ICS removal was only possible in this subgroup of "sicker" subjects (i.e., with markers of higher disease severity and worse symptomatic control despite pre-study maintenance therapy with ICS) who could be predicted to show more negative effects after ICS removal. In contrast, subjects in the ICS-naïve subgroup were not at risk of ICS removal at randomization, and within-subgroup comparisons of this ICS-naïve subgroup may provide the most straightforward assessment of the effect of ICS addition on ACM in COPD from the IMPACT trial.*

Table 19. IMPACT: Pre-study ICS Subgroups: Demographic and Baseline Disease Characteristics Across Subgroups (ITT+VS+VSFU)

Demographic/Baseline Characteristics	Pre-study ICS Yes	Pre-study ICS No
Total, N	7,360	2,995
Smoking history		
Current	2,408 (33)	1,179 (39)
Former	4,952 (67)	1,816 (61)
Postbronchodilator FEV1*		
Mean FEV1%p (SD)	44.7 (14.7)	47.7 (15.1)
AECOPD category**		
<2 mod and no sev	2,141 (29)	915 (31)
≥2 mod or ≥1 sev	5,219 (71)	2,080 (69)

Source: Reviewer, adapted from Applicant's submitted materials.
All values are expressed as n (%) unless specified otherwise.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
*FEV1 data for 5 subjects were missing from this analysis; calculated proportions incorporate this adjusted denominator
**AECOPD category was based on COPD exacerbations within 12 months prior to Screening
Abbreviations: %p, percent predicted; AECOPD, acute exacerbation of COPD; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroid; ITT, intention to treat; mod, moderate; SD, standard deviation; sev, severe; VS, end of study vital status; VSFU, vital status follow-up

Despite across-subgroup differences, within-subgroup baseline characteristics do not show clinically significant differences between trial arms (see Table 20), suggesting that comparisons within each subgroup were not influenced by differences in baseline characteristics.

Table 20. IMPACT: Pre-study ICS Subgroups: Demographic and Baseline Disease Characteristics by Subgroup and Treatment Arm (ITT+VS+VSFU)

Demographic/Baseline Characteristics	Pre-study ICS = Yes			Pre-study ICS = No		
	FF/UMEC/VI	FF/VI	UMEC/VI	FF/UMEC/VI	FF/VI	UMEC/VI
Total, N	2,971	2,908	1,481	1,180	1,226	589
Smoking history						
Current	978 (33)	937 (32)	493 (33)	458 (39)	486 (40)	235 (40)
Former	1,993 (67)	1,971 (68)	988 (67)	722 (61)	740 (60)	354 (60)
Postbronchodilator FEV1*						
Mean FEV1%p (SD)	44.7 (14.7)	44.6 (14.6)	44.8 (14.7)	48.3 (15.3)	47.6 (15)	46.9 (14.6)
AECOPD category**						
<2 mod and no sev	862 (29)	858 (30)	421 (28)	336 (28)	384 (31)	589 (33)
≥2 mod or ≥1 sev	2,109 (71)	2050 (70)	1060 (72)	844 (72)	842 (69)	394 (67)

Source: Reviewer, adapted from Applicant's submitted materials.
All values are expressed as n (%) unless specified otherwise.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
*FEV1 data for 5 subjects were missing from this analysis; calculated proportions incorporate this adjusted denominator
**AECOPD category was based on COPD exacerbations within 12 months prior to Screening
Abbreviations: %p: percent predicted; AECOPD, acute exacerbation of COPD; FEV1, forced expiratory volume in one second; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; mod, moderate; SD, standard deviation; sev, severe; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg; VSFU, vital status follow-up

4.5.5. Data Monitoring Committee Comments Pertinent to ICS Removal and Early Mortality in IMPACT

The IMPACT trial's IDMC commented on the early mortality signal in the UMEC/VI arm of the IMPACT trial. The IDMC Meeting Minutes note the following points during the November 3rd, 2015 meeting (the text is quoted directly from Meeting Minutes, without revisions for clarity; Data Monitoring Committee was denoted as "DMC" in closed session Meeting Minutes):

- *The DMC was particularly concerned with the number of deaths that appear to have occurred either on the same day as first dose of soon thereafter. It was asked if this study population may include a high number of patients who have washed out of their previous therapies where they received inhaled steroid. The protocol was reviewed the DMC found that inhaled steroid use is prohibited 30 days prior to screening and during the study.*

***Reviewer's Comment**: Based on these Meeting Minutes, it is reasonable to conclude that the IDMC had concerns about early mortality in the IMPACT trial. It is also reasonable to conclude that the IDMC asked questions related to the possibility of ICS removal as a potential contributor. At this point a protocol review occurred. The determination reached from this protocol review was*

incorrect in stating that "inhaled steroid use is prohibited 30 days prior to screening and during the study"; in fact, only systemic, oral, and parenteral corticosteroids were prohibited during that time. ICS removal events did, in fact, occur during the timeframe that the IDMC noted as a concern based on the number of deaths. In the setting of this erroneous determination regarding the presence and timeframe of ICS removal events in IMPACT, the trial was allowed to proceed after this meeting of the DMC.

In addition, the IDMC reviewed incomplete data on prior history of AECOPD during their data review. The IDMC Meeting Minutes note the following points during the November 3rd, 2015 meeting (the shaded text is quoted directly from Meeting Minutes, without revisions for clarity. The only change to the text is the replacement of a committee member's name with "XX"):

- *The DMC noted that there were a large number of subjects missing data for exacerbation reported within 12 months prior to screening. XX explained that the data were not clean and that many dates of exacerbation prior to screening were either partially or entirely missing. As a result, determining whether or not an exacerbation occurred within 12 months of screening was proving difficult. XX mentioned that the data would be cleaned by end of study and before the database was locked.*

***Reviewer's Comment**: The frequency of prior exacerbations and the proportion of subjects with a frequent exacerbator phenotype may also have influenced the determination of whether the early mortality signal could be due to randomization-mandated ICS removal. These data were not available during the IDMC meetings during this early portion of the trial.*

Based on the available information provided by the complete IDMC Meeting Minutes, the fact that ICS removal events occurred at the time of randomization in over two-thirds of subjects in the UMEC/VI arm subjects – and not in the FF/VI or FF/UMEC/VI study arms – was likely not incorporated by the IDMC into its decision regarding study continuation. In addition, based on the same IDMC Meeting Minutes, the IDMC did not have sufficient data at the time of trial decision-making to incorporate symptomatic severity measures that indicated that over two-thirds of these same IMPACT participants had a history of frequent AECOPD in the prior year, despite their prior COPD maintenance medication use.

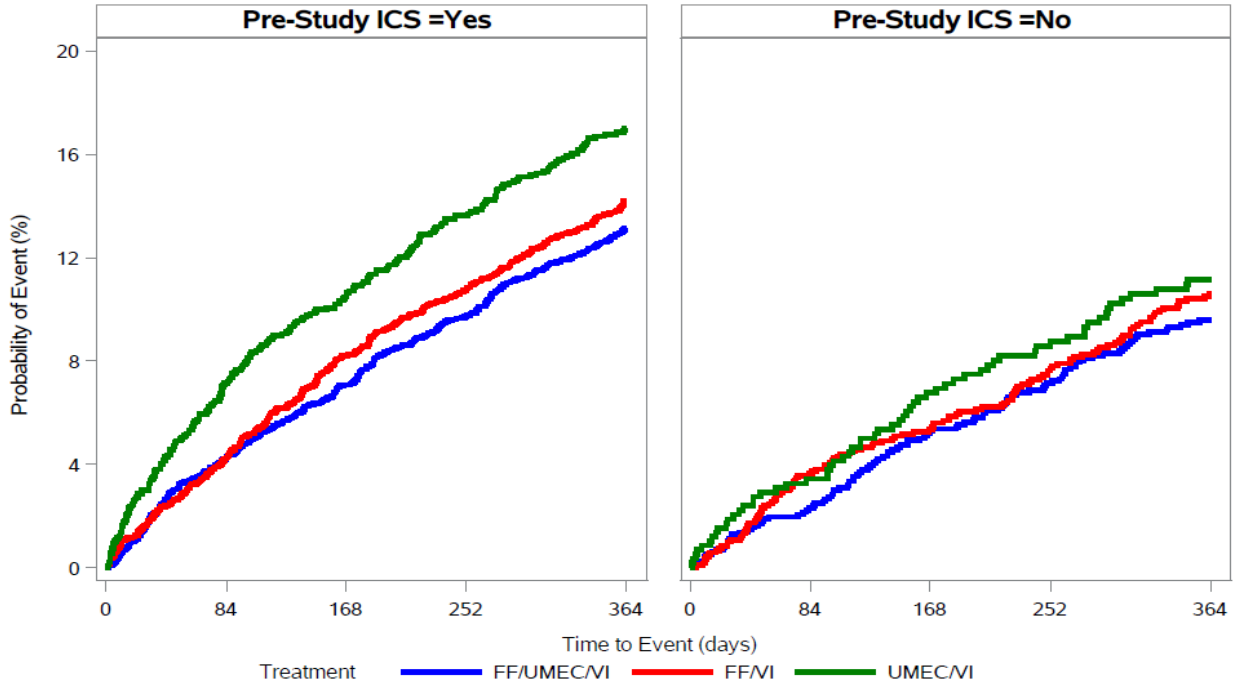
4.5.6. IMPACT: Severe AECOPD and Pre-Study ICS

Increased severe AECOPD are associated with increased mortality in observational studies. Negative effects of ICS removal, if present, could also lead to a higher risk of severe AECOPD events among subjects in the IMPACT trial among those at risk of ICS removal. To examine this further, the Agency requested exploratory analyses of time-to-first severe AECOPD by pre-study

ICS subgroup. Similar to the pattern observed in the subgroup analyses of ACM, the Kaplan-Meier curves for the time-to-first severe AECOPD endpoint also show a higher early event rate in the UMEC/VI arm of the pre-study ICS subgroup (Figure 17, left panel, green curve), while the ICS-naïve subgroup does not demonstrate this early trend in the UMEC/VI arm (Figure 17, right panel, green curve).

***Reviewer's Comment**: Analogous to the interpretation of the ACM subgroup data, the pre-study ICS Kaplan-Meier plot may suggest an early at-risk period for first severe AECOPD among subjects in the subgroup prescribed pre-study ICS who were then randomized to UMEC/VI (i.e., those that underwent ICS removal; left panel, green curve) compared to those randomized to FF/UMEC/VI or FF/VI (i.e., those who continued ICS; left panel, blue and red curves).*

Figure 17. IMPACT: Pre-Study ICS Subgroups: Probability of First Severe AECOPD Through Week 52 by Treatment Arm (ITT Including On- and Off-treatment Data)



Day:	0	84	168	252	364	0	84	168	252	364
FF/UMEC/VI:	2971	2794	2655	2534	2309	1180	1131	1079	1038	950
FF/VI:	2908	2697	2522	2390	2151	1226	1143	1095	1036	940
UMEC/VI:	1481	1321	1236	1163	1055	589	554	526	502	451

Source: Reviewer program .sevex_onoff_kmplot_ics.sas These analyses incorporate available on- and off-treatment AECOPD data from the IMPACT.
Abbreviations: ITT: intention-to-treat; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

Analyses in the Pre-study ICS Subgroup

Following the paradigm in Figure 12 and Sections 4.5.2 and 4.5.4, the pre-study ICS subgroup analysis of severe AECOPD comparing UMEC/VI (i.e. ICS removal) to FF/UMEC/VI (i.e., ICS continuation) could be interpreted as showing the effect of abrupt removal of ICS among subjects with symptomatically uncontrolled COPD and a history of frequent exacerbations. Under this "flipped" interpretation paradigm, subjects with pre-study ICS randomized to UMEC/VI (i.e., ICS removal) demonstrated a hazard ratio for severe AECOPD of 1.39 (95% CI 1.18 to 1.61) compared to those randomized to FF/UMEC/VI (i.e., ICS continuation). Both methods of hazard ratio calculation are presented in Table 21.

These data suggesting higher risk of severe AECOPD in the setting of ICS removal align with the ACM result from this subgroup, both of which may support an interpretation of negative outcomes with ICS removal (see Section 4.5.4). In addition, this observed increase in Severe AECOPD after ICS removal aligns with extant data suggesting increased severe AECOPD after ICS removal from published randomized withdrawal trials of ICS (see Section 4.5.8 ICS Removal in COPD).

Table 21. IMPACT: Probability of First Severe AECOPD Through Week 52, Pre-study ICS = Yes (ITT Including Both On- and Off-treatment Data)

Category	FF/UMEC/VI N=1180	FF/VI N=1226	UMEC/VI N=589
Number of subjects with event, n (%)	379 (13)	393 (14)	245 (17)
HR (95% CI for FF/UMEC/VI vs. comparator)		0.91 (0.79, 1.04)	0.72 (0.62, 0.85)
HR (95% CI for comparator vs. FF/UMEC/VI)		1.09 (0.96, 1.27)	**1.39 (1.18, 1.61)**

Source: Applicant submitted materials and Division statistical reviewer analyses. These analyses incorporate on- and off-treatment data from the IMPACT study for subjects who discontinued study drug. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on severe AECOPD endpoints as part of the FF/UMEC/VI FDC. These **bold text** comparisons are based on the "UMEC/VI vs. FF/UMEC/VI" comparison orientation that may capture the effect of ICS removal, described previously.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Abbreviations: CI, confidence interval, FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; HR, hazard ratio; ITT, intention to treat; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

Analyses in the ICS-naïve Subgroup

Conversely, severe AECOPD results from the ICS-naïve subgroup comparison of FF/UMEC/VI versus UMEC/VI does not demonstrate a significant difference that could be attributable to the addition of ICS (Table 22), similar to the results for ACM in this ICS-naïve subgroup. It must be acknowledged again, however, that this ICS-naïve subgroup contains fewer subjects and less statistical power than might be needed to demonstrate a significant result, and that these subgroup results are exploratory.

Table 22. IMPACT: Time-to-First Severe AECOPD, Week 52, Prestudy ICS = No (ITT Including Both On- and Off-Treatment Data)

Category	FF/UMEC/VI N=1,180	FF/VI N=1,226	UMEC/VI N=589
Number of subjects with event, n (%)	109 (9)	123 (10)	63 (11)
HR (95% CI for FF/UMEC/VI vs. comparator)		0.93 (0.72, 1.21)	**0.87 (0.64, 1.19)**

Source: Applicant submitted materials and Division statistical reviewer analyses
These analyses incorporate on- and off-treatment data from the IMPACT study for subjects who discontinued study drug.
Comparisons in **bold text** provide data to inform the efficacy and safety of FF on severe AECOPD endpoints as part of the FF/UMEC/VI FDC.
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
Abbreviations: CI, confidence interval; FF/UMEC/VI: fluticasone furoate 100 µg/umeclidinium 62.5 µg/vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg/vilanterol 25 µg; HR, hazard ratio; ITT: intention to treat; UMEC/VI: umeclidinium 62.5 µg/vilanterol 25 µg

4.5.7. Pre-study Therapy and ICS Removal in SUMMIT and TORCH

The SUMMIT and TORCH trials both evaluated ACM in COPD using a design that included subjects with pre-study ICS use. Both trials randomized these pre-study ICS subjects to arms that could involve ICS removal. However, the designs of both SUMMIT and TORCH included interventions that led to ICS removal prior to randomization through a run-in and/or pre-enrollment requirements that could span approximately 2 weeks (see study schematics for SUMMIT and TORCH, Figure 2 and Figure 3, respectively). In addition, the randomized populations of these two trials differed in clinically meaningful ways compared to the population randomized in IMPACT (see Table 5 in Section 4.2.1).

Despite these differences in designs and populations compared to IMPACT, an early signal for increased ACM due to ICS removal in TORCH and SUMMIT might provide supportive evidence to better evaluate the exploratory analyses of ICS removal and early risk for ACM performed in IMPACT. Similar results in the pre-study ICS subgroup would raise uncertainty in the appropriate interpretation of the ACM data from IMPACT and in the ACM claim for fluticasone furoate as a component of TRELEGY ELLIPTA. In addition, ACM data from ICS-naïve subjects in TORCH and SUMMIT (i.e., those who were not at risk of ICS removal) might provide additional insight into the efficacy of ICS as an add-on therapy for this endpoint.

Exploratory subgroup analyses by pre-study ICS use for the SUMMIT and TORCH trials are presented in Appendices 5.5.5 and 5.6.5, respectively. Additional data regarding death events by pre-study ICS subgroup during the run-in periods of these trials are presented in Appendices 5.5.6 and 5.6.6, respectively. Similar to the trend observed in IMPACT pre-study ICS group, data from SUMMIT's and TORCH's comparisons that isolate the contribution of the ICS support a similar – but attenuated – early risk period for mortality events among the subgroup of pre-study ICS subjects who experienced ICS removal. Further supporting subgroup results from IMPACT's ICS-naïve subgroup, data from SUMMIT's and TORCH's comparisons that isolate the contribution of the ICS do not support the efficacy of ICS on ACM endpoints in the ICS-naïve subgroups.

Reviewer's Comment: *The subgroup analyses of SUMMIT and TORCH support the results of the subgroup analyses performed for IMPACT. While these studies*

recruited different patient populations than IMPACT, the ACM results from the pre-study ICS subgroups of SUMMIT and TORCH may also suggest increased early mortality due to ICS removal. Although the magnitude of the observed ICS removal effect on ACM is lower than in IMPACT, this could potentially be attributed to attrition during the run-in and to a less severe patient population undergoing ICS removal. The ICS-naïve subgroup results from SUMMIT and TORCH also do not provide data that would adequately support a claim of mortality benefit attributable to the addition of ICS.

4.5.8. ICS Removal in COPD

The scientific literature includes multiple studies and trials of ICS removal in COPD, but these trials have not been designed or powered to detect mortality differences. Moreover, differences in the study designs make cross-study comparisons and a straight-forward summation of the literature difficult. With these caveats to interpretation, trends in this body of literature suggest that ICS removal may cause clinically significant deterioration in lung function, patient-reported outcomes, and rates of AECOPD among COPD subjects with uncontrolled and symptomatic disease. In contrast, randomized trials of ICS removal among subjects with better disease control (i.e., fewer exacerbations in the previous year in the randomized cohort than observed in IMPACT) suggest that there may be a population of controlled patients with COPD in whom the detrimental effects on lung function and rates of ModSev AECOPD associated with ICS removal may be clinically acceptable when weighed against the potential risks of ICS use. No trial has proposed randomized ICS removal among a group of COPD patients with markers of uncontrolled and symptomatic COPD that are clinically comparable to those in the IMPACT trial.

Despite the overall trends, examination of the publicly available data reveals potential safety signals for increased severe AECOPD immediately after ICS removal[45,68] and trends of increased rates of severe AECOPD[47] over time. These trends raise concerns about the effects of ICS removal in a more symptomatically uncontrolled group.

In addition, and important for the discussion of the current submission, the literature on ICS removal has never raised the prospect of significant clinical improvement on meaningful endpoints such as lung function or AECOPD after the removal of ICS, much less an improvement on mortality measures. The literature has focused on whether the observed clinical decline after ICS removal was clinically significant or acceptable to the patient's overall health given the known risks of ICS use. While not powered to assess this endpoint, no study has presented data suggesting that ICS removal might lead to an improvement in ACM.

ICS removal studies and trials relevant to the discussion of the pre-study ICS subgroup results of IMPACT, SUMMIT, and TORCH are summarized below. These trials present similarities and contrasts in study design that may aid the interpretation of ACM data based on pre-study ICS

subgroups in IMPACT, SUMMIT, and TORCH. Additional trials of ICS removal in COPD are summarized in Appendix 5.7.

Studies of ICS removal Effects in Uncontrolled COPD

Data on ICS removal effects may suggest that removal of ICS maintenance therapy in patients with COPD could have significant clinical consequences, especially among patients with a history of exacerbations despite inhaled medication use. It should be noted that the primary data for these studies have not been formally reviewed by the Agency for this application, and the information presented here for each study relies on the peer-reviewed publications in the public domain.

Jarad, et al.

In a non-randomized study published in 1999, Jarad and colleagues[34] followed 272 COPD patients with and without pre-study ICS maintenance therapy (59% and 41%, respectively) entering the 8-week run-in phase of the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study. The demographic and clinical characteristics of the subjects in the study were comparable to symptomatic COPD subjects entering clinical trials, with a mean age of 65 years, FEV1 of 42.8% predicted, and clinical stability over the previous 12 weeks. Subjects with pre-study ICS discontinued ICS over the course of one week and were followed for an additional 7 weeks. Among the 67 patients who experienced an AECOPD during the 8-week run-in, 60 (90%) were subjects who discontinued pre-study ICS. While the authors of the study acknowledge multiple limitations in the study design, the data may suggest that discontinuation of ICS among symptomatic patients could be associated with increased AECOPD.

Importantly, this study was conducted among symptomatically uncontrolled COPD patients entering a clinical trial, and results were reported at the 8-week timepoint, suggesting an early effect of ICS removal. While the study by Jarad and colleagues suggested decreases in FEV1 and symptomatic decline after removal of ICS, it was neither designed nor powered to show differences in endpoints such as rates of ModSev AECOPD or all-cause mortality.

***Reviewer's Comment**: This non-randomized evaluation of AECOPD during the run-in of the ISOLDE trial shares design elements with the non-randomized evaluation of mortality during the of SUMMIT and TORCH described in Appendices 5.5.6 and 5.6.6, respectively.*

Wouters, et al.

A study sponsored by GlaxoSmithKline led to the publication of an article entitled "Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial" by Wouters and colleagues[38]. This publication also may suggest that ICS removal leads to clinical decline in COPD. Wouters and colleagues conducted a 12-month, randomized, double-blind, placebo-controlled clinical trial of ICS removal (fluticasone propionate) in 497 COPD patients. Subjects completed a 3-month run-in period on ICS/LABA, followed by randomization to

placebo + LABA (i.e., ICS removal), or continuation of ICS/LABA (i.e., ICS continuation). Enrolled COPD subjects had a mean age of 63.5 years, mean FEV1 of 48.5% predicted, and were required to have a history of at least two moderate AECOPD in the prior year for inclusion. During the 12-month randomization period, subjects randomized to ICS removal experienced a statistically significant 4.1% decrease in FEV1 compared to those randomized to ICS continuation. While this trial was not able to show a statistically significant difference in the rate of ModSev AECOPD over the course of the trial, the model-adjusted rate ratio of ModSev AECOPD was 1.6 per patient-year in the ICS removal group compared to 1.3 per patient-year in the ICS continuation group. In addition, the authors report a shorter time-to-first ModSev AECOPD among patients with FEV1 <50% predicted. Neither all-cause mortality data nor AECOPD endpoints summary data from earlier timepoints were reported in this trial.

Reviewer's Comment*: This trial suggested immediate and sustained disease deterioration after ICS removal. Multiple trials and studies have suggested that uncontrolled COPD patients undergoing ICS removal experience worsening symptoms, decreases in FEV1, and worsening measures of AECOPD control. However, few of these trials formally assessed severe exacerbation rates, and these trials were neither appropriately designed nor powered to rigorously evaluate the effect of ICS removal on mortality among COPD patients with frequent exacerbations and uncontrolled symptoms despite multiple medications.*

Recent Randomized ICS removal Trials in Controlled COPD

Since the recognition of ICS removal as a potential source of clinical deterioration among COPD patients with a history of exacerbations or uncontrolled symptoms, multiple studies have attempted to define COPD populations with few prior AECOPD and greater symptomatic control, in whom ICS removal could be safe and clinically feasible. To address the clinical safety concerns and inform clinical decision-making, three double-blind, randomized, controlled trials evaluated the safety of ICS removal using randomized-withdrawal methodologies. The first trial was published in 2014 by Magnussen and colleagues, under the eponym of WISDOM[45]. The second trial was published in 2014 by Rossi and colleagues, under the eponym of INSTEAD[44]. The third trial was published in 2018 by Chapman and colleagues, under the eponym of SUNSET[59]. The published results of these trials are discussed below. It should again be noted that the primary data for these studies have not been formally reviewed by the Agency for this application, and the information presented for each study relies on the peer-reviewed publications in the public domain.

Fundamentally, the WISDOM, INSTEAD, and SUNSET trials assessed the effect of ICS removal in COPD populations who exhibited different levels of disease control compared to the IMPACT trial. Subjects in INSTEAD had no history of ModSev AECOPD, subjects in SUNSET could not meet criteria for frequent exacerbators, and subjects in WISDOM had at least one ModSev AECOPD. Importantly, while these trials are informative to the discussion of the effects of ICS removal, all three of these trials focused on ICS removal in a population of patients with COPD who might be considered candidates for ICS removal in clinical practice. This trial design is

consistent with clinical practice, since current international guidelines are equivocal on the safety of ICS removal even among subjects who are otherwise symptomatically controlled. Compared to the population of the IMPACT trial, these trials randomized patients who exhibited comparatively fewer or zero AECOPD in the previous year and who exhibited greater symptomatic control on inhaled COPD maintenance therapy.

***Reviewer's Comment**: These three trials enrolled comparatively controlled patients with COPD – in whom a clinical decision of ICS removal might be considered in common practice – and randomized them to ICS removal versus ICS continuation. In contrast to each of these three trials, the IMPACT trial enrolled COPD patients with uncontrolled symptomatic disease and a history of AECOPD. IMPACT subjects with pre-study ICS therapy could then be randomized to ICS removal. Notably, the clinical ICS removal scenario described in IMPACT occurred in patients with uncontrolled symptoms and AECOPD events in the prior year despite multiple COPD medications would generally have a compelling indication for adding medications to the COPD maintenance therapy regimen, not removing them. Whether the ICS removal events in IMPACT provide information relevant to clinical practice merits discussion with the Advisory Committee.*

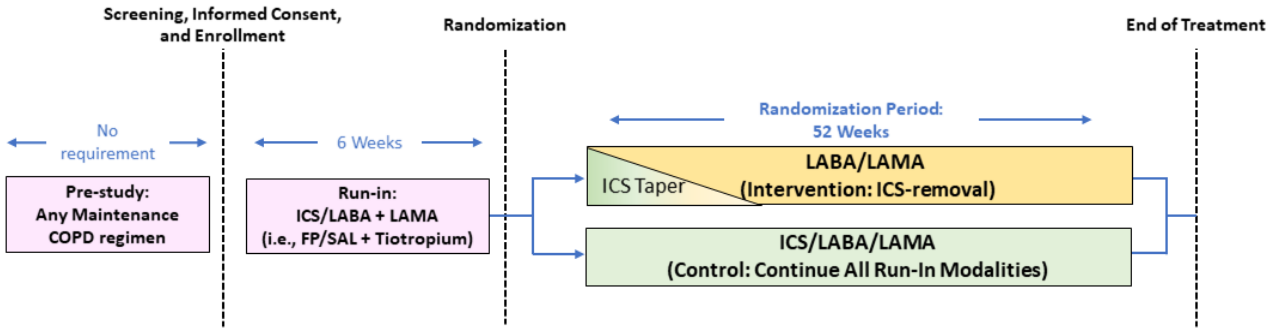
Importantly, ICS addition was not a clinical intervention performed in these studies, and extant articles and commentaries have not suggested that ICS removal data from WISDOM, INSTEAD, or SUNSET should be used to inform conclusions about the addition of ICS to a medication regimen. Interpretations of the data from these three randomized ICS removal trials have focused on drawing conclusions on the potential for negative effects due to ICS removal in patients with COPD.

***Reviewer's Comment**: The WISDOM, INSTEAD, and SUNSET trials each were not powered to evaluate mortality endpoints, but these three trials are presented to show examples of the conceptual interpretation of data from ICS removal events. Whether data from a trial intervention of randomized ICS removal – as demonstrated in WISDOM, SUNSET, INSTEAD, and the pre-study ICS subgroups of IMPACT, SUMMIT, and TORCH – can be used to support a claim of efficacy about the addition of ICS merits discussion by the Advisory Committee.*

Magnussen, et al.

In 2014, Magnussen and colleagues published the WISDOM trial[45], a 52-week, randomized, double-blind, double-dummy clinical trial of ICS removal 2,485 COPD patients with a history of ≥1 AECOPD in the prior year. Subjects completed a 6-week run-in period on ICS/LABA/LAMA. Subjects were then randomized to a 12-week step-wise ICS removal or continuation of ICS. Subjects remained on LABA and LAMA components of therapy throughout the 12-month randomized period. A schematic of the trial design is provided in Figure 18 below.

Figure 18. ICS Removal: WISDOM Trial Schematic



Source: Reviewer, based on published data from Magnussen and colleagues.
ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

***Reviewer's Comment**: the trial schematic for the WISDOM trial is fundamentally similar to the schematic of ICS removal for the IMPACT trial's pre-study triple therapy and pre-study ICS-subgroups (see Figure 13 and Figure 14, respectively). Subjects had pre-study ICS-containing medications, continued these modalities through the run-in, and were randomized to ICS removal versus ICS continuation.*

Enrolled COPD subjects had a mean age of 63.8 years, mean FEV1 of 34.2% predicted, and 67% were former smokers. The authors state that 39% of the trial population reported pre-study triple therapy (i.e., ICS/LABA/LAMA), and 70% of the trial population reported pre-study ICS-containing therapy. A history of one or more AECOPD of any severity in the prior year was a requirement for inclusion, and while data on prior history of AECOPD are not directly included in the WISDOM baseline characteristics table, data from the WISDOM trial and separate post hoc analyses by Calverley and colleagues[69] and Watz and colleagues[70] relying on WISDOM data suggest that at least 60% of enrolled patients had a history of only one AECOPD of any severity in the prior year.

The authors reported that this trial met its primary endpoint of non-inferiority for the hazard ratio of first ModSev AECOPD comparing ICS removal to ICS continuation, although the adjusted event rate for ModSev AECOPD in the ICS removal arm was numerically higher. Importantly, the authors also reported a numerically higher risk of first severe AECOPD among the ICS removal arm compared to ICS continuation, with a hazard ratio for first severe AECOPD of 1.2 (95% confidence interval 0.98 to 1.48). The authors did not report rate data for severe AECOPD. In a commentary on the article, Cosio and colleagues[68] noted a trend toward an increase in severe AECOPD after ICS removal. The WISDOM authors responded that this "was a transient increase after inhaled glucocorticoids were completely stopped."

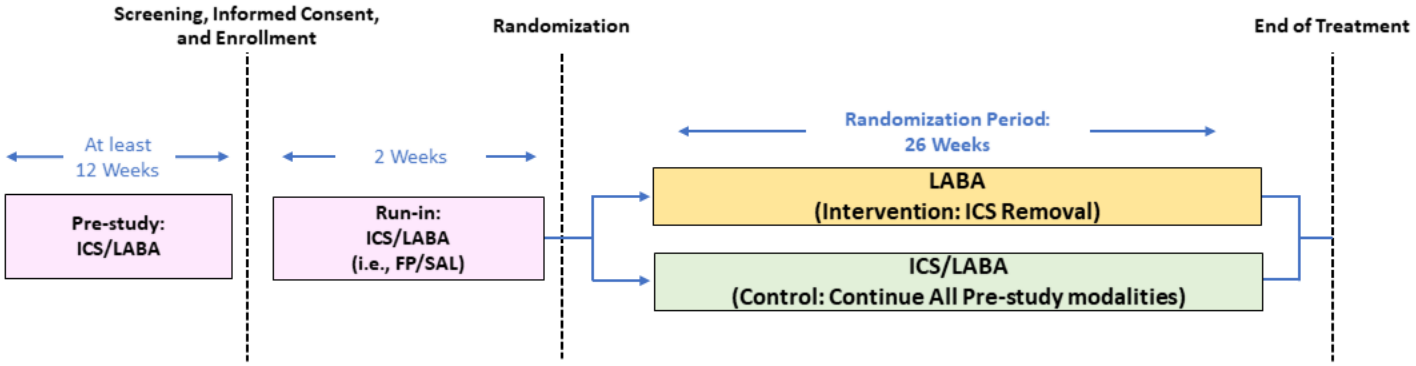
***Reviewer's Comment:** The ICS removal arm of the WISDOM trial randomized patients with severe obstruction and a history of at least one AECOPD to a gradual tapering of ICS over 12 weeks followed by 9 months of further follow-up. While the WISDOM trial achieved its primary efficacy endpoint of non-inferiority in the rate of ModSev AECOPD between ICS removal and ICS continuation at 52*

weeks, there were concerning trends in severe AECOPD measures. Despite this gradual taper approach and a comparatively controlled COPD patient population, a numerical increase in severe AECOPD was observed during the trial, with a peak incidence that occurred soon after complete discontinuation of the ICS. The trial was not powered nor designed to detect non-inferiority for a severe AECOPD outcome, however, so this observation must be interpreted with caution. In addition, while the WISDOM trial was not powered for mortality endpoints, the authors report numerically increased death events in the ICS removal arm during the study period and including vital-status follow-up.

Rossi, et al.

Also in 2014, Rossi and colleagues published the INSTEAD trial[44], a 26-week, randomized, double-blind, double-dummy trial involving ICS removal in COPD patients with a history of no ModSev AECOPD in the prior year. From a pre-study maintenance regimen of ICS/LABA, the INSTEAD trial mandated an additional 2-week run-in on ICS/LABA, and then randomized 581 COPD patients to either indacaterol alone (i.e., ICS removal with a change of LABA) or continuation of ICS/LABA. A schematic of the trial design is provided in Figure 19.

Figure 19. ICS Removal: INSTEAD Trial Schematic



Source: Reviewer, based on published data from Rossi and colleagues.
ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

***Reviewer's Comment**: the trial schematic for the INSTEAD trial is fundamentally similar to the schematic of ICS removal for the IMPACT pre-study ICS subgroup (see Figure 14). Subjects had pre-study ICS-containing medications, continued these modalities through the run-in, and were randomized to ICS removal versus ICS continuation.*

Enrolled COPD subjects had a mean age of 66 years, mean post-bronchodilator FEV1 of 64.1% predicted, and 74% were former smokers. Enrolled subjects had received pre-study salmeterol/fluticasone (i.e., ICS/LABA) COPD maintenance therapy for ≥3 months without additional COPD therapies. Importantly, subjects with a history of AECOPD in the prior year were excluded from the INSTEAD trial.

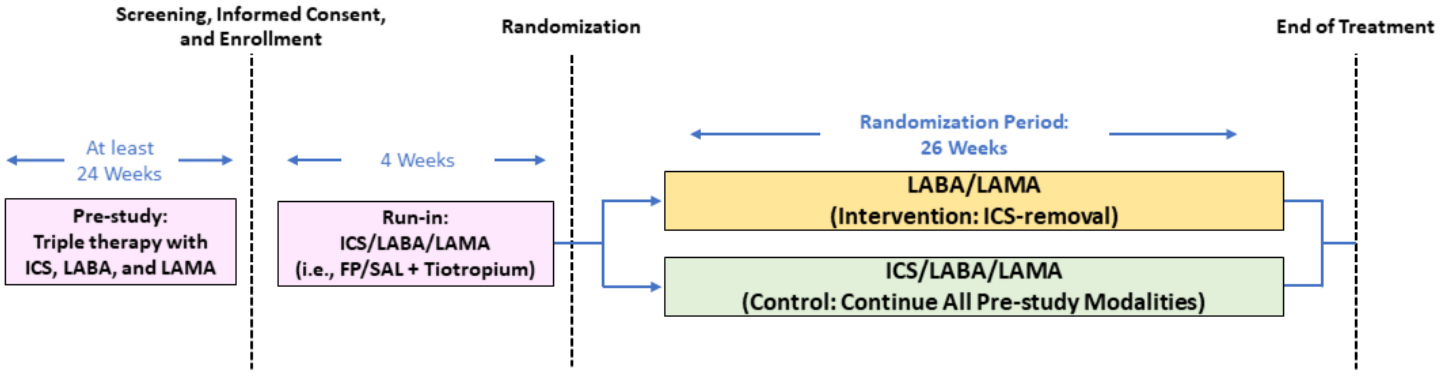
The INSTEAD trial recruited patients without a history of AECOPD, and it focused on lung function as a primary endpoint. While AECOPD data were collected in the INSTEAD trial, the authors state that the INSTEAD trial was not powered to detect a difference in AECOPD rates nor for time-to-event measures of AECOPD. In addition, the trial duration may not have been adequate for the assessment of AECOPD endpoints. With these limitations in mind, the trial did not observe a difference in the rates for ModSev AECOPD between arms in the collected AECOPD data. The authors reported that this trial met its primary endpoint of non-inferiority for the difference in FEV1 at Week 12 comparing ICS removal to ICS continuation arms.

***Reviewer's Comment**: In contrast to the IMPACT trial, the INSTEAD trial enrolled a particular subset of well-controlled COPD patients with a history of no ModSev AECOPD in the prior year and only a moderate obstructive deficit. This trial presented data on randomized ICS removal in a patient population in which ICS therapy was less likely to provide a meaningful symptomatic benefit, which might mimic a clinical practice decision. Importantly, INSTEAD was not powered to detect a difference in AECOPD rates or mortality measures. These data are presented primarily as an example of entry criteria for ICS removal trials and to provide a contrast to IMPACT's enrolled patient population.*

Chapman, et al.

In 2018, Chapman and colleagues published the SUNSET trial[59], a multicenter, randomized, double-blind, double-dummy, parallel group ICS removal trial in 1053 patients with COPD without a history of frequent AECOPD in the prior year (i.e., ≤1 moderate AECOPD and no severe AECOPD in the prior year). From a pre-study maintenance regimen of triple therapy (i.e., ICS/LABA/LAMA), the SUNSET trial mandated a 4-week run-in period of tiotropium plus FP/SAL (i.e., triple therapy) and then randomized subjects to indacaterol/glycopyrronium (i.e., ICS removal) or tiotropium plus FP/SAL (i.e., ICS continuation) for 26 weeks. A schematic of the trial design is provided in Figure 20.

Figure 20. ICS Removal: SUNSET Trial Schematic



Source: Reviewer, based on published data from Chapman and colleagues.
ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist

***Reviewer's Comment**: the trial schematic for the SUNSET trial is fundamentally similar to the schematic of ICS removal for the IMPACT trial's pre-study triple therapy and pre-study ICS subgroups (see Figure 13 and Figure 14, respectively). Subjects were on pre-study ICS-containing medications, continued these modalities through the run-in, and were randomized to ICS removal versus ICS continuation.*

Enrolled COPD subjects had a mean age of 65.3 years, mean post-bronchodilator FEV1 of 56.6% predicted, and 65.9% of the subjects had no history of AECOPD in the prior year. The proportion of current/former smokers was not reported. Enrolled subjects had received pre-study tiotropium + salmeterol/fluticasone (i.e., ICS/LABA+LAMA) COPD maintenance therapy for ≥24 weeks.

The SUNSET trial recruited patients without a history of frequent AECOPD. SUNSET focused on lung function as a primary endpoint. While AECOPD data were collected in the SUNSET trial as a secondary endpoint, the authors state that the SUNSET trial was powered to detect a non-inferiority result in FEV1 measures. The trial was not powered to detect a difference in AECOPD rates, nor was it powered to detect a difference in time-to-event measures of AECOPD, and the duration of follow-up may not have been adequate for the assessment of these AECOPD endpoints. Accepting these limitations, the trial did not observe a difference in the rates for ModSev AECOPD between arms in the collected AECOPD data. However, the authors report that a subset of subjects with increased peripheral blood eosinophils exhibited a higher risk of AECOPD after ICS removal compared to ICS continuation. This trial did not meet its primary endpoint of non-inferiority for the difference in FEV1 at Week 26 comparing ICS removal to ICS continuation arms.

***Reviewer's Comment**: In contrast to the IMPACT trial, the SUNSET trial enrolled a particular subset of comparatively well-controlled COPD patients with a history of ≤1 ModSev AECOPD and no severe AECOPD in the prior year. As with the INSTEAD trial, this trial presented data on randomized ICS removal in a patient population in which ICS therapy was less likely to provide a meaningful symptomatic benefit; this setup might more closely mimic a clinical practice decision. Importantly, SUNSET was also not powered to detect a difference in AECOPD rates or mortality measures. As with INSTEAD, these data are presented primarily as an example of entry criteria for ICS removal trials and as a contrast to IMPACT's enrolled patient population.*

Meta-analysis of ICS removal trials

In an analysis published in 2017, Calzetta and colleagues[47] undertook a meta-analysis of many of the ICS removal studies mentioned above[35,36,38,39,44,45], as well as additional ICS removal studies by Vogelmeier and colleagues[71], Kunz and colleagues[41], Rodriguez-Roisin and colleagues[56], and an additional study by Rossi and colleagues[72]. This meta-analysis did not

attempt to account for differences in baseline disease severity or prior history of exacerbations between patient populations and studies.

The authors of this meta-analysis report that the data failed to show a statistically significant increase in the overall rate of AECOPD comparing ICS removal to ICS continuation in patients with varying measures of COPD control in the selected randomized and non-randomized trials. However, the meta-analysis did report a statistically significantly shorter time-to-first AECOPD comparing ICS removal versus ICS continuation, as well as a numerically increased rate of severe AECOPD for the same comparison, with a relative risk of 1.2.

The authors acknowledged limitations in the meta-analysis methodology including a lack of consistent definitions for AECOPD and AECOPD severity across trials. Despite these limitations, from a safety perspective, the observation of numerically increased rates of severe AECOPD is consistent with data from the WISDOM trial. While it combined data from available studies designed explicitly to evaluate the effects of ICS removal, this study did not include pre-study ICS subgroup data from clinical efficacy trials of ICS medications that could have provided additional information such as IMPACT, SUMMIT, or TORCH (see Sections 4.5.4 and 4.5.7).

Reviewer's Comment*: Despite the increased statistical power gained through meta-analysis in general, the meta-analysis by Calzetta and colleagues reinforced the concern for increased severe AECOPD after ICS removal suggested by the WISDOM data. In addition, it is important to note that none of the included trials were characterized by baseline severity measures comparable to the population of the IMPACT trial.*

Guidelines on ICS removal in COPD

For temporal context, the 2014 update of the GOLD guidelines[3] (i.e., during the timeframe of the IMPACT trial's design) stated that "withdrawal from treatment with inhaled corticosteroids may lead to exacerbations in some patients", citing a study by van der Valk and colleagues[36]. It also suggested that "long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations" and that "long-term treatment with inhaled corticosteroids is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators." For Group D patients, the GOLD guidelines recommended a first choice of ICS/LABA or LAMA and listed ICS/LABA/LAMA as a second-choice option.

Reviewer's Comment*: Review of the 2014 GOLD guidelines suggest that at the time of study design and initiation in 2014, expert opinion and data suggested a negative effect of ICS removal in COPD. However, the available data did not explicitly describe an effect on mortality.*

More recent GOLD guidelines from 2019[4] state that "most studies that found a beneficial effect of LABA/ICS fixed dose combination (FDC) over LABA alone on exacerbation rate, recruited patients with a history of at least one exacerbation in the previous year." They also state that

"the treatment effect of ICS containing regimens (ICS/LAMA/LABA and ICS/LABA versus LABA/LAMA) is higher in patients with high exacerbation risk (≥2 exacerbations and / or 1 hospitalization in the previous year)." Perhaps most pertinent to the current application, the 2019 GOLD guidelines devote a paragraph to the withdrawal (i.e., removal) of ICS, stating:

> *Results from withdrawal studies provide equivocal results regarding consequences of withdrawal on lung function, symptoms, and exacerbations. Some studies, but not all, have shown an increase in exacerbations and/or symptoms following ICS withdrawal, while others have not. There has been evidence for a modest decrease in FEV1 (approximately 40 mL) with ICS withdrawal… Differences between studies may relate to differences in methodology, including the use of background long-acting bronchodilator medication(s) which may minimize any effect of ICS withdrawal.*

Pursuant to the data from ICS removal trials cited above, the GOLD Guidelines also state:

> *If [sic] patients treated with LABA/LAMA/ICS who still have exacerbations the following options may be considered…*
>
> *Stopping ICS. This can be considered if there are adverse effects (such as pneumonia) or a reported lack of efficacy. However, a blood eosinophil count ≥300 cells/µL identifies patients with the greatest likelihood of experiencing more exacerbations after ICS withdrawal and who subsequently should be followed closely for relapse of exacerbations.*

Both 2014 and 2019 GOLD guidelines suggest the use of ICS in a fixed dose combination with LABA for patients with COPD and a history of frequent exacerbations. In contrast to the 2014 guidelines, 2019 GOLD guidelines note that the results of ICS removal studies have been mixed and do not definitively describe equivocal results regarding clinical deterioration after ICS removal. While the 2019 GOLD guidelines do allow for ICS removal as a potential treatment option in patients treated with ICS/LABA/LAMA who still have exacerbations, they suggest that this clinical decision should be limited to subjects who experience adverse effects such as pneumonia or report lack of efficacy.

Reviewer's Comment*: 38% of the randomized population of the IMPACT trial met the exacerbation inclusion criteria despite the use of pre-study triple therapy with ICS/LABA/LAMA; 71% of the randomized population of the IMPACT trial met exacerbation inclusion criteria despite the use of pre-study ICS therapies. Functionally, the IMPACT trial imposed ICS removal on these pre-study triple therapy subjects as well as pre-study ICS subjects if they were randomized to the UMEC/VI arm. At the time of trial design, 2014 guidelines and available data suggested that ICS removal could lead to an increase in AECOPD. While 2019 guidelines allow ICS removal as a potential treatment intervention for COPD patients with triple therapy that still experience AECOPD, this recommendation is*

contextually limited in the guidelines to those patients who experience adverse events associated with ICS use such as pneumonia.

4.6. Uncertainties in the Interpretation of the All-Cause Mortality Results

This section discusses and summarizes uncertainties in the interpretation of IMPACT's ACM data. The first two subsections address the statistical persuasiveness of the ACM analyses from the IMPACT trial as stand-alone data to support an efficacy claim, followed by discussion of the IMPACT trial's ACM results in the context of previous COPD trials that examined ACM. The next subsection discusses the timeframe of the efficacy results observed in IMPACT in the context of previous trials and expectations. The following subsection reviews the pre-study ICS subgroup analyses and the potential effect of ICS removal events on IMPACT's ACM results in a clinical context. The final subsection provides a discussion of the generalizability of the IMPACT trial's results to clinical practice in the context of the previous uncertainties.

4.6.1. Statistical Persuasiveness of the ACM Results in IMPACT

The all-cause mortality analysis including all vital status follow-up data comparing FF/UMEC/VI versus UMEC/VI produced a hazard ratio of 0.72 (95% CI: 0.53, 0.99) and a nominal p-value of 0.042 (Table 12). However, IMPACT was not designed to evaluate treatment effects on ACM and the evaluation of the effect of ICS on ACM was one of a long list of exploratory analyses of 'other endpoints' for which there was no Type I error control. Therefore, it is difficult to interpret the results (e.g., estimates, confidence intervals, and p-values) from this analysis. We acknowledge that all analyses of primary and secondary endpoints were statistically significant, that mortality is a clinically important outcome, and that many (but not all) of the exploratory analyses of 'Other' endpoints had nominal p-values below the 0.05 threshold. Nevertheless, the ACM evaluation was one of a very large number of exploratory analyses. It would not be unusual to find nominal p-values below 0.05 just by chance when evaluating multiple exploratory endpoints, and such analyses may also be subject to substantial random high bias. Furthermore, other aspects of the ACM results from IMPACT call into question whether they provide evidence of a meaningful benefit that is generalizable to clinical practice, including the observed very early separation of mortality curves (Figure 4), issues with the study design related to ICS removal, and subgroup analysis results by pre-study ICS status. These uncertainties are discussed further below.

4.6.2. Evidence Across Trials for the Efficacy of Fluticasone on ACM

Due to the uncertainties of the IMPACT trial's ACM results, the Agency considered the totality of evidence from previous mortality trials to provide additional context to the results from IMPACT and the contribution of fluticasone to ACM in COPD. Multiple trials have collected mortality data on the effect of ICS on ACM in COPD. Two of these trials, SUMMIT and TORCH, were designed and powered to evaluate effects on mortality as a primary objective, and each

provides data on larger numbers of mortality events. The fluticasone comparisons in these trials failed to achieve statistical significance to demonstrate a difference in ACM (Table 23).

Table 23. ACM Across Trials: Totality of Evidence for Comparisons Evaluating ICS Effects Across IMPACT, SUMMIT, and TORCH

	IMPACT	SUMMIT		TORCH	
	N=10,355	N=16,485		N=6,112	
Patient/Event Categories	**FF/UMEC/VI vs. UMEC/VI**	**FF/VI vs. VI**	**FF vs. Pbo**	**FP/SAL vs. SAL**	**FP vs. Pbo**
Patients in ICS comparison	6,221	8,239	8,246	3,054	3,057
Mortality events in comparison	164	511	526	398	477
ACM analyses					
Hazard ratio	0.72	0.91	0.91	0.95	1.06
95% CI	0.53 to 0.99	0.77 to 1.09	0.77 to 1.08	0.78 to 1.15	0.88 to 1.26

Source: Reviewer, adapted from Applicant's submitted materials. Note: Values are based on the ITT-E population for SUMMIT, the ITT population for TORCH, and the ITT+VS+VSFU population for IMPACT, isolating only those subjects in the corresponding treatment arms that isolate the contribution of the ICS component. Data presented are from each study's analysis at study end: IMPACT's analysis at 52 weeks, SUMMIT's analysis at the CED, with a median duration of 1.8 years, and TORCH's analysis at 156 weeks.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate 100 µg; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; FP, fluticasone propionate 500 µg; FP/ SAL, fluticasone propionate 500 µg / salmeterol 50 µg; Pbo, placebo; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg;

As described above, the SUMMIT trial provided data on over 1,000 mortality events over the course of up to 4 years of follow-up – with a median follow-up of approximately 1.8 years – and provided data to inform analyses of ACM for fluticasone furoate through the FF versus placebo comparison or through the FF/VI versus VI comparison. SUMMIT was longer in duration than IMPACT, had a primary objective of evaluating mortality (as compared to IMPACT, for which mortality was exploratory), and had ~250 events per treatment arm (as compared to ~60-100 for IMPACT, resulting in SUMMIT providing roughly three times the statistical information as IMPACT). However, the SUMMIT trial did not provide statistically or clinically significant evidence to support a claim of an ACM benefit for fluticasone furoate despite the increased statistical power provided by the higher number of mortality events and longer trial duration. SUMMIT's overall ACM comparisons (i.e., not accounting for ICS removal effects) yielded a hazard ratio of 0.91 (95% CI 0.77 to 1.08) for the comparison of FF versus placebo and a hazard ratio of 0.91 (95% CI 0.77 to 1.09) for the comparison of FF/VI versus VI.

Similarly, the TORCH trial provided data on over 850 mortality events over the course of a three-year trial and provided data to inform analyses of ACM for fluticasone propionate through the FP versus placebo comparison or through the FP/SAL versus SAL comparison. TORCH was longer in duration than IMPACT, had a primary objective of evaluating mortality (as compared to IMPACT, for which mortality was exploratory), and had ~200-250 events per treatment arm (as compared to ~60-100 for IMPACT, resulting in TORCH providing roughly three times the statistical information as IMPACT). However, the TORCH trial did not provide statistically or clinically significant evidence to support a claim of an ACM benefit for fluticasone propionate despite the increased statistical power provided by the higher number of mortality events and longer trial duration. TORCH's overall ACM comparisons yielded a hazard ratio of

1.06 (95% CI 0.88 to 1.26) for the comparison of FP versus placebo and a hazard ratio of 0.95 (95% CI 0.78 to 1.15) for the FP/SAL versus SAL comparison.

By comparison, the IMPACT trial includes a total of 273 mortality events, of which only 164 provide evidence to inform an efficacy decision for the ICS component through the FF/UMEC/VI versus UMEC/VI comparison. In the context of the totality of evidence presented above, it is worth noting that the upper bound of the 95% confidence interval for the FF/UMEC/VI versus UMEC/VI comparison is 0.99.

In summary, multiple trials and analyses have failed to show a mortality benefit for ICS in COPD. ACM analyses from TORCH and SUMMIT – designed to evaluate mortality and each including data on roughly three times the mortality events of IMPACT – failed to show a statistically significant effect. Even setting aside issues of pre-study therapy and ICS removal in these trials, data from multiple trials with a higher number of events do not provide independent supportive evidence of the ACM results from IMPACT. We acknowledge that these trials involved different populations and different comparisons to evaluate the ICS effect (i.e., ICS versus placebo and ICS/LABA versus LABA rather than LAMA/LABA/ICS versus LAMA/LABA), and that the fluticasone study drug evaluated in TORCH was fluticasone propionate. Nevertheless, these data provide the most reliable independent data to help inform the proposed claim based on IMPACT and are considered critical in light of the uncertainties about the persuasiveness of the results from that single study. Whether the totality of evidence supports the claim that addition of fluticasone furoate, as a component of TRELEGY ELLIPTA, improves mortality in COPD is an important issue for the Advisory Committee's consideration.

4.6.3. Efficacy Timeframe in IMPACT

The observed efficacy timeframe for the FF/UMEC/VI versus UMEC/VI comparison in IMPACT raises uncertainty in the interpretation of the ACM results. Time-to-event visualizations show separation between the UMEC/VI arm and the two ICS-containing arms (i.e., FF/UMEC/VI and FF/VI) within the first 90 days. Further complicating the interpretation of the ACM results, the ACM trend between the FF/UMEC/VI and UMEC/VI treatment curves is not robust after this initial 90-day period. These analyses are exploratory, and analyses after Day 90 condition on the post-randomization variable of surviving to Day 90 and may be subject to bias. Nevertheless, these additional observations may help explore the time course of the separation in survival curves and their implications for an efficacy claim. After the initial separation, the magnitude of the difference between the two curves remains comparatively stable, suggesting that the observed difference at trial completion was driven by the early events. Analyses examining data after Day 90 reinforce the suggestion that the trial's observed efficacy results were driven by early events, creating uncertainty in a claim of persistent efficacy on ACM.

If interpreted as a benefit, this early signal for ACM is unexpected, given that data from previous trials such as TORCH and SUMMIT suggest that ICS may not provide benefit on ACM endpoints despite a multi-year evaluation period. Indeed, given previous data in the field of COPD, it is uncertain whether an early mortality effect such as this should be attributed to a

drug class with such a well-known safety and efficacy profile as ICS. If the efficacy of ICS on ACM in COPD relied on a mechanism such as prevention of severe AECOPD events – which have been associated with mortality in previous studies of COPD – the timeframe of efficacy might be expected to follow a pattern of gradual accumulation, since severe AECOPD are rare events. This pattern is not clearly observed in IMPACT's ACM results.

Notably, the IMPACT trial enrolled a higher proportion of subjects with pre-study ICS-containing therapies than both TORCH and SUMMIT. One possible interpretation of the data is that ACM events occurred earlier in this trial due to the higher acuity of the enrolled patient population and a "healthy survivor" effect. After these initial events led to a difference in event rates between study arms, fewer late events occurred that could influence the results due to a healthy survivor effect. However, this approach ignores the fact that some subjects had pre-study medication modalities removed at randomization.

Different conclusions must be considered when applying the subgroup interpretation based on pre-study ICS therapy. Under this interpretation, the subgroup analyses of the pre-study ICS subgroup could suggest that ICS removal in the IMPACT trial led to an increased risk of ACM compared to ICS continuation arms. This interpretation could also suggest that the increased risk of ACM occurred early after ICS removal. The effects of ICS removal, when present, occur within an early timeframe, followed by sustained deterioration. In particular, the WISDOM trial described a numerically increased rate of severe AECOPD at trial end, potentially driven by events occurring near the time of complete ICS removal. While severe AECOPD and ACM are fundamentally different endpoints, data suggest that severe AECOPD may be a risk factor for mortality events in COPD[20,73]. However, no randomized ICS removal trials have directly evaluated early effects on mortality with adequate statistical power, nor has any ICS removal trial enrolled a population with the same baseline characteristics as IMPACT. In contrast, the pre-study ICS-naïve subgroup in IMPACT (i.e., those not at risk of ICS removal at randomization) do not suggest an early separation between treatment arms, nor do they suggest a benefit on ACM endpoints between the ICS/LABA/LAMA arm and the LABA/LAMA arm at trial end. Data from this subgroup must be interpreted cautiously, however, since only 30% of the IMPACT trial population did not receive pre-study ICS, limiting the power to inform conclusions based on data from this subgroup alone.

These exploratory subgroup analyses should be interpreted with caution. However, if the overall analysis were taken at face value (i.e., without consideration of pre-study ICS use and the effects of ICS removal) these data would suggest that the efficacy of ICS on ACM endpoints occurs primarily within the first 90 days, and that efficacy after this timeframe would potentially be lessened or negligible. This conclusion would be largely inconsistent with previous data regarding the efficacy of ICS in COPD. Alternatively, analyses examined by pre-study ICS subgroup may suggest that the observed timeframe of these results could be consistent with a time-limited effect of ICS removal on ACM among patients with symptomatic and uncontrolled COPD. After this initial ~90-day risk period for death after ICS removal, the acute effect of ICS removal on ACM appears to lessen.

4.6.4. ICS Removal in IMPACT, SUMMIT, and TORCH

The data presented in Section 4.5.4 that isolate the efficacy comparison to the ICS component suggest that ICS removal may have played a role in the observed ACM results of IMPACT. Meeting Minutes from IMPACT's IDMC reinforce that this concern may have been shared by members of the IDMC. As shown in Figure 16 and Table 17, subjects in IMPACT who had ICS removed at randomization (i.e., pre-study ICS subjects randomized to UMEC/VI) experienced a hazard ratio of 1.64 for ACM by Week 52 compared to those who had ICS continued (i.e. pre-study ICS subjects randomized to FF/UMEC/VI). In contrast, the FF/UMEC/VI to UMEC/VI comparison among ICS-naïve subjects – while underpowered to detect a difference – does not suggest an efficacy signal for ACM attributable to the addition of ICS. These analyses are exploratory, but despite their exploratory nature, they raise considerable uncertainty in the interpretation of the ACM results at Week 52.

Clinical trial data that describe changes in clinical outcomes comparing an ICS removal arm (i.e., intervention) and an ICS continuation arm (i.e., control) could have value to guide clinical decisions regarding the cessation of ICS therapy. For example, prior data on ICS removal suggest the potential for harmful effects on FEV1, symptom scores, and AECOPD, depending on the COPD patient population studied. While controversy still exists, extant data from randomized ICS removal trials in COPD may suggest that the risks of ICS removal on AECOPD endpoints may be clinically reasonable in particular COPD subjects with well-controlled COPD including those who are not frequent exacerbators. However, even in these clinical trials of well-controlled COPD, the observed data suggest clinical decline in COPD including FEV1 and other measures. No data have suggested that removing ICS from a regimen should improve any efficacy measure of COPD in a clinically meaningful way, and no data have suggested that removing ICS should improve mortality substantially.

In this context – and given IMPACT's trial design that allowed ICS removal – interpreting the UMEC/VI versus FF/UMEC/VI results of IMPACT's pre-study ICS subgroup as showing a benefit for FF/UMEC/VI does not properly account for the trial's actual interventions for each subject. The subgroup analyses of the pre-study ICS subgroup in IMPACT (comprising 71% of the randomized population) may suggest that patients with uncontrolled COPD and frequent AECOPD on an ICS-containing COPD maintenance medication regimen could experience a substantially higher risk of ACM if ICS is abruptly removed. In addition, a similar early trend was observed for the risk of Sev AECOPD. These are exploratory analyses where the 90-day time period of evaluation was in part data-driven and therefore may be subject to bias, and there is considerable uncertainty around the estimates due to the small numbers of events. Nevertheless, the results are striking, with a point estimate that would suggest a potentially clinically significant, five-fold increased risk of mortality attributable to ICS removal in this COPD patient population from baseline to Day 90.

This early risk result attributable to ICS removal may represent an important safety signal for consideration among clinicians treating patients with COPD, however, the applicability of these ICS removal data to an ACM benefit claim for fluticasone furoate as a component of TRELEGY

ELLIPTA is uncertain. The clinical meaning of data from the pre-study ICS subgroup of patients in IMPACT may be more appropriately interpreted as showing a clinically significant risk of death when ICS are removed from the maintenance regimen of subjects who exhibit poor COPD control and continue to experience exacerbations despite the use of approved maintenance medications.

These observations of worsening ACM in the setting of ICS removal are also reinforced by subgroup analyses of both SUMMIT and TORCH (Appendices 5.5.5 and 5.6.5, respectively). In both these trials, an early ~90-day risk period for ACM for those subjects who experienced ICS removal was also identified using the comparisons that isolated the contribution of the ICS. This early risk period was observed despite TORCH and SUMMIT's target populations of comparatively better controlled COPD subjects, suggesting that the effect may not simply be a chance occurrence observed in IMPACT.

It will be important for the Advisory Committee to consider whether these data may suggest a safety signal for increased mortality within the first 90 days among subjects with uncontrolled COPD – primarily among those who have frequent AECOPD – who have ICS removed from their maintenance medication regimen.

4.6.5. Clinical Generalizability of IMPACT Results

The generalizability of ACM data generated from the IMPACT trial is uncertain, based on the uncertainties described in the preceding sections. If ACM data from IMPACT were included in labeling, how should they be interpreted by clinicians? If clinicians interpreted the proposed labeling claim from the IMPACT trial on face value using the ACM analysis of FF/UMEC/VI versus UMEC/VI, then these data might imply that initiating ICS therapy in ICS-naïve patients with a history of AECOPD could improve survival in those patients. Based on the trends observed in IMPACT data, this mortality benefit would take effect within a few months of treatment initiation.

However, the above interpretation and clinical decision-making would potentially ignore relevant information. First, it is uncertain whether ACM data from all subjects in IMPACT would be applicable to decision-making surrounding ICS-initiation in ICS-naïve patients, since 71% of the IMPACT trial population received pre-study ICS prior to randomization and could not have ICS added in the trial. Second, the early establishment of the observed mortality benefit is not consistent with larger trials examining fluticasone, or extant data in the literature regarding ICS in general. Finally, the overall result does not correspond with the results of larger trials with greater statistical power (but lower proportions of pre-study ICS users) that were designed with a primary objective of examining COPD mortality.

If, on the other hand, the pre-study medication subgroup interpretation proposed by Suissa and colleagues[50] is applied to the IMPACT trial, the data might suggest different management considerations for clinical decision-making that are not communicated by the proposed efficacy claim. A substantial proportion of the subjects in IMPACT fall into the pre-study ICS medication

subgroup that may have been randomized to ICS removal. Subjects in IMPACT randomized to ICS removal experienced a higher risk of death compared to those randomized to ICS discontinuation as described above, implying that the efficacy results among this subgroup could be interpreted as describing a potential harmful effect of ICS removal. It is unclear whether clinical trial data describing potentially harmful clinical outcomes after ICS removal should be used to inform the clinical decision of whether ICS addition is beneficial.

While these subgroup conclusions may be complicated by mitigating factors (e.g., potential between-subgroup severity differences, potential healthy survivor effects in enrolled populations, and the contribution of LAMA-initiation and LAMA-removal on the results), the potential interpretation of these data as an early safety signal for increased mortality after ICS removal is difficult to ignore.

Further complicating a potential claim of benefit for fluticasone furoate as a component of TRELEGY ELLIPTA, the ICS-naïve subgroup data from IMPACT do not suggest a trend for an ACM benefit due to ICS addition in the FF/UMEC/VI versus UMEC/VI comparison, although the analysis of this ICS-naïve subgroup is underpowered to detect such a benefit. However, additional ICS-naïve subgroup data from SUMMIT and TORCH do not suggest a trend for an ACM benefit due to ICS addition in any comparison that isolates the effect of the ICS component, despite the longer duration of these trials and the higher proportions of ICS-naïve subjects compared to IMPACT. The ICS-naïve subgroup data across these three trials reinforce the uncertainty in a claim of benefit for fluticasone on ACM.

An additional consideration when determining whether data from IMPACT support the proposed labeling claim for TRELEGY ELLIPTA is whether data based on this trial's design and interventions could be generalizable to COPD patients encountered in practice. Randomized removal designs may be viable study designs to generate evidence to support an efficacy claim, but they should be conducted in an appropriate patient population. IMPACT's mortality difference relies on data generated by the pre-study ICS subgroup through randomized ICS removal, but this ACM difference due to ICS removal occurred among patients in whom an ICS removal decision would not generally be considered in normal clinical practice. Well-powered trials examining all-cause mortality endpoints after ICS removal are lacking in the COPD literature, and certainly in a patient population with severity measures comparable to the IMPACT trial. While randomized removal of ICS in trials such as WISDOM, INSTEAD, and SUNSET occurred among relatively well-controlled COPD subjects where the risks of ICS use may outweigh the benefits, subjects in the IMPACT trial did not exhibit well-controlled COPD, and it is questionable whether ICS removal would be a realistic or viable treatment option among these patients in clinical practice.

In summary, while ICS removal data suggesting a potential signal for increased mortality may be useful to guide decisions about whether or not to stop ICS therapy, it is uncertain whether the same ICS removal data can be applied to decisions regarding the initiation of ICS therapy among ICS-naïve patients in clinical practice. This uncertainty is amplified if the ICS removal data do not describe a decision that would be considered in routine clinical practice. Because of these

concerns, it is uncertain whether ICS removal data from IMPACT (i.e., comparisons comprising 71% of the subjects) should be used to support a claim of efficacy for fluticasone furoate as a component of TRELEGY ELLIPTA. This question merits discussion with the Advisory Committee.

4.7. Integrated Summary of Efficacy Across Trials

The proposed labeling ACM claim for TRELEGY ELLIPTA in COPD relies on a comparison of FF/UMEC/VI versus UMEC/VI in the IMPACT trial over 52 weeks that suggests potential lower mortality in the FF/UMEC/VI arm, i.e., an effect of the FF component on ACM. However, there are multiple uncertainties in the application which warrant discussion by the committee.

FDA reviews of potential claims of effectiveness rely on determining whether there is substantial evidence of effectiveness from adequate and well-controlled trials. FDA Guidance to Industry suggests that – to minimize the influence of bias and chance findings – evidence from at least two adequate and well-controlled investigations is generally needed[74,75]. In certain circumstances, "one adequate and well-controlled clinical investigation plus confirmatory evidence" may be acceptable. Key factors for a determination of substantial evidence based on a single trial include the "persuasiveness of evidence" from the single study and the "robustness of confirmatory evidence." The Applicant's proposed ACM mortality relies primarily on results from a single study, IMPACT. The Applicant also submitted supportive evidence from SUMMIT and TORCH, although the populations and certain design features from those studies differ from IMPACT, as detailed in Section 4.2.1.

Therefore, it is critical to consider both the statistical and clinical persuasiveness of the evidence from the single study, IMPACT, as well as the degree of independent evidence to support the proposed claim. The primary study objective of IMPACT was to show reduction in annual rate of moderate/severe exacerbations on TRELEGY ELLIPTA compared to the two double therapy arms. IMPACT was not designed to evaluate treatment effects on ACM and the evaluation of the effect of ICS on ACM was one of a long list of exploratory analyses of 'other endpoints' for which there was no Type I error control. Therefore, it is difficult to interpret the results (e.g., estimates, confidence intervals, and p-values) from this analysis. The nominal p-value for the exploratory FF/UMEC/VI versus UMEC/VI ACM comparison of 0.042 is close to the typical 2-sided significance threshold of 0.05 and comes from only a single study.

Furthermore, the totality of evidence for the efficacy of fluticasone on ACM in COPD includes additional trials designed specifically to evaluate ACM in COPD (i.e., TORCH and SUMMIT). These additional trials did not provide independent supportive evidence of the efficacy of ICS on ACM in COPD, despite a larger numbers of ACM events, a longer duration of assessment, and greater statistical power to detect a difference. Whether the totality of the evidence bolsters our ability to rely on a single trial to support an ACM benefit for TRELEGY ELLIPTA in COPD is an important issue for discussion.

Finally, there are other aspects of the ACM results from IMPACT that call into question whether they provide evidence of a meaningful benefit that is generalizable to clinical practice, including

the observed very early separation of mortality curves and issues with ICS removal. IMPACT, SUMMIT, and TORCH each enrolled different proportions of subjects with pre-study ICS. If Suissa and colleagues' association between higher proportions of enrolled subjects with pre-study ICS and study results were to hold true for ACM endpoints, the results across these three trials could reflect such an association. If pre-study therapy is considered, extant COPD literature on ICS removal supports a clinical interpretation of data from ICS removal events as clinically significant and potentially harmful in the care of patients with COPD.

Analyses of ACM data from IMPACT may suggest an ACM signal in the direction of harm due to ICS removal from the pre-study ICS subgroup over the course of the 52-week trial, without a suggestion of an ACM benefit due to ICS addition from the ICS-naïve subgroup. The evaluation of a potential statistical interaction between pre-study ICS and treatment effect suggests that the most appropriate interpretation of IMPACT's results may come from these pre-study ICS subgroup analyses. These are exploratory analyses where the 90-day time period of evaluation was in part data-driven and therefore may be subject to bias, and there is considerable uncertainty around the estimates due to the small numbers of events. Nevertheless, the results under this pre-study ICS subgroup interpretation are striking, with a point estimate that would suggest a potentially clinically significant, five-fold increased risk of mortality attributable to ICS removal (i.e., the UMEC/VI versus FF/UMEC/VI comparison) from baseline to Day 90 in this COPD patient population. These same data may further support that this mortality difference in the direction of harm attributable to ICS removal persisted until the study was stopped at Week 52. Pre-study ICS subgroup results from the SUMMIT and TORCH trial at 90 days support a similar phenomenon of early increased mortality among subjects undergoing ICS removal in these trials.

The most straightforward comparison to determine whether adding ICS to a patient's COPD regimen (i.e., in the form of TRELEGY ELLIPTA compared to UMEC/VI) would only include evidence from ICS-naïve subjects. Among subjects in IMPACT who were ICS-naïve – and thus not at risk of ICS removal – the FF/UMEC/VI versus UMEC/VI comparison, while underpowered, does not suggest an ACM benefit attributable to the addition of ICS. This potential lack of efficacy among ICS-naïve subjects is supported by data in both the TORCH and SUMMIT trials' ICS-naïve subgroups that do not support an ACM benefit attributable to the addition of ICS.

The results of IMPACT's subgroup analyses bring into question the generalizability and clinical significance of IMPACT's ACM results. When considering the generalizability of the data provided by IMPACT to the proposed efficacy claim and to the care of patients with COPD, it is uncertain whether the data from IMPACT provide substantial evidence of the efficacy of TRELEGY ELLIPTA on ACM. When the proposed claim is considered in the context of potential clinical decision-making for a healthcare provider, the claim would likely be interpreted to suggest that the addition of FF to a regimen of UMEC/VI in an uncontrolled and symptomatic ICS-naïve COPD patient would lead to improved mortality over continuing UMEC/VI. However, this interpretation would be incorrect, since nearly 70% of the subjects in IMPACT used pre-study ICS and could not have added ICS to their COPD regimen. Even if we eliminate those 70% of subjects with pre-study ICS and attempt to apply only the data that would inform decision to

add ICS, the subgroup comparison of FF/UMEC/VI versus UMEC/VI among the 30% of ICS-naïve subjects in IMPACT was not able to demonstrate a mortality benefit for the FF component, increasing uncertainty in the validity of the clinical interpretation and of the proposed labeling claim.

No COPD medication has demonstrated an improvement in ACM. The TRELEGY ELLIPTA product is already approved, and the decision by the Advisory Committee will not introduce or remove the product from the market. However, a labeling claim of improved all-cause mortality may substantially affect clinical decision-making and requires robust and convincing evidence. Given the statistical issues with the persuasiveness of the results from a single study, the lack of supportive evidence from two independent studies designed and powered to evaluate mortality effects, the complexities of the trial design, and the potential for the unintended intervention of ICS removal to affect the interpretation of the trial's results, the Advisory Committee's input is requested on whether the data provide substantial evidence to support the proposed efficacy claim that fluticasone furoate (as part of FF/UMEC/VI) reduces ACM in COPD.

5. Appendices

5.1. References

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5.2. Regulatory History Appendix

As discussed in Section 1.8, the contents of relevant interactions in the regulatory history of TRELEGY ELLIPTA are summarized below:

Pre-IND meeting for TRELEGY ELLIPTA development on May 7, 2012

- The clinical program to support the approval of TRELEGY ELLIPTA is expected to identify a patient population requiring treatment with all three components; GOLD criteria should be considered when defining this population.
- The clinical program is expected to provide data justifying the use of a combination product over the individual component products and the two-component FDC products relevant in the treatment of COPD (e.g., FF/VI and UMEC/VI); the Division recommended omission of the proposed FF/UMEC arm.

- The Division agreed that a placebo arm might not be required to demonstrate the efficacy of TRELEGY ELLIPTA, presuming the following:
  - There are sufficient data to support the efficacy and safety of FF/VI and UMEC/VI in COPD lung function endpoints
  - The effect of FF/VI and UMEC/VI in COPD exacerbations has been assessed
- Potential pharmaceutical differences between the proposed TRELEGY ELLIPTA three-component FDC and its components should be fully characterized prior to Phase 3 efficacy and safety trials.
- The Sponsor's proposal to support efficacy based on lung function alone was questioned, and the Division stated that the clinical program should demonstrate a clinically meaningful benefit (e.g., an exacerbation benefit) to justify approval.

EOP2 teleconference for TRELEGY ELLIPTA development on September 18, 2013

- The Division recommended that the Sponsor submit in vitro and PK data to support the absence of any major pharmaceutical differences between the three-component FDC product and the comparators prior to initiating a pivotal efficacy and safety trial
- The Division requested that the protocol submission for Trial CTT116855 include details on the handling of early withdrawals and missing data
- The Division recommended that the safety analyses include the adjudication of deaths
- The Division recommended that the time-to-first moderate/severe exacerbation endpoint be elevated to a higher position in the testing hierarchy with placement before the evaluation of lung function and symptomatic improvement.

Type C meeting written responses for TRELEGY ELLIPTA development on February 27, 2014

- The Division reiterated the recommendation that the time-to-first moderate/severe exacerbation endpoint be moved to a higher position in the testing hierarchy before the evaluation of lung function and symptoms improvement
- The Division noted that the Sponsor's approach to handling early withdrawals was acceptable
- The Division noted the in-vitro data which supported the absence of major pharmaceutical differences between the triple combination product and the double products. The Division affirmed that these data were sufficient to address the Division's concerns and sufficient for the Sponsor to proceed to Phase 3 efficacy and safety trials.
  - The Division noted that the results of a single study suggested a PK difference between systemic exposure of VI in the triple combination and UMEC/VI which remained unexplained, but this is not a barrier to initiating confirmatory trials.
- In discussions regarding the primary analysis, the Division noted that the rate of exacerbations for patients who remains on treatment for only a short time was not viewed as a measure of benefit; rather the Division noted that this discontinuation could suggest an absence of benefit. As a suggested sensitivity analysis, the Division suggested that an analysis of all randomized patients' exacerbation rate values at the end of the

trial (i.e., regardless of treatment discontinuation, using an "treatment policy" estimand) could help accomplish the objective of demonstrating benefit on exacerbation endpoints.

- Whether the trial would be stopped for overwhelming evidence of efficacy based on the planned interim analysis for safety and efficacy was unclear in the Sponsor's materials. The Division suggested that, if this were a possibility, an interim analysis stopping rule which tests for efficacy using a nominal Type I error below 0.05 should be pre-specified.

Comments from clinical review of IMPACT trial protocol on May 28, 2014

- The Division recommended the use of SGRQ due to regulatory precedent, and stated that the use of SGRQ-C was at the Sponsor's discretion.

Comments from statistical review of IMPACT trial protocol on November 12, 2014

- The Division recommended defining and justifying the causal estimand of interest for the IMPACT trial, and justifying that the estimand is meaningful and can be estimated with minimal and reasonable assumptions. The Division suggested a "de facto treatment effect" estimand, incorporating data from all primary and key secondary efficacy endpoints regardless of whether they discontinue the initially assigned randomized treatment or whether they fail to actively maintain contact with their investigational site
- The Division stated that the presentation of results with missing data will be a review issue, and suggested techniques to establish consistent and effective data collection.
- The Division disagreed with the Sponsor's plan to terminate collection of mortality data after withdrawal of consent, and the Division stated that presentation of results with missing data for the mortality endpoint would be a review issue. The Division suggested that the patient consent form should include permission to collect mortality/survival data after patient withdrawal from treatment.
- Due to sensitivity of the truncated Hochberg procedure to correlation between endpoints, the Division recommended use of a truncated Holm or Bonferroni procedure to control Type I error instead of the Sponsor's proposal to use a truncated Hochberg procedure.
- The Division noted that the Sponsor proposed to assess assessment of secondary endpoints controlling the probability of Type I error at 0.05. The Division noted that, if the Sponsor included mortality as a "hard" endpoint to argue in favor of approval if one of the primary endpoints failed in study CTT116855, the Sponsor should control the probability of Type I error in these secondary endpoints at 0.01.

Initial approval of TRELEGY ELLIPTA on September 18, 2017

- The initial approval of TRELEGY ELLIPTA relied on data from trials other than the IMPACT trial.
- The initial COPD indication read as follows: for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone

furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and fixed-dose combination of fluticasone furoate and vilanterol

Approval of supplemental NDA application for TRELEGY ELLIPTA on April 24, 2018

- The approval of this supplemental NDA relied primarily on data from the IMPACT trial.
- The revised COPD indication read as follows: for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). TRELEGY ELLIPTA is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Pre-sNDA meeting to discuss supplemental NDAs for Anoro Ellipta (UMEC/VI) and Incruse Ellipta (UMEC) on June 7, 2018

- The Division noted that the review of the Sponsor's proposed labeling claims for both products would rely primarily on data from the IMPACT trial.
- The Division requested stratified analyses of the IMPACT trial's AECOPD endpoints for subjects with and without pre-study triple therapy, as well as subjects with and without pre-study LAMA-containing therapy.

Approval of supplemental NDAs for Anoro Ellipta (UMEC/VI) and Incruse Ellipta (UMEC) on June 6, 2019

- The approval of these two supplements relied primarily on data from the IMPACT trial.
- The review supporting the approval describes uncertainty related to the effect of pre-study COPD maintenance medication and protocol-mandated removal of either LAMA or ICS in the context of efficacy assessments on exacerbation endpoints.

Pre-sNDA meeting minutes for TRELEGY ELLIPTA all-cause mortality application

- The Division inquired whether the Applicant's proposed application fundamentally relied on the premise that the ICS component of FF/UMEC/VI contributed to the observed all-cause mortality results, or whether the Applicant also proposed some efficacy of the UMEC component on all-cause mortality. The Applicant replied that their understanding of the all-cause mortality data relied primarily on the efficacy contribution of the ICS component. The Applicant noted plans to include supportive data for ICS efficacy on all-cause mortality from two previous factorial design mortality trials in COPD, TORCH and SUMMIT
- The Division notified the Applicant that the review of the submitted all-cause mortality claims for TRELEGY ELLITPA would rely on the intention-to-treat plus vital status data including both on- and off-treatment deaths, as well as the intention-to-treat plus vital status follow-up data including on- and off-treatment deaths plus additional post hoc vital status collection

- The Division requested additional analyses of both all-cause mortality stratified by pre-study therapy measures (e.g., presence/absence of pre-study triple therapy, presence/absence of pre-study ICS-containing therapy)
- Given that severe exacerbation events are a risk factor for mortality in COPD, the Division also requested stratified analyses of severe exacerbation endpoints by pre-study therapy measures.
- The Division noted potential statistical issues with the all-cause mortality analyses such as multiplicity control, since the all-cause mortality analyses of the two most complete datasets were not part of the original statistical hierarchy for IMPACT and had no statistically significant replicate data showing an all-cause mortality benefit of ICS from another COPD trial for confirmatory support.
- The Division requested that the Applicant discuss the potential impact of abrupt ICS removal on the analyses results including the early separation of Kaplan-Meier mortality curves, and also that the Applicant discuss the event rates among subjects who received pre-study ICS therapy and were randomized to non-ICS containing regimens compared to those whose baseline therapy did not include ICS.
- The Division requested additional discussion of the potential impact of abrupt "step-down" of COPD therapy (i.e., ICS removal or LAMA-removal) among those with baseline triple therapy who were randomized to a dual therapy.
- The Division requested tipping point analyses of the primary analysis to evaluate the effect of missing data on the trial results.
- The Division questioned whether the assumption of proportional hazards was appropriate in the IMPACT trial; if this assumption violated by the trial, the Division noted that this would increase uncertainty in the primary analysis results, and also that sensitivity analyses relying on the proportional hazards assumption would also not be valid.
- In post-meeting comments, the Division notified the Applicant that, should they choose to include data from TORCH and SUMMIT as supportive data for their sNDA, that analogous stratified analyses of these trials might be necessary for review.

5.3. Analyses Requested by the Agency Appendix

The Division sent multiple information requests to the Applicant during the review period. While this list does not detail all analyses requested by the Division, the pertinent requested analyses of data from IMPACT, SUMMIT, and TORCH over the course of the sNDA review period are presented below.

Pre-sNDA meeting minutes for TRELEGY ELLIPTA all-cause mortality application on March 13, 2019

In addition to other analyses, the Division requested that the Applicant discuss the possible impact of abrupt ICS removal on the analysis results. To obtain further data on this subject, the Division requested analyses of ACM and of severe AECOPD in the overall analysis and in the

following subgroups in the ITT+VS+VSFU dataset (among others) of IMPACT, focusing on timepoints of Day 30, Day 60, and study end:

1) Subgroup with pre-study triple therapy
2) Subgroup without pre-study triple therapy
3) Subgroup with pre-study ICS-containing medications
4) Subgroup without pre-study ICS-containing medications

Information request on August 26, 2019

In addition to other analyses, the Division requested analyses of ACM in the same pre-study medication subgroups, focusing on analyses that excluded the first 30 days, the first 60 days, and the first 90 days post-randomization. The Division also requested baseline disease characteristics for the same pre-study medication subgroups in IMPACT. In addition, the Division requested analyses of ACM including a categorical variable of baseline ICS-containing therapy as well as a test for interaction of this variable-by-treatment with the outcome variable.

Regarding SUMMIT and TORCH, the Division requested that the Applicant discuss the possible impact of ICS removal on the analysis results of these trials as well. In addition to other analyses, the Division requested analyses of ACM in the overall analysis and in the following subgroups in the ITT-E dataset of SUMMIT and TORCH, focusing on timepoints of Day 30, Day 60, Day 90 and study end (i.e., CED and Week 156, respectively):

1) Subgroup with pre-study triple therapy
2) Subgroup without pre-study triple therapy
3) Subgroup with pre-study ICS-containing medications
4) Subgroup without pre-study ICS-containing medications

Information request on December 16, 2019

The Division requested that the Applicant discuss the sufficiency of evidence to support an effectiveness claim from IMPACT, in addition to discussing the sufficiency of evidence in the context of other studies.

The Division also requested analyses of lung function, SGRQ total scores, rescue medication use by the same pre-study medication therapy groups of IMPACT. In addition, the Division requested analyses of the primary endpoint of annual rate of ModSev AECOPD as well as the time-to-first ModSev AECOPD by the same pre-study medication therapy groups.

Information request on February 3, 2020

To obtain further data on the timeframe of efficacy observed in IMPACT, the Division requested analyses of ACM and of severe AECOPD in the overall analysis in the following subgroups in the largest dataset (i.e., ITT+VS+VSFU, ITT-E, as appropriate) of IMPACT, SUMMIT, and TORCH focusing on timepoints of Day 90:

1) Subgroup with pre-study triple therapy
2) Subgroup without pre-study triple therapy
3) Subgroup with pre-study ICS-containing medications
4) Subgroup without pre-study ICS-containing medications

Information request on March 4, 2020
In response to the Applicant's proposal to present data on a selected subset of subjects from SUMMIT, the Division requested that they provide analyses of ACM endpoints in this same selected subset by the same pre-study medication subgroups detailed previously.

Information request on March 11, 2020
The Division requested the meeting minutes of the IDMC for the IMPACT trial.

5.4. IMPACT Data Appendix

5.4.1. IMPACT Data Appendix: Analysis of Primary Efficacy Endpoints

The IMPACT trial did not examine ACM as its primary efficacy endpoint (See Section 4.4.1 IMPACT: All-cause Mortality, above). A summary of IMPACT's primary efficacy endpoint is provided for context and for purposes of discussion of the pre-specified statistical hierarchy (See Table 24). ACM was an "other" endpoint and was not included in the statistical multiplicity gatekeeping hierarchy of the IMPACT trial.

The co-primary efficacy analyses of the IMPACT trial examined the annualized rate of on-treatment ModSev AECOPD over 52 weeks among subjects administered FF/UMEC/VI compared to subjects administered UMEC/VI (FF/UMEC/VI versus UMEC/VI) and compared to subjects administered FF/VI (FF/UMEC/VI versus FF/VI) using a statistical model that adjusted for categorical variables of treatment group, exacerbation history, smoking status, geographical region, and post-bronchodilator percent predicted FEV1. In summary, the IMPACT trial demonstrated a statistically significant benefit on its co-primary endpoints of the rate of ModSev AECOPD for both the FF/UMEC/VI versus UMEC/VI and FF/UMEC/VI versus FF/VI comparisons.

Reviewer's Comment*: The Agency's initial evaluation and review of the primary endpoint for IMPACT did not include exploratory analyses by pre-study therapy or evaluate the contribution of ICS removal to trial results.*

Table 24. IMPACT: Primary Efficacy Analysis of On-treatment Annual Rate of ModSev AECOPD (ITT)

Category Analysis	FF/UMEC/VI	FF/VI	UMEC/VI
Number of subjects with analyzable data	4,145	4,133	2,069
Mean annual rate			
Model estimated annual rate	0.91	1.07	1.21
95% CI for rate	0.87, 0.95	1.02, 1.12	1.14, 1.29
Model-adjusted efficacy, FF/UMEC/VI vs. comp			
Rate ratio (95% CI)		0.85 (0.8, 0.9)	0.75 (0.7, 0.81)
p-value		<0.001	<0.001

Source: Reviewer. Adapted from Agency's previous review of the IMPACT study, Table 15 (Division Director Review submitted 24 APR 2018 under NDA 209482-S0001, publicly available at https://www.accessdata.fda.gov/scripts/cder/daf/)
Abbreviations: AECOPD, acute exacerbation of COPD; CI, confidence interval; comp, comparator; FF/UMEC/VI, fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; ModSev, moderate-to-severe; UMEC/VI, umeclidinium 62.5 µg / vilanterol 25 µg

5.4.2. IMPACT Data Appendix: List of Efficacy Analyses in IMPACT

Table 25. IMPACT: Primary, Secondary, and Exploratory Efficacy Endpoints Analyzed in IMPACT

Number of Comparisons	Endpoints	Data Included	Population
COPD exacerbations			
2 (primary)	Annual rate moderate/severe	On-treatment	ITT
4 (secondary)	Moderate/severe[4]	On-treatment	≥150 eosinophils/µL <150 eosinophils/ µL
2 (secondary)	Severe[4]	On-treatment	ITT
4 (secondary)	Moderate/severe	On-treatment	≥150 eosinophils/ µL <150 eosinophils/ µL
Lung function			
2	Trough FEV_1	Week 52	ITT
SGRQ			
2	Total score	Week 52	ITT
Total number of comparisons for multiplicity-controlled endpoints: 16			
Exploratory analyses			
COPD exacerbations			
2	Time to first moderate/severe	On-treatment	ITT
2	Annual rate moderate/severe	On- and off-treatment	ITT
4	Severe	On-treatment	≥150 eosinophils/µL <150 eosinophils/µL
8	Mild/moderate/severe	On-treatment	ITT
	Moderate	On-treatment	ITT
	Moderate/severe requiring oral/systemic corticosteroids	On-treatment	ITT
	Moderate/severe requiring antibiotics	On-treatment	ITT
10	Time to first moderate/severe	On- and off- treatment	ITT
	Moderate/severe	On-treatment or premature discontinuation	ITT
	Moderate/severe	On-treatment	≥150 eosinophils/µL <150 eosinophils/µL
	Severe	On-treatment	ITT

Number of Comparisons	Endpoints	Data Included	Population
6	Severe	On-treatment	≥150 eosinophils/µL <150 eosinophils/µL
	Mild/moderate/severe	On-treatment	ITT
6	Moderate	On-treatment	ITT
	Moderate/severe requiring oral/systemic corticosteroids	On-treatment	ITT
	Moderate/severe requiring antibiotics	On-treatment	ITT
4	**Time to each** moderate/severe	On-treatment	ITT
	Severe	On-treatment	ITT
Lung function			
4	Trough FEV_1	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
2	100 mL increase FEV_1	Week 52	ITT
4	100 mL increase FEV_1	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
8	Post-bronchodilator FEV_1	Week 52	ITT
	FEV_1 reversibility	Week 52	ITT
	Trough FVC	Week 52	ITT
	Post-bronchodilator FVC	Week 52	ITT
SGRQ			
4	Total score	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
2	Responders	Week 52	ITT
4	Responders	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
2	Moderate/major responders	Week 52	ITT
2	Major responders	Week 52	ITT
Transition dyspnea index			
2	Focal score	Week 52	TDI
4	Focal score	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
2	Responders	Week 52	TDI
4	Responders	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
4	Moderate/major responders Major responders[10]	Week 52 Week 52	TDI TDI
COPD assessment test			
12	Score	Week 52	ITT
	Score	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
	Responders	Week 52	ITT
	Responders	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
E-diary endpoints			
8	Subject global rating of activity limitation	Week 52	ITT
	Subject global rating of change in COPD severity	Week 52	ITT
	Occasions of rescue medication use per day by four weekly period	Weeks 49 to 52	ITT

Number of Comparisons	Endpoints	Data Included	Population
	Percentage of rescue-free days by four weekly period	Weeks 49 to 52	ITT
2	Number of nighttime awakenings per night by four weekly period	Weeks 49 to 52	ITT
2	Percentage of days symptoms stopped usual activities by four weekly period	Weeks 49 to 52	ITT
All-cause mortality			
4	Time to all-cause mortality	On-treatment	ITT
	Time to all-cause mortality	On- and off-treatment	ITT
2	Time to all-cause mortality	On- and off-treatment plus vital status follow-up	ITT

Source: Applicant. Adapted from Table 93, IMPACT Clinical Study Report
Abbreviations: FEV1: forced expiratory volume in one second; ITT: intent-to-treat; SGRQ, St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index

5.5. SUMMIT Data Appendix

5.5.1. SUMMIT Data Appendix: Secondary Objectives

Stated secondary objectives included:

- To evaluate the effect of FF/VI compared with placebo on the rate of decline in FEV1
- To evaluate the effect of FF/VI compared with placebo on a cardiovascular composite event comprised of on-treatment CV death, MI, stroke, unstable angina, and transient ischemic attack.

Other objectives included:

- To evaluate the following treatment comparisons on all primary, secondary, other, and exploratory endpoints:
  - FF/VI compared with FF
  - FF/VI compared with VI
  - FF compared with placebo
  - VI compared with placebo

To evaluate the effect of FF/VI compared with placebo on ModSev AECOPD
To evaluate the effect of FF/VI compared with placebo on COPD-related mortality
Additional endpoints

5.5.2. SUMMIT Data Appendix: Trial Design

Additional details of the SUMMIT trial design are included below, to supplement the relevant study design elements discussed in Section 3.2.

Trial Duration and Clinical Visits

The SUMMIT trial comprised pre-enrollment discontinuation of inhaled COPD maintenance medications by the healthcare providers of the potential SUMMIT subjects, followed by a screening visit where informed consent was signed, a 4- to 10-day run-in period where subjects were maintained on only short-acting bronchodilators, an investigational product (IP) treatment period of variable duration with scheduled trial visits approximately every 12 weeks, and an additional safety follow-up clinic visit 14 days after the common end date (CED). Because the trial was event-driven, enrolled subjects had variable exposure to investigational product, spanning 40 to 185 weeks. The trial assessed all-cause mortality after the CED.

Inclusion Criteria

Subjects enrolled in the SUMMIT trial were required to meet the following inclusion criteria, among others:

- Outpatient males or females ≥40 and ≤80 years of age
  - Women of child-bearing potential who fulfilled requirements for highly effective contraceptive methods and demonstrated a negative pregnancy test were included
- Post-bronchodilator FEV1/FVC ratio of ≤0.7
- COPD spirometric severity commensurate with the following:
  - A post-bronchodilator FEV1 ≥50% and ≤70% predicted normal
- Modified Medical Research Council score ≥2
- Current or former tobacco smoker with ≥10 pack-year history
- Cardiovascular disease defined using the following age-based criteria
  - For patients ≥40 years of age, any one of the following criteria:
    - Established diagnosis of coronary artery disease (by clinical signs or imaging)
    - Established diagnosis of peripheral artery disease (by clinical signs or imaging)
    - Previous stroke
    - Previous myocardial infarction
    - Diabetes mellitus with target organ disease

    OR
  - For patients ≥60 years of age, any two of the following criteria:
    - Treatment for hypercholesterolemia
    - Treatment for hypertension
    - Treatment for diabetes mellitus
    - Treatment for peripheral arterial disease

Exclusion Criteria

Subjects were excluded if they met any of the following criteria, among others:

- ModSev AECOPD that has not resolved at least 14 days prior to Visit 1 and at least 30 days following the last dose of oral/systemic corticosteroids.
- Pneumonia or ModSev AECOPD during the run-in period

- Long-term oxygen therapy at rest ≥12 hr/day
- Other respiratory disorders including active tuberculosis, lung cancer, sarcoidosis, pulmonary hypertension, and others
  - Subjects with a current diagnosis of asthma were included; subjects with a prior history of asthma could be included if they had a current diagnosis of COPD
- Subjects with known alpha-1 antitrypsin deficiency as the underlying cause of COPD
- Lung volume reduction surgery within the previous 12 months or lung transplant
- Subjects with current severe heart failure (New York Heart Association Class IV), known ejection fraction of <30%, or implantable cardioverter defibrillator.
- Any other life-threatening condition with life-expectancy <3 years, other than vascular disease or COPD, that might prevent the subject from completing the study
- End-stage chronic renal disease
- History of allergy or hypersensitivity to any study drug or component
- Women who are pregnant, lactating, or planned to become pregnant during the study
- Use of the following medications prior to screening:
  - Inhaled LABA within 48 hours
  - Inhaled ICS/LABA combination products within 48 hours
  - ICS within 48 hours
  - Systemic, oral, parenteral, or intra-articular corticosteroids within 30 days
  - Cytochrome P450 3A4 strong inhibitors within 6 weeks
  - Any other investigational drug within 30 days or 5 half-lives

Randomization and Blinding

The randomization in the SUMMIT trial was adequate. Randomization was conducted using randomization schedules generated for each country using RANDALL software. Following the run-in period, an interactive voice response system assigned subjects to a randomized treatment. The blinding in the SUMMIT trial was adequate. The dry powder inhalers for each study drug were identical in appearance. Each dry powder inhaler contained the study medications in two “strips.” Each inhaler contained excipients of lactose and magnesium stearate.

Concomitant Medications

There was no pre-study requirement for the presence or duration of COPD maintenance medication use described in the SUMMIT protocol. The protocol did, however, include a requirement to discontinue inhaled pre-study COPD therapy prior to enrolling in SUMMIT (see Section 3.2.5). Pre-study COPD medications were reviewed during the screening visit (Visit 1).

In addition to investigational products, the protocol allowed for the use of the following concomitant medications and therapies for COPD:

- Study-supplied rescue medication
  - Albuterol as MDI or nebules

- Ipratropium or ipratropium/albuterol fixed dose combination
- Oral corticosteroids and antibiotics for the short-term treatment of AECOPD
- Antibiotics for the short-term treatment of acute non-respiratory tract infections, for the treatment of pneumonia, and for the treatment of AECOPD
- Theophyllines and roflumilast
- Mucolytics
- Oxygen
- Intranasal cromolyns or nedocromil
- While tiotropium use (or any LAMA use) was not permitted in the 7 days prior to the screening visit and during the run-in, subjects who experienced a severe AECOPD requiring additional treatment or that experienced multiple moderate AECOPD were allowed to initiate tiotropium (or any LAMA) during the double-blind randomized treatment period.
  - The same AECOPD criteria applied to initiation of a phosphodiesterase-4 inhibitor, although these medications were allowed during the run-in

The protocol also allowed for the use of the following non-COPD medications:

- Vaccinations including influenza and pneumonia vaccines
- Antihistamines and nasal decongestants
- Over the counter cough suppressants
- Intranasal, ophthalmic, and topical corticosteroids
- Tricyclic antidepressants and monoamine oxidase inhibitors
- Diuretics
- Smoking cessation medications
- Cardioselective beta-blockers and ophthalmic beta-blockers; noncardioselective beta-blockers could also be used if deemed appropriate by the principal investigator
- All medications for other disorders as long as the dose remained constant wherever possible.

Restricted Medications

The protocol did not allow subjects to use the following therapies during the randomized period:

- Any ICS (other than investigational product)
- Any LABA (other than investigational product)

5.5.3. SUMMIT Data Appendix: Secondary Efficacy Endpoints and Safety Assessments

Secondary Efficacy Endpoints

- Rate of decline in FEV1 comparing FF/VI versus Pbo
- Time to cardiovascular event (i.e., time to MACE) comparing FF/VI versus Pbo

Other Efficacy Endpoints

- The annual rate of ModSev AECOPD
- The time-to-first ModSev AECOPD
- Quality of life using the SGRQ-COPD
- Change from baseline in FEV1
- Change from baseline in forced vital capacity (FVC)
- Additional Endpoints

Safety Assessments

The safety assessments of the SUMMIT trial have been reviewed during prior submissions, and the schedule of safety assessments during the trial was adequate for the stated objectives of the trial.

***Reviewer's Comment**: No new safety analyses of SUMMIT were undertaken for this supplement outside of those used to support discussion of the all-cause mortality data.*

5.5.4. SUMMIT Data Appendix: Study Population Results

The demographic characteristics for the ITT population of SUMMIT are presented in Table 26, below. There were no clinically meaningful differences in demographics across study arms.

Table 26. SUMMIT: Demographic Characteristics, ITT-E Population

Characteristics	FF/VI	FF	VI	Pbo	Total
N	4,121	4,135	4,118	4,111	16,485
Sex					
Female	1,009 (24)	1,082 (26)	1,065 (26)	1,040 (25)	4,196 (25)
Male	3,112 (76)	3,053 (74)	3,053 (74)	3,071 (75)	12,289 (75)
Age					
Mean in years (SD)	65.3 (8.0)	65.0 (8.0)	65.2 (7.7)	65.2 (7.9)	65.2 (7.9)
Age group					
<65 years	1,820 (44)	1,889 (46)	1,852 (45)	1,823 (44)	7,384 (45)
≥65 to <75 years	1,749 (42)	1,726 (42)	1,771 (43)	1,774 (43)	7,020 (43)
≥75 years	552 (13)	520 (13)	495 (12)	514 (13)	2,081 (13)
Smoking history					
Mean pack-years (SD)	40.4 (24.4)	40.9 (23.9)	40.8 (24.4)	40.9 (24.7)	40.8 (24.4)
Current	1,868 (45)	1,945 (47)	1,929 (47)	1,936 (47)	7,678 (47)
Former	2,253 (55)	2,190 (53)	2,189 (53)	2,175 (53)	8,807 (53)
Geographical region					
US	647 (16)	647 (16)	650 (16)	646 (16)	2,590 (16)
Not US	3,474 (84)	3,488 (84)	3,468 (84)	3,465 (84)	13,895 (84)

Characteristics	FF/VI	FF	VI	Pbo	Total
Race					
AI/AN	9 (<1)	5 (<1)	4 (<1)	9 (<1)	27 (<1)
Asian	679 (16)	683 (17)	680 (17)	681 (17)	2,723 (17)
AA or African heritage	69 (2)	62 (1)	67 (2)	60 (1)	258 (2)
NHPI	2 (<1)	2 (<1)	0	1 (<1)	5 (<1)
White	3,332 (81)	3,358 (81)	3,339 (81)	3,328 (81)	13,357 (81)
Other	41 (1)	32 (<1)	32 (<1)	42 (1)	115 (<1)

Source: Reviewer. Adapted from data from Clinical Study Report for SUMMIT
All values are expressed as n (%) unless specified otherwise.
Abbreviations: AA, African American; AI/AN, American Indian/Alaska Native; FF, fluticasone furoate 100 µg; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; ITT, intention to treat; NHPI, Native Hawaiian or Pacific Islander; Pbo, placebo; SD, standard deviation; US, United States; VI, vilanterol 25 µg

The baseline disease characteristics for the ITT population of SUMMIT are presented in Table 27, below. There were no clinically meaningful differences in baseline disease characteristics across study arms.

Table 27. SUMMIT: Baseline Disease Characteristics, ITT-E Population

Baseline Characteristics	FF/ VI	FF	VI	Pbo	Total
Total, N	4,121	4,135	4,118	4,111	16,485
Postbronchodilator FEV1*					
N with available data	4,127	4,141	4,118	4,108	16,483
Mean FEV1%p (SD)	59.7 (6.1)	59.6 (6.1)	59.7 (6.1)	59.6 (6.1)	59.7 (6.1)
GOLD spirometric severity grade*					
N with available data	4,121	4,134	4,118	4,110	16,483
Mild	2 (<1)	2 (<1)	3 (<1)	1 (<1)	8 (<1)
Moderate	4,051 (98)	4,055 (98)	4,027 (98)	4,043 (98)	16,176 (98)
Severe	68 (2)	77 (2)	88 (2)	64 (2)	297 (2)
Very severe	0	0	0	2 (<1)	2 (<1)
Moderate AECOPD history**					
N with available data	4,121	4,135	4,118	4,111	16,485
<2	3,730 (91)	3,756 (91)	3,708 (90)	3,712 (90)	14,906 (90)
≥2	391 (9)	379 (9)	410 (10)	399 (10)	1,579 (10)
Severe AECOPD history**					
N with available data	4,121	4,135	4,118	4,111	16,485
0	3,551 (86)	3,610 (87)	3,570 (87)	3,549 (86)	14,280 (87)
≥1	570 (14)	525 (13)	548 (13)	562 (14)	2,205 (13)
AECOPD category					
N with available data	4,121	4,135	4,118	4,111	16,485
<2 moderate and no severe	3,256 (79)	3,295 (80)	3,252 (79)	3,254 (79)	13,057 (79)
≥2 moderate or ≥1 severe	865 (21)	840 (20)	866 (21)	857 (21)	3,428 (21)
SGRQ total score					
N with analyzable data	1,112	1,113	1,101	1,107	4,403
Mean (SD)	45.6 (16.2)	46 (16.0)	46.8 (16.3)	47 (15.4)	46.6 (16.1)

Source: Adapted from Applicant's submitted data for the SUMMIT trial.
All values are expressed as n (%) unless specified otherwise.
*GOLD spirometric severity grades: Mild = FEV1 ≥80%p; moderate = FEV1 <80%p to ≥50%p; severe = FEV1 <50%p to ≥30%p; very severe = FEV1 <30%
**AECOPD history evaluated over the prior 12 months. Enrolled COPD subjects were not required to have a history of moderate or severe AECOPD in the prior 12 months.
Abbreviations: AECOPD, Acute Exacerbation of COPD; FEV1, forced expiratory volume in one second; FF, fluticasone furoate 100 µg; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ITT-E, intention to treat; Pbo, placebo; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; VI, vilanterol 25 µg

The pre-study COPD medication categories of the ITT population of SUMMIT are presented in Table 28, below. There were no clinically meaningful differences in pre-study medications across study arms.

Table 28. SUMMIT: Pre-study COPD Medication Groups, ITT-E Population

Regimen	FF/VI	FF	VI	Pbo	Total
Total	4,121	4,135	4,118	4,111	16,485
Triple therapy*					
Yes	363 (9)	351 (8)	360 (9)	359 (9)	1,433 (9)
No	3,758 (91)	3,784 (92)	3,758 (91)	3,752 (91)	15,052 (91)
ICS-containing regimen					
Yes	1,394 (34)	1,369 (33)	1,374 (33)	1,349 (33)	5,486 (33)
No	2,727 (66)	2,766 (67)	2,744 (67)	2,762 (67)	10,999 (67)

Source: Adapted from Applicant's submitted materials for the SUMMIT trial
All values are expressed as n (%) unless specified otherwise.
* Triple therapy: ICS/LABA/LAMA-containing regimen
Abbreviations: FF, fluticasone furoate 100 µg; FF/VI, fluticasone furoate 100 µg / vilanterol 25 µg; ICS, inhaled corticosteroid; ITT, intention to treat; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; Pbo, placebo VI, vilanterol 25 µg

The disposition of the ITT population of SUMMIT is presented in Table 29, below. A numerically higher proportion of patients in the placebo arm prematurely discontinued study drug compared to the other investigational drug arms. A similar trend was seen for study withdrawal.

Table 29. SUMMIT: Subject Disposition, ITT-E Population

Disposition	FF/VI	FF	VI	Pbo	Total
ITT-E total	4,121	4,135	4,118	4,111	16,485
Treatment completion status					
Completed	3,171 (77)	3,061 (74)	3,079 (75)	2,919 (71)	12,230 (74)
Prematurely discontinued	950 (23)	1,074 (26)	1,039 (25)	1,192 (29)	4,255 (26)
Adverse event	329 (8)	360 (9)	366 (9)	387 (9)	1,442 (9)
Decision by subject/proxy	476 (12)	516 (12)	497 (12)	619 (15)	2,108 (13)
Lack of efficacy	46 (1)	90 (2)	65 (2)	98 (2)	299 (2)
Study completion status					
Stayed on study drug/finished all visits	3,171 (77)	3,061 (74)	3,079 (75)	2,919 (71)	12,230 (74)
Vital status data (ITT-E population with on-and-off treatment data)					
Alive	3,874 (94)	3,884 (94)	3,853 (94)	3,832 (93)	15,443 (94)
Dead	246 (6)	251 (6)	265 (6)	275 (7)	1,037 (6)
Unknown	1 (<1)	0	0	4 (<1)	5 (<1)

Source: Sponsor's clinical study report for SUMMIT, Figure 1 and Table 1.027. Partially verified by statistical reviewer (NDA 209482\Analysis\SUMMIT\reviewer programs\disp.sas).
All values are expressed as n (%) unless specified otherwise.
Percentages for subheadings of "Prematurely Discontinued" and "Prematurely withdrawn" are based upon the total number of subjects who prematurely discontinued and prematurely withdrew, respectively.
Abbreviations: ITT-E: intention to treat-efficacy; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo

5.5.5. SUMMIT Data Appendix: All-cause Mortality and Pre-study ICS

In SUMMIT, since subjects on pre-study ICS-containing therapy were already prescribed ICS as a component of their maintenance COPD medications prior to randomization, the randomization resulted in the following scenarios (analogous to situations described in IMPACT in Figure 14):

1) Removal of ICS, if randomized to the VI or placebo arm, with the possible addition of other components
2) Continuation of ICS, if randomized to the FF/VI or FF arm, with the possible addition or removal of other components

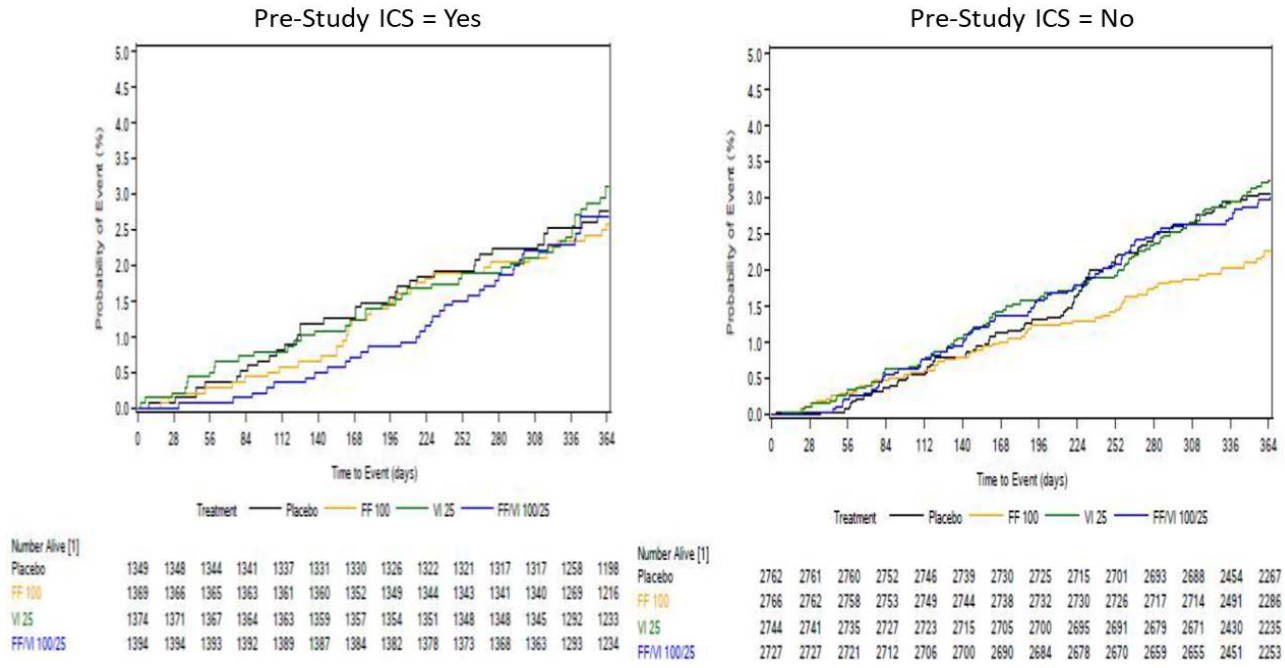
In SUMMIT, the FF/VI versus VI comparison and the FF versus placebo comparison isolate the contribution of the ICS component, whether FF was removed (i.e., among the pre-study ICS = Yes subgroup) or added (i.e., among the ICS-naïve subgroup).

***Reviewer's Comment**: A hazard ratio for ACM that is <1 for the FF/VI versus VI comparison suggests that the VI arm experienced a higher proportion of death events and the FF/VI arm experienced a lower proportion of death events. However, under the subgroup interpretation of the data, the clinical interpretation of this hazard ratio is uncertain. In the subgroup of subjects with pre-study ICS, no subjects had ICS added to their regimen, so the result of this comparison cannot be described as decreased ACM for the FF/VI arm due to the addition of ICS to a regimen of VI. Instead, in this subgroup, subjects who were randomized to VI experienced ICS removal while subjects randomized to FF/VI continued ICS. Because of this ICS removal event in the VI arm, the higher proportion of deaths in the VI arm could potentially be described as increased ACM for the VI arm due to the removal of ICS. This interpretation suggesting ICS removal would also apply to the FF versus placebo comparison among those with pre-study ICS.*

Analyses of the SUMMIT trial examined by pre-study ICS subgroup suggest that ICS removal may have played a role in the SUMMIT trial's observed results as well. Since the SUMMIT trial utilized an event-driven design, the trial ended at a CED and subjects were not all in the randomized treatment phase of the trial for the same amount of time. However, ACM results at Day 365 still show clinically meaningful differences between subgroups when examined by pre-study ICS subgroup (see Figure 21) that may suggest an ICS removal effect.

Kaplan-Meier curves for the ACM endpoint suggest that – among those with pre-study ICS therapy (Figure 21, left panel) – division of the study arms occurred early in the trial period, but that this result was not durable over the course of one year. In contrast, the graph for the ICS-naïve subgroup (Figure 21, right panel) does not suggest this pattern.

Figure 21. SUMMIT: Pre-Study ICS Subgroups: Probability of All-cause Mortality at Day 365 by Treatment Arm (ITT-E Including Both On- and Off-treatment Data)



Source: Adapted from Applicant's submitted materials.
Abbreviations: ITT-E: intention to treat-efficacy; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo; Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

Analyses in the Pre-study ICS Subgroup

Figure 21 and Table 30, below, suggests a similar pattern of differing ACM results based on the presence or absence of pre-study ICS evaluated at the CED. Among the subgroup with pre-study ICS, at the CED, subjects in the FF/VI arm demonstrated a hazard ratio for ACM of 0.79 (95% CI 0.59 to 1.06) versus the VI arm; similarly, subjects in the FF arm demonstrated a hazard ratio for ACM of 0.83 (95% CI 0.63 to 1.10) compared to the placebo arm.

Similar to the paradigm of ICS removal discussed for IMPACT subgroup comparison (Section 4.5.4), under this "flipped" interpretation that describes the potential effects of ICS removal, subjects with pre-study ICS randomized to VI (i.e., ICS removal) demonstrated a hazard ratio for death of 1.27 (95% CI 0.94 to 1.69) compared to those randomized to FF/VI (i.e., ICS continuation) at the CED, and subjects with pre-study ICS randomized to placebo (i.e., ICS removal) demonstrated a hazard ratio for death of 1.20 (95% CI 0.91 to 1.59). While additional trial interventions may play a role in the interpretation of these data and caution should be exercised when interpreting these exploratory subgroup results, the subgroup data may suggest subjects who experienced ICS removal events (i.e., the VI arm or the placebo arm subjects randomized to ICS removal) also experienced an increased risk of death events. Both hazard ratio orientations are presented in Table 30.

***Reviewer's Comment**: Under the pre-study ICS subgroup interpretation where ICS removal serves as the intervention and ICS continuation serves as the control, SUMMIT provides data on ICS removal suggesting a hazard ratio for death of 1.27 for ACM using the VI versus FF/VI comparison or a hazard ratio for death of 1.20 using the placebo versus FF comparison at the CED. Similar to subgroup results from IMPACT, this interpretation suggests an increased risk of death among those who experienced ICS removal despite the requirement for pre-enrollment ICS removal, a run-in period that served as a further ICS washout, and the longer trial duration compared to IMPACT. The clinical significance of these results at the CED are uncertain. However, these results may still suggest clinically meaningful efficacy estimate differences compared to the results of the ICS-naïve subgroup (see below), supporting the suggestion that the results of ICS removal among subjects with pre-study ICS are not comparable to results of ICS addition among ICS-naïve subjects. In addition, the pre-study ICS subgroup data up to Day 90 may suggest that an early risk period for ACM events due to ICS removal was also present in the SUMMIT trial (see ACM Analyses by Pre-study ICS Subgroup at Day 90, below).*

Table 30. SUMMIT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Common End Date (ITT-E Including Both On- and Off-treatment Data)

Pre-study ICS = Yes	**FF/VI N=1,394**	**FF N=1,369**	**VI N=1,374**	**Pbo N=1,349**
Subjects with event, n (%)	82 (5.9)	93 (6.8)	99 (7.2)	110 (8.2)
FF/VI vs. comparator				
ACM HR			0.79 (0.59, 1.06)	0.70 (0.52, 0.93)
95% CI			0.30	0.14
Comparator vs. FF/VI				
ACM HR			**1.27**	1.43
95% CI			**0.94, 1.69**	1.08, 1.92
FF vs. comparator				
ACM HR				0.83
95% CI				0.63, 1.10
Comparator vs. FF				
ACM HR				**1.20**
95% CI				**0.91, 1.59**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the SUMMIT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; FF, fluticasone furoate 100 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo, placebo; VI, vilanterol 25 µg

Analyses in the ICS-naïve Subgroup

Further examination of the data suggests that – among the ICS-naïve subgroup of subjects in SUMMIT – that the addition of ICS did not demonstrate a difference on ACM endpoints (see Table 31). Both the FF/VI versus VI and the FF versus placebo comparisons demonstrate hazard ratios that approach 1, despite the higher statistical power in this subgroup.

***Reviewer's Comment**: Analyses of the ICS-naïve subgroup in SUMMIT do not support an ACM benefit for the ICS component (i.e., addition of ICS among ICS-naïve subjects) in either the FF/VI versus VI or the FF versus placebo comparison, despite including data from over 600 events in over 10,000 patients.*

Table 31. SUMMIT: Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Common End Date (ITT-E Including Both On- and Off-treatment Data)

ACM Analysis Category	FF/VI N=2,727	FF N=2,766	VI N=2,744	Pbo N=2,762
Subjects with event, n (%)	164 (6.0)	158 (5.7)	166 (6.1)	165 (6.0)
ACM analysis of FF/VI vs. comparator				
ACM HR			**0.99**	1.00
95% CI			**0.80, 1.23**	0.81, 1.24
ACM analysis of FF vs. comparator				
ACM HR				**0.96**
95% CI				**0.77, 1.19**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the SUMMIT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints.
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF, fluticasone furoate 100 µg; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo, placebo; VI, vilanterol 25 µg

SUMMIT: ACM Analyses by Pre-study ICS Subgroup at Day 90

Supporting similar data from IMPACT suggesting a risk period for ICS removal prior to the Day 90 timepoint (see Sections 4.4.1 and 4.5.4), the SUMMIT trial's ACM data at the Day 90 timepoint also suggest a trend towards early mortality events in subjects who experienced ICS removal. In the subgroup of subjects with pre-study ICS (see Table 32), the hazard ratio for death by Day 90 was 0.26 (95% CI 0.07 to 0.93) for those randomized to FF/VI (i.e., ICS continuation) compared to VI (i.e., ICS removal) and the hazard ratio for death at Day 90 was 0.74 for those randomized to FF (i.e., ICS continuation) compared to placebo (i.e., ICS removal).

Similar to the "flipped" UMEC/VI versus FF/UMEC/VI subgroup comparisons in the IMPACT trial, both of these SUMMIT subgroup comparisons may suggest that increased deaths were experienced by subjects randomized to ICS removal by Day 90 compared to those randomized to ICS continuation. Under this "flipped" orientation that focuses on an interpretation of ICS removal effects, SUMMIT provides data on ICS removal suggesting a hazard ratio for death of 3.85 for ACM at Day 90 using the VI versus FF/VI comparison or a hazard ratio for death of 1.35 using the placebo versus FF comparison.

***Reviewer's Comment**: In this subgroup of subjects with pre-study ICS, randomization to VI or placebo arms involved ICS removal prior to enrollment and run-in that was maintained throughout the study. While these exploratory subgroup analyses at Day 90 should be interpreted with caution and are based upon few events, the data from subjects prescribed pre-study ICS describes a numerically higher number of ACM events in both trial arms where ICS removal occurred (i.e., the VI and placebo arms) compared to those where ICS was*

continued (i.e., the FF/VI and FF arms). Under the ICS removal interpretation, these data suggest a hazard ratio for death of 3.85 for ACM in the first 90 days using the VI versus FF/VI comparison or a hazard ratio of 1.35 for ACM in the first 90 days using the placebo versus FF comparison. This result occurred despite pre-enrollment ICS removal and a run-in that only allowed short-acting inhaled medications. This result reinforces the early safety signal for ACM among those that experienced ICS removal observed in the IMPACT trial.

Table 32. SUMMIT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT-E Including Both On- and Off-treatment Data)

ACM Analysis Category	FF/VI N=1,394	FF N=1,369	VI N=1,374	Pbo N=1,349
Subjects with event by day 90, n (%)	3 (0.2)	6 (0.4)	11 (0.8)	8 (0.6)
FF/VI vs. comparator				
ACM HR			0.26	0.36
95% CI			0.07, 0.93	0.09, 1.35
Comparator vs. FF/VI				
ACM HR			**3.85**	2.78
95% CI			**1.08, 14.29**	0.74, 11.11
FF vs. comparator				
ACM HR				0.74
95% CI				0.26, 2.12
Comparator vs. FF				
ACM HR				**1.35**
95% CI				**0.50, 3.85**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the SUMMIT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FF/ VI, fluticasone furoate 100 µg / vilanterol 25 µg; FF, fluticasone furoate 100 µg; HR, hazard ratio; ITT-E: intention to treat, efficacy; Pbo, placebo; VI, vilanterol 25 µg

In contrast, in the subgroup of subjects without pre-study ICS (i.e. ICS-naïve) in which patients were not at risk of ICS removal (see Table 33), comparisons that isolate the effect of the ICS component do not support a difference in ACM due to ICS at Day 90. In this ICS-naïve subgroup, the hazard ratio for death for subjects on FF/VI was 0.94 compared to VI, while the hazard ratio for FF compared to placebo was 1.29.

***Reviewer's Comment**: In contrast to those who took pre-study ICS and may have experienced ICS removal, the Day 90 data for the subgroup of ICS-naïve subjects – who were not at risk of ICS removal events – do not suggest an ACM benefit for addition of an ICS component within the first 90 days.*

Table 33. SUMMIT: Pre-Study ICS = No Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT-E Including Both On- and Off-treatment Data)

ACM Analysis Category	FF/VI N=2,727	FF N=2,766	VI N=2,744	Pbo N=2,762
Subjects with event at day 90, n(%)	16 (0.6)	14 (0.5)	17 (0.6)	11 (0.4)
FF/VI vs. comparator				
ACM HR			**0.94**	1.46
95% CI			**0.47, 1.86**	0.68, 3.15
FF vs. comparator				
ACM HR				**1.29**
95% CI				**0.58, 2.83**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the SUMMIT study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FF on ACM endpoints.
Abbreviations: ITT-E: intention to treat, efficacy; CI: confidence interval; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo; Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

5.5.6. SUMMIT Data Appendix: Additional Pre-randomization ICS Removal Effects

The pre-study ICS subgroup data at Day 90 presented for the SUMMIT trial may suggest an early safety signal for ACM among those that underwent ICS removal. However, additional data on ICS removal effects from this trial can be assessed among subjects who enrolled and underwent ICS removal but were not randomized. In contrast to the IMPACT trial, the SUMMIT trial included a pre-enrollment requirement for ICS removal along with a run-in period that allowed only short-acting COPD therapies. Functionally this design meant that any subject with pre-study ICS had their ICS removed prior to the beginning of safety or mortality data collection.

Reviewer's Comment*: SUMMIT required ICS removal prior to enrollment. Since ICS removal events occurred prior to enrollment and data collection, the observed data collected during the run-in could underestimate the repercussions of ICS removal. Deaths or adverse events that may have occurred prior to study enrollment as a result of ICS removal were not collected.*

When the run-in data are examined, a numerically increased proportion of subjects undergoing ICS removal as part of the run-in for SUMMIT withdrew from the trial due to adverse events compared to the ICS-naïve group who did not undergo ICS removal (see Table 34, below). These adverse events during the run-in led to subjects not being randomized.

More pertinent to the discussion of ACM endpoints, SUMMIT data shows that there was 1 death among the 306 subjects who had undergone ICS removal prior to or during the run-in compared to 3 deaths among the 6939 ICS-naïve subjects who did not undergo ICS removal during that timeframe.

Reviewer's Comment*: Functionally, the run-in of the SUMMIT trial (in addition to SUMMIT's pre-enrollment requirements) required ICS removal among potential*

randomized subjects with pre-study ICS. However, if subjects did not tolerate this ICS removal (e.g., due to an AECOPD or adverse event) they were not randomized. The attrition of vulnerable pre-study ICS patients prior to enrollment in the SUMMIT trial may have left these studies less enriched for patients at greatest risk of ICS removal effects in their final study populations. Analogous to a "healthy survivor" effect, only those pre-study ICS users in SUMMIT who tolerated an initial ICS removal during prior to enrollment would enter the run-in and be randomized. Indeed, SUMMIT's protocol required pre-study ICS removal prior to enrollment in the trial and informed consent (see Section 3.2.5), and no trial data were collected to characterize or quantify how these pre-enrollment ICS removal events may have affected the potential enrollees. By contrast, the IMPACT trial's run-in consisted of continuation of the pre-study maintenance COPD regimen and ICS removal occurred abruptly at the time of randomization, so the effect of ICS removal may not have been mitigated by excluding those with functional decline prior to randomization.

Table 34. SUMMIT: Study Attrition Among Subjects Who Did Not Start Treatment by Pre-study ICS Subgroup

	Pre-study ICS Use	
Reason for Withdrawal	**Yes**	**No**
Subjects withdrawn prior to starting randomized treatment, N (%)	306	6,939
Run-in failure*	90 (30)	523 (8)
Primary reason for run-in failure*		
Adverse event, n (%)	13 (4)	48 (<1)
FAEs among subjects who dd not start treatment*		
Subjects with FAE	1 (<1)	3 (<1)

Source: Adapted from Applicant's submitted materials.
N = 7,425
*Proportions of subjects with the stated reason for run-in failure or fatal adverse event are calculated using a denominator of the "Subjects withdrawn prior to starting randomized treatment" entry. Not all recorded reasons for Run-in Failure are listed on this table.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
Abbreviations: FAE, fatal adverse event; ICS, inhaled corticosteroid

5.6. TORCH Data Appendix

5.6.1. TORCH Data Appendix: Secondary Objectives

Stated secondary objectives included

- To show a significant reduction in COPD morbidity with FP/SAL compared with placebo, as measured by the rate of ModSev AECOPD
- To show a significant difference in Quality of Life with FP/SAL compared with placebo, as measured by the SGRQ
- To investigate and compare the number of adverse events in each treatment group

Other objectives included

- To investigate and compare rates of all-cause mortality in COPD subjects treated with the following, in addition to usual COPD therapy:
  - FP/SAL compared with FP
  - FP/SAL compared with SAL
  - FP compared with placebo
  - SAL compared with placebo
  - Additional endpoints

5.6.2. TORCH Data Appendix: Trial Design

Additional details of the TORCH trial design are included below, to supplement the relevant study design elements discussed in Section 3.3.

Trial Duration and Clinical Visits

The TORCH trial comprised a screening visit where informed consent was signed, a 2-week run-in period where subjects were maintained on only short-acting bronchodilators, an investigational product (IP) treatment period of 156 weeks (i.e., 3 years) with scheduled trial visits approximately every 12 weeks, and an additional safety follow-up clinic visit 14 days after the end of the randomized treatment period. The TORCH trial assessed all-cause mortality at 3 years using a factorial design.

Inclusion Criteria

Subjects enrolled in the TORCH trial were required to meet the following inclusion criteria, among others:

- Outpatient male or female subjects ≥40 years of age
  - Women of child-bearing potential who fulfilled protocol-mandated requirements for highly effective contraceptive methods and demonstrated a negative pregnancy test were included
- Established clinical history of COPD by 1995 ERS Consensus Statement[76]
- Pre-bronchodilator FEV1 to FVC ratio of ≤0.7
- COPD severity commensurate with the following:
  - A pre-bronchodilator FEV1 <60% predicted normal
- Poor reversibility of airflow obstruction, defined as <10% increase in FEV1 as a percentage of normal predicted 30 minutes after albuterol administration via MDI
- Current or former tobacco smoker with ≥10 pack-year history

Exclusion Criteria

Subjects were excluded if they met any of the following criteria, among others:

- Current respiratory disorder other than COPD (e.g., lung cancer, sarcoidosis, tuberculosis, lung fibrosis)
- A current diagnosis of asthma, in the opinion of the investigator
- Chest X-ray (within the prior 6 months) indicating diagnosis other than COPD that might interfere with the study
- Prior lung volume reduction surgery or lung transplant
- Requirement for long-term oxygen therapy for >12 hours/day at start of study
- Long-term oral corticosteroid therapy (defined as continuous use for >6 weeks)
- Serious, uncontrolled disease likely to interfere with the study or likely to cause death within the 3-year study duration
- Other investigational drugs in the last 4 weeks prior to Visit 1
- Evidence of alcohol, drug, or solvent abuse
- Known or suspected hypersensitivity to inhaled corticosteroids, bronchodilators, or lactose
- Known deficiency of alpha-1 antitrypsin
- AECOPD during the run-in period

Randomization and Blinding

The randomization in the TORCH trial was adequate. Randomization was conducted using a computer-generated randomization schedule. Following the run-in period, an interactive voice response service assigned subjects to a randomized treatment. The blinding in the TORCH trial was adequate. Each dry powder inhaler contained the study medications as well as a lactose excipient.

Concomitant Medications

There was no requirement for pre-study COPD maintenance medication use or for duration of pre-study COPD therapy described in the TORCH protocol. Pre-study COPD medications were reviewed during the screening visit.

In addition to investigational products, the protocol allowed for the use of the following concomitant medications and therapies for COPD:

- Study-supplied albuterol as a rescue medication
- Short-acting beta-agonists
- Short-acting muscarinic antagonists
- Theophyllines
- Long-term oxygen therapy, if requirement for oxygen met study entry criteria
- Oral corticosteroids for the short-term treatment of AECOPD
- Any additional COPD medication, excluding Restricted Medications (see below)

The protocol designated that all medication for other disorders may be used.

Restricted Medications

The protocol did not allow the use of the following therapies during the randomized period:

- Any ICS (other than investigational product)
- Any long-acting bronchodilators, including any LABA medication or LAMA medication (other than investigational product)
- Long-term oxygen use for ≥12 hours per day on entry
- Long-term use of oral corticosteroids, defined as continuous use for >6 weeks

5.6.3. TORCH Data Appendix: Secondary Efficacy Endpoints and Safety Assessments

Secondary Efficacy Endpoints

- Rate of ModSev AECOPD
- Quality of life determined using the SGRQ

Other Efficacy Endpoints

- COPD-related (cardiopulmonary) mortality
- Requirement for long-term oxygen therapy
- Post-bronchodilator FEV1
- Number of withdrawals from treatment
- Additional Endpoints

Safety Assessments

The safety assessments of the TORCH trial have been reviewed during prior submissions, and the schedule of safety assessments during the trial was adequate for the stated objectives of the trial.

Reviewer's Comment*: No new safety analyses of TORCH were undertaken for this supplement outside of those used to support discussion of the all-cause mortality data.*

5.6.4. TORCH Data Appendix: Study Population Results

The demographic characteristics for the ITT population of TORCH are presented in Table 35 below. There were no clinically meaningful differences in demographics across study arms.

Table 35. TORCH: Demographic Characteristics, ITT Population

Characteristics	FP/SAL	FP	SAL	Pbo	Total
N	1,533	1,534	1,521	1,524	6,112
Sex					
Female	382 (25)	377 (25)	361 (24)	361 (24)	1,481 (24)
Male	1,151 (75)	1,157 (75)	1,160 (76)	1,163 (76)	4,631 (76)
Age					
Mean in years (SD)	65.0 (8.3)	65.0 (8.4)	65.1 (8.2)	65.0 (8.2)	65.0 (8.3)
Age group					
<65 years	665 (43)	677 (44)	660 (43)	671 (44)	2,673 (44)
≥65 to <75 years	683 (45)	648 (42)	670 (44)	669 (44)	2,670 (44)
≥75 years	185 (12)	209 (14)	191 (13)	184 (12)	769 (13)
Smoking history					
Mean pack-years (SD)	47.0 (26.5)	49.2 (28.6)	49.3 (27.7)	48.6 (26.9)	48.5 (27.4)
Current	660 (43)	661 (43)	651 (43)	658 (43)	2,630 (43)
Former	873 (57)	873 (57)	870 (57)	866 (57)	3,482 (57)
Geographical region					
US	349 (23)	348 (23)	346 (23)	345 (23)	1,388 (23)
Not US	1,184 (77)	1,186 (77)	1,175 (77)	1,179 (77)	4,724 (77)
Race					
Asian	191 (12)	196 (13)	192 (13)	190 (12)	769 (13)
Black	26 (2)	24 (2)	20 (1)	25 (2)	95 (2)
White	1,254 (82)	1,253 (82)	1,250 (82)	1,249 (82)	5,006 (82)
Other*	62 (4)	61 (4)	59 (4)	60 (4)	242 (4)

Source: Reviewer. Adapted from data from Clinical Study Report for TORCH
All values are expressed as n (%) unless specified otherwise.
* Data on subjects with race identification categorizations of "Other" and "American Hispanic" from the TORCH trial are presented for the TORCH trial as "Other" in this table
Abbreviations: FP, fluticasone propionate 500 µg; FP/ SAL, fluticasone propionate 500 µg / salmeterol 50 µg; ITT-E: intention to treat efficacy population; Pbo, Placebo; SAL, salmeterol 50 µg; US, United States

The baseline disease characteristics for the ITT population of TORCH are presented in Table 36, below. There were no clinically meaningful differences in baseline disease characteristics across study arms.

Table 36. TORCH: Baseline Disease Characteristics, ITT Population

Baseline Characteristics	FP/SAL	FP	SAL	Pbo	Total
Total	1,533	1,534	1,521	1,524	6,112
Postbronchodilator FEV1					
N with available data	1,524	1,529	1,516	1,515	6,084
Mean FEV1%p (SD)	44.7 (13.5)	44.6 (13.3)	43.7 (13.3)	44.2 (13.1)	44.3 (13.5)
GOLD spirometric severity grade*					
N with available data	1,524	1,529	1,516	1,515	6,084
Mild	12 (1)	9 (1)	2 (<1)	5 (<1)	28 (<1)
Moderate	549 (36)	525 (34)	517 (34)	527 (35)	2,118 (35)
Severe	722 (47)	776 (51)	738 (49)	769 (51)	3,005 (49)
Very severe	241 (16)	219 (14)	259 (17)	214 (14)	933 (15)
Moderate AECOPD history**					
N with available data	1,533	1,534	1,521	1,524	6,112
<2	1,164 (75)	1,144 (75)	1,131 (74)	1,126 (74)	4,645 (75)
≥2	369 (25)	390 (25)	390 (26)	398 (26)	1,467 (25)

Baseline Characteristics	FP/SAL	FP	SAL	Pbo	Total
Severe AECOPD history**					
N with available data	1,533	1,534	1,521	1,524	6,112
0	1,254 (82)	1,244 (81)	1,244 (82)	1,263 (83)	5,005 (82)
≥1	279 (18)	290 (19)	277 (18)	261 (17)	1,107 (18)
AECOPD category					
N with available data	1,533	1,534	1,521	1,524	6,112
<2 moderate and no severe	991 (65)	976 (64)	972 (64)	975 (64)	3,914 (64)
≥2 moderate or ≥1 severe	542 (35)	558 (36)	549 (36)	549 (36)	2,198 (36)
SGRQ total score					
N with analyzable data	1,133	1,155	1,148	1,149	4,585
Mean (SD)	48.9 (17.4)	49.5 (17.1)	49.9 (16.6)	49.0 (17.4)	49.3 (17.1)

Source: Adapted from Applicant's submitted data for the TORCH trial.
All values are expressed as n (%) unless specified otherwise.
*GOLD spirometric severity grades: Mild = FEV1 ≥80%p; moderate = FEV1 <80%p to ≥50%p; severe = FEV1 <50%p to ≥30%p; very severe = FEV1 <30%
**AECOPD history evaluated over the prior 12 months. Enrolled COPD subjects were not required to have a history of moderate or severe AECOPD in the prior 12 months.
Abbreviations: AECOPD, Acute Exacerbation of COPD; FEV1, forced expiratory volume in one second; FP, fluticasone propionate 500 µg; FP / SAL, fluticasone propionate 500 µg / salmeterol 50 µg; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ITT-E, intention to treat; Pbo, Placebo; SAL, salmeterol 50 µg; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire

The pre-study COPD medication categories of the ITT population of TORCH are presented in Table 37 below. There were no clinically meaningful differences in pre-study medications across study arms. Note that the concomitant use of ICS, LABA, and LAMA therapy was not common practice prior to and during the three-year duration of TORCH.

Table 37. TORCH: Pre-study COPD Medication Groups, ITT Population

Medication Groups	FP/SAL	FP	SAL	Pbo	Total
Total	1,533	1,534	1,521	1,524	6,112
ICS-containing regimen					
Yes	740 (48)	732 (48)	701 (46)	803 (53)	2,976 (49)
No	761 (50)	768 (50)	776 (51)	679 (45)	2,984 (49)
Unknown or no data	42 (3)	44 (3)	34 (2)	32 (2)	152 (2)

Source: Adapted from Applicant's submitted data for the TORCH trial.
All values are expressed as n (%) unless specified otherwise.
Abbreviations: FP, fluticasone propionate 500 µg; FP / SAL, fluticasone propionate 500 µg / salmeterol 50 µg; ICS, inhaled corticosteroid; ITT-E, intention to treat; Pbo, placebo; SAL, salmeterol 50 µg

The disposition of the ITT population of TORCH is presented in Table 38, below. A numerically higher proportion of patients in the placebo arm prematurely discontinued study drug compared to the other investigational drug arms. A similar trend was seen for study withdrawal.

Table 38. TORCH: Subject Disposition, ITT Population

Category	FP/SAL	FP	SAL	Pbo	Total
Total	**1,533**	**1,534**	**1,521**	**1,524**	**6,112**
Tx completion status					
Completed	**1,011 (66)**	**947 (62)**	**960 (63)**	**851 (56)**	**3,769 (62)**
Prematurely d/c	**522 (34)**	**587 (38)**	**561 (37)**	**673 (44)**	**2,318 (38)**
Adverse event	289 (19)	360 (23)	303 (20)	366 (24)	1,311 (57)
Lack of efficacy	33 (2)	45 (3)	63 (4)	103 (7)	244 (10)
Other reasons	200 (13)	182 (12)	195 (13)	204 (13)	781 (13)
Study completion status					
Completed	**1,011 (66)**	**947 (62)**	**960 (63)**	**851 (56)**	**3,769 (62)**
Prematurely w/d	**522 (34)**	**587 (38)**	**561 (37)**	**673 (44)**	**2,343 (38)**
Vital status data (ITT population with on-and-off treatment data)					
Complete data	**1,532 (>99)**	**1,534 (100)**	**1,521 (100)**	**1,524 (100)**	**6,111 (>99)**

Source: Reviewer, adapted from Applicant's submitted materials for the TORCH trial. Percentages for subheadings of "Prematurely Discontinued" and "Prematurely withdrawn" are based upon the total number of subjects who prematurely discontinued and prematurely withdrew, respectively.
All values are expressed as n (%) unless stated otherwise.
Abbreviations: d/c, discontinued; FP/ SAL, fluticasone propionate 500 µg / salmeterol 50 µg; FP, fluticasone propionate 500 µg; f/u, follow-up; ITT, intention to treat; Pbo, placebo; SAL, salmeterol 50 µg; w/d, withdrawn

5.6.5. TORCH Data Appendix: All-cause Mortality and Pre-study ICS

Analogous to the situation in SUMMIT, subjects on pre-study ICS-containing therapy in the TORCH trial were already prescribed ICS as a component of their maintenance COPD medications prior to randomization. Because they used ICS maintenance therapy prior to the study, the randomization resulted in the following scenarios (analogous to situations described in IMPACT in Figure 14):

1) Removal of ICS, if randomized to the SAL or placebo arm, with the possible addition of other components
2) Continuation of ICS, if randomized to the FP/SAL or FP arm, with the possible addition or removal of other components

In TORCH, the FP/SAL versus SAL comparison and the FP versus placebo comparison isolate the contribution of the ICS component, whether FP was removed (i.e., among the pre-study ICS = Yes subgroup), or added (i.e., among the pre-study ICS = No subgroup).

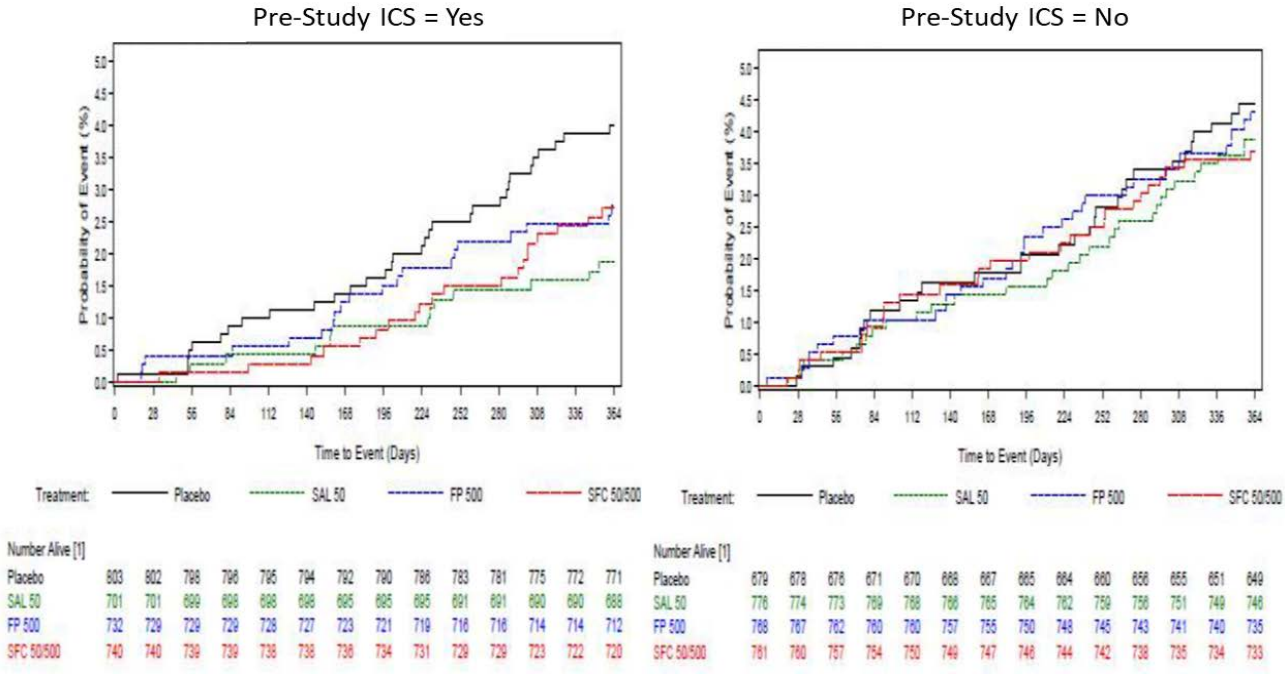
***Reviewer's Comment**: A hazard ratio for ACM that is <1 for the FP/SAL versus SAL comparison suggests that the SAL arm experienced a higher proportion of death events and the FP/SAL arm experienced a lower proportion of death events. However, under the subgroup interpretation of the data, the clinical interpretation of this hazard ratio is uncertain. In the pre-study ICS subgroup, no subjects had ICS added to their regimen, so the result of this comparison cannot be described as decreased ACM for the FP/SAL arm due to the addition of ICS to a regimen of SAL. Instead, in this subgroup, subjects randomized to SAL experienced ICS removal while subjects randomized to FP/SAL continued ICS. Because of this ICS removal event in the SAL arm, the higher proportion of deaths could potentially be described as increased ACM for the SAL arm due to the*

removal of ICS. This interpretation suggesting ICS removal would also apply to the FP versus placebo comparison among those with pre-study ICS.

Analyses of the TORCH trial examined by pre-study ICS subgroup suggest that ICS removal may have played a role in the TORCH trial's observed results as well. In contrast to the IMPACT trial's one-year duration, the TORCH trial's randomized treatment duration was three years. Despite this increased duration, ACM results at trial end still show clinically meaningful differences between subgroup as examined by pre-study ICS subgroup (see Figure 22) and may suggest an ICS removal effect.

In the pre-study ICS subgroup (Figure 22, left panel), Kaplan-Meier curves up to Day 365 for the ACM endpoint suggest that the division of the study arms occurred early in the trial period, and that this overall trend was potentially maintained over time. In contrast, the graph for the ICS-naïve subgroup (Figure 22, right panel) does not suggest this pattern.

Figure 22. TORCH: Pre-Study ICS Subgroups: Probability of All-cause Mortality by Day 365 by Treatment Arm (ITT Including Both On- and Off-treatment Data)



Source: Applicant
Abbreviations: ITT: intention to treat; FP/ SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo; Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

Analyses in the Pre-study ICS Subgroup

Figure 22 and Table 39 suggests a similar pattern of differing results based on the presence or absence of pre-study ICS at the 156-week timepoint. Among the pre-study ICS subgroup at 156 weeks, subjects in the FP/SAL arm demonstrated a hazard ratio for ACM of 0.93 (95% CI 0.69 to

1.25) versus the SAL arm; similarly, subjects in the FP arm demonstrated a hazard ratio for ACM of 0.96 (95% CI 0.74 to 1.25) compared to the placebo arm.

Similar to the paradigm of ICS removal discussed for IMPACT subgroup comparison (Section 4.5.4), under this "flipped" interpretation that describes the potential effects of ICS removal, subjects with pre-study ICS randomized to SAL (i.e., ICS removal) demonstrated a hazard ratio for death of 1.07 (95% CI 0.8 to 1.45) compared to those randomized to FP/SAL (i.e., ICS continuation), and subjects with pre-study ICS randomized to placebo (i.e., ICS removal) demonstrated a hazard ratio for death of 1.04 (95% CI 0.8 to 1.35) compared to those randomized to FP (i.e., ICS continuation) at Week 156. While additional trial interventions may play a role in the interpretation of these data and caution should be exercised when interpreting these exploratory subgroup results, the subgroup data may suggest subjects who experienced ICS removal events (i.e., the SAL arm or the placebo arm subjects randomized to ICS removal) also experienced a numerically increased risk of death events at Week 156, although the clinical significance of these hazard ratios are unclear. Both hazard ratio orientations are presented in Table 39.

Reviewer's Comment*: Under the pre-study ICS subgroup interpretation where ICS removal serves as the intervention and ICS continuation serves as the control, TORCH provides data on ICS removal suggesting a hazard ratio of 1.07 for ACM up to Week 156 using the SAL versus FP/SAL comparison or a hazard ratio of 1.04 for ACM up to Week 156 using the placebo versus FP comparison, despite the two-week run-in period that required ICS removal. The hazard ratios for ACM reported in these ICS removal comparisons at 156 weeks are less striking than those reported from IMPACT at 52 weeks, perhaps due to the longer timeframe of the study and differences in the enrolled patient population. However, these results may still suggest clinically meaningful efficacy estimate differences compared to the results of the ICS-naïve subgroup (see below), supporting the suggestion that the results of ICS removal among subjects with pre-study ICS are not comparable to results of ICS addition among ICS-naïve subjects. In addition, the pre-study ICS subgroup data up to Day 90 may suggest that an early risk period for ACM events due to ICS removal was also present in the TORCH trial (see ACM Analyses by Pre-study ICS Subgroup at Day 90, below).*

Table 39. TORCH: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Week 156 (ITT Including Both On- and Off-treatment Data)

ACM Analysis Category	FP/SAL N=740	FP N=732	SAL N=701	Pbo N=803
Number of subjects with event, n(%)	86 (11.6)	107 (14.6)	88 (12.6)	115 (14.3)
FP/SAL vs. comparator				
ACM HR			0.93	0.76
95% CI			0.69, 1.25	0.58, 1.01
Comparator vs. FP/SAL				
ACM HR			**1.07**	1.31
95% CI			**0.80, 1.45**	0.99, 1.72
FP vs. comparator				
ACM HR				0.96
95% CI				0.74, 1.25
Comparator vs. FP				
ACM HR				**1.04**
95% CI				**0.80, 1.35**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity.
These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study.
Comparisons in **bold text** provide data to inform the efficacy and safety of FP on ACM endpoints.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Abbreviations: ACM all-cause mortality; CI, confidence interval; FP, fluticasone propionate 500 µg; FP/SAL, fluticasone propionate 500 µg / salmeterol 50 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo: placebo; SAL: salmeterol 50 µg

Analyses in the ICS-naïve Subgroup

Further examination of the data suggests that – among the ICS-naïve subgroup in TORCH – that the addition of ICS did not demonstrate a difference on ACM endpoints (see Table 40). Both the FF/VI versus VI and the FF versus placebo comparisons demonstrate hazard ratios that approach 1, despite the higher statistical power in this subgroup.

Reviewer's Comment*: Analyses of the ICS-naïve subgroup in TORCH do not support an ACM benefit for the ICS component (i.e., addition of ICS) in either the FP/SAL versus SAL or the FP versus placebo comparison at 156 weeks, despite including data from over 400 events in over 2900 patients.*

Table 40. TORCH: Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Week 156 (ITT Including Both On- and Off-treatment Data)

ACM Analysis Category	FP/SAL N=761	FP N=768	SAL N=776	Pbo N=679
Number of subjects with event, n(%)	101 (13.3)	132 (17.2)	106 (13.7)	109 (16.1)
FP/SAL vs. comparator				
ACM HR			**0.98**	0.83
95% CI			**0.75, 1.29**	0.64, 1.09
FP vs. comparator				
ACM HR				**1.13**
95% CI				**0.87, 1.45**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity.
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study.
Comparisons in **bold text** provide data to inform the efficacy and safety of FP on ACM endpoints.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FP/SAL, fluticasone propionate 500 µg / salmeterol 50 µg; FP, fluticasone propionate 500 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo: placebo; SAL: salmeterol 50 µg

TORCH: ACM Analyses by Pre-study ICS Subgroup at Day 90

Supporting similar data from IMPACT suggesting a risk period for ICS removal around the Day 90 timepoint (see Sections 4.4.1 and 4.5.4), the TORCH trial's ACM data at the Day 90 timepoint also suggest a trend towards early mortality events in subjects who experienced ICS removal. In the subgroup of subjects with pre-study ICS (see Table 41), the hazard ratio for death by Day 90 was 0.33 (95% CI 0.03 to 3.23) for those randomized to FP/SAL (i.e., ICS continuation) compared to SAL (i.e., ICS removal) and the hazard ratio for death at Day 90 was 0.52 for those randomized to FP (i.e., ICS continuation) compared to placebo (i.e., ICS removal).

Similar to the "flipped" UMEC/VI versus FF/UMEC/VI subgroup comparisons in the IMPACT trial, both of these TORCH subgroup comparisons may suggest that increased deaths were experienced by subjects randomized to ICS removal by Day 90 compared to those randomized to ICS continuation. Under this "flipped" orientation that focuses on an interpretation of ICS removal effects, TORCH provides data on ICS removal suggesting a hazard ratio for death of 3.03 for ACM at Day 90 using the SAL versus FP/SAL comparison or a hazard ratio for death of 1.92 using the placebo versus FP comparison.

Reviewer's Comment*: in this subgroup of subjects with pre-study ICS, randomization to SAL or placebo arms involved ICS removal during the run-in that was maintained throughout the study. While these exploratory subgroup analyses at Day 90 should be interpreted with caution and are based upon few events, the data from subjects prescribed pre-study ICS describes a numerically higher number of ACM events in both trial arms where ICS removal occurred (i.e., the SAL and placebo arms) compared to those where ICS was continued (i.e., the FP/SAL and FP arms). This result reinforces the early safety signal for ACM among those that experienced ICS removal observed in the IMPACT trial. Under the ICS removal interpretation, these data suggest a hazard ratio for death of 3.03 for ACM in the first 90 days using the SAL versus FP/SAL comparison or a hazard ratio of 1.92 for ACM in the first 90 days using the placebo versus FP comparison.*

This result occurred despite a run-in that required ICS removal and only allowed short-acting inhaled medications. This result reinforces the early safety signal for ACM among those that experienced ICS removal observed in the IMPACT trial.

Table 41. TORCH: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT Including Both On- and Off-treatment Data)

ACM Analysis Category	FP/SAL N=740	FP N=732	SAL N=701	Pbo N=803
Number of subjects with event, n(%)	1 (0.1)	4 (0.5)	3 (0.4)	7 (0.9)
FP/SAL vs. comparator				
ACM HR			0.33	0.13
95% CI			0.03, 3.23	0.02, 1.04
Comparator vs. FP/SAL				
ACM HR			**3.03**	7.69
95% CI			**0.31, 33.33**	0.96, 50.00
FP vs. comparator				
ACM HR				0.52
95% CI				0.15, 1.80
Comparator vs. FP				
ACM HR				**1.92**
95% CI				**0.56, 6.67**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FP on ACM endpoints.
Pre-study ICS = Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA)
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FP, fluticasone propionate 500 µg; FP/SAL, fluticasone propionate 500 µg / salmeterol 50 µg; ITT-E, intention to treat, efficacy; Pbo, placebo; SAL, salmeterol 50 µg

In contrast, in the ICS-naïve subgroup (i.e., subjects without pre-study ICS), comparisons that isolate the effect of the ICS component do not support a difference in ACM due to ICS at Day 90. In this ICS-naïve subgroup in which patients were not at risk of ICS removal (Table 42), the hazard ratio for death for subjects on FP/SAL was 1.18 compared to SAL, while the hazard ratio for FP compared to placebo was 0.92.

***Reviewer's Comment**: In contrast to those who took pre-study ICS and may have experienced ICS removal, the Day 90 data for the subgroup of ICS-naïve subjects – who were not at risk of ICS removal events – do not suggest an ACM benefit for the addition of an ICS component within the first 90 days.*

Table 42. TORCH: Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT Including Both On- and Off-treatment Data)

ACM Analysis Category	FP/SAL N=740	FP N=732	SAL N=701	Pbo N=803
Number of subjects with event, n(%)	8 (1.1)	8 (1.0)	7 (0.9)	8 (1.2)
FP/SAL vs. comparator				
ACM HR			**1.18**	0.92
95% CI			**0.43, 3.27**	0.34, 2.45
FP vs. comparator				
ACM HR				**0.92**
95% CI				**0.35, 2.46**

Source: Adapted from Applicant-submitted materials. Not all trial comparisons are included, for clarity. These analyses incorporate on- and off-treatment vital status data from the TORCH study and available vital status follow-up data for subjects who withdrew from the study. Comparisons in **bold text** provide data to inform the efficacy and safety of FP on ACM endpoints.
Pre-study ICS = No: subjects without prestudy ICS-containing therapy
Abbreviations: ACM, all-cause mortality; CI, confidence interval; FP, fluticasone propionate 500 µg; FP/SAL, fluticasone propionate 500 µg / salmeterol 50 µg; HR, hazard ratio; ITT-E, intention to treat, efficacy; Pbo, placebo; SAL, salmeterol 50 µg

5.6.6. TORCH Data Appendix: Pre-randomization ICS Removal Effects

The pre-study ICS subgroup data at Day 90 presented for the SUMMIT and TORCH trials may suggest an early safety signal for ACM among those that underwent ICS removal. However, additional data on ICS removal effects from these trials can be assessed among subjects who enrolled and underwent ICS removal but were not randomized. In contrast to the IMPACT trial, the TORCH trial included a run-in period that involved discontinuation of maintenance COPD treatments including ICS. Functionally this design meant that any subject with pre-study ICS had ICS removed along with other long-acting medications.

When these run-in data are examined, a numerically increased proportion of subjects undergoing ICS removal as part of the run-in for TORCH withdrew from the trial due to adverse events compared to the ICS-naïve group who did not undergo ICS removal (see Table 43, below). These adverse events during the run-in led to subjects not being randomized.

More pertinent to the discussion of ACM endpoints, TORCH data shows that there were 11 deaths among 552 subjects who underwent ICS removal as part of the run-in compared to only 2 deaths among 523 ICS-naïve subjects who did not undergo ICS removal. While these run-in attrition results do not rely on a randomized comparison and should be interpreted with caution, the attrition rates for adverse events may align with the results of a previous study by Jarad and colleagues[34], that suggested symptomatic decline upon removal of ICS during a trial run-in (see Section 4.5.8, ICS Removal in COPD, above).

***Reviewer's Comment**: Functionally, the run-in of the TORCH trial required ICS removal among potential subjects with pre-study ICS. However, if subjects did not tolerate this ICS removal (e.g., due to an AECOPD or death) they were not randomized. The attrition of vulnerable pre-study ICS subjects during the run-ins of the TORCH trial may have left this trial less enriched for patients at greatest*

risk of ICS removal effects in their final study populations. Analogous to a "healthy survivor" effect, only those pre-study ICS users in TORCH who tolerated an initial ICS removal during run-in would be randomized. By contrast, the IMPACT trial's run-in consisted of continuation of the pre-study maintenance COPD regimen and ICS removal occurred abruptly at the time of randomization, so the effect of ICS removal may not have been mitigated by excluding those with functional decline prior to randomization.

Table 43. TORCH: Study Attrition Among Subjects Who Did Not Start Treatment by Pre-study ICS Subgroup

	Pre-Study ICS Use	
Reason for Withdrawal	**Yes**	**No**
Subjects withdrawn prior to starting randomized treatment, N (%)	552	523
Primary reason for withdrawal		
Adverse event, N(%)	172 (31)	61 (12)
SAEs among subjects who did not start treatment**		
Subjects with SAEs**	48 (9)	25 (5)
COPD as SAE	28 (5)	11 (2)
Fatal adverse events among subjects who did not start treatment***		
Subjects with fatal adverse events***	11 (2)	2 (<1)

Adapted from Applicant's submitted materials. Proportions of subjects with the stated reason for run-in failure are calculated using a denominator of the "Subjects Withdrawn Prior to Starting Randomized Treatment" entry.
*A total of 2370 subjects withdrew prior to starting randomized treatment in TORCH, but pre-study ICS data are only available for 1075. The available data for these 1075 is presented in this table.
**Not all recorded terms for "Subjects with Serious Adverse Events" are presented in this table.
***Data for 3 subjects with mortality events prior to starting treatment in the TORCH trial were attributed to "unknown" or "no data" categories.
Abbreviations: FAE, fatal adverse event; Pre-study ICS, Yes: subjects with prestudy ICS therapy (such as ICS/LABA/LAMA or ICS/LABA); Pre-study ICS, No: subjects without prestudy ICS-containing therapy; SAE, serious adverse event

5.7. Additional Relevant Studies and Trials of ICS Removal in COPD From the Literature

In addition to the studies described in Section 4.5.8, the following studies offer additional information regarding ICS removal in COPD.

Schermer, et al.

A study by Schermer and colleagues[37], investigated the probability of respiratory events (i.e. ModSev AECOPD or "unremitting worsening of respiratory symptoms") after removal of ICS and also attempted to define risk factors for AECOPD in that clinical setting. This unblinded study prospectively followed 201 COPD subjects who discontinued maintenance ICS therapy, assessing their time-to-first respiratory event and probability of a respiratory event over the course of over 200 days. Subjects enrolled in the study had a mean age of 60.6 years, 49% were current smokers, mean post-bronchodilator FEV1 was 65.6% predicted, and 57.7% had a prior history ≥2 AECOPD within the prior 2 years. The authors report that 86 subjects (43%) withdrew from this study during the follow-up period; 54 of these patients withdrew due to an AECOPD event after ICS removal, while an additional 21 withdrew due to unremitting worsening of

respiratory symptoms after ICS removal. Overall, the probability of study withdrawal due to a respiratory event was 0.37. The authors did not report mortality data in this population.

O'Brien, et al.

Clinical decline after ICS removal among symptomatic patients with COPD was also suggested in a trial by O'Brien and colleagues[35] from 2001. This small, double-blind, placebo-controlled trial enrolled 24 male subjects with severe, irreversible airflow obstruction receiving pre-study ICS and randomized them to placebo (i.e., ICS removal) or continuation of ICS therapy for 6 weeks, followed by crossover. The mean age of the patients was 67 years, and their mean FEV1 was 47% predicted. Three subjects withdrew due to worsening symptoms, while an additional six subjects withdrew after the first study visit. At the 6-week comparison, data from the ICS removal arm showed a significant decrease in mean FEV1 and symptomatic worsening on patient-reported outcome measures compared to the ICS continuation arm. While the authors of this randomized trial acknowledge the limitations of their data, most notably the small sample size, these data may suggest that discontinuation of ICS among vulnerable patients leads to worsening of lung function and patient-reported outcomes.

Van der Valk, et al.

Further supporting the suggestion of increased AECOPD after ICS removal, van der Valk and colleagues[36] conducted a 6-month randomized, double-blind, placebo-controlled clinical trial of ICS removal in 244 patients with COPD. After 4 months of continuous pre-study ICS use, subjects were randomized to placebo (i.e., ICS removal) or continuation of ICS therapy for 6 months. Enrolled COPD subjects had a mean age of 64 years, mean FEV1 of 57% predicted, and an average of 1.3 AECOPD in the 12 months prior to the study. During the 6-month randomized period, in addition to experiencing a numerically greater FEV1 decline, subjects randomized to ICS removal had a statistically significant worsening in SGRQ total score compared to the ICS continuation group. During this same timeframe, 57% of the ICS removal group developed at least one AECOPD compared with 47.2% of the ICS continuation group. The time to first AECOPD was also shorter in the ICS removal group (42.7 days) compared to the ICS continuation group (75.2 days), with a hazard ratio of 1.5; the hazard ratio of a second AECOPD was 2.4 for the same comparison. Moreover, this trial suggested a vulnerable population that may show clinical deterioration after ICS removal, 26 patients (21.5%) in the ICS removal group experienced recurrent AECOPD that necessitated the prescription of additional maintenance therapy compared to only 6 patients (5%) in the ICS continuation group. Of these 26 patients in the ICS removal group, 10 of them continued to experience AECOPD over the remaining trial period despite prescription of an ICS.

Choudhury, et al.

In 2007, Choudhury and colleagues[39] published a pragmatic, double-blind, randomized trial of ICS removal among 260 patients with COPD enrolled from a primary care setting. After at least 6 months of continuous pre-study ICS therapy, subjects were randomized to placebo (i.e., ICS removal) or continuation of ICS therapy for 12 months. Enrolled subjects had a mean age of 67.4 years, mean post-bronchodilator FEV1 of 54.1% predicted, and an average 1.53 AECOPD requiring systemic antibiotic or systemic steroid treatment reported in the prior year. Out of

132 patients randomized to ICS removal, 78 discontinued placebo by returning to their pre-study inhaler over the course of the trial. Despite this high attrition rate, in the ITT analysis, the mean exacerbation frequency for ModSev AECOPD was numerically higher for the ICS removal group, with an adjusted risk ratio of 1.25. Using a Cox PH model to evaluate time-to-first AECOPD, the authors reported statistically significant higher risk of AECOPD (odds ratio 1.43) in the ICS removal-arm for the same comparison. While the high rate of study drug discontinuation limits interpretation of the on-treatment data, the authors report a statistically significant risk ratio of 1.48 for the rate of ModSev AECOPD in the per-protocol analysis. This study was not powered to assess mortality endpoints.