FDA Pulmonary-Allergy Drugs Advisory Committee Meeting
FDA Summary Presentation

sNDA 209482: Trelegy for the reduction in all-cause mortality in patients with chronic obstructive pulmonary disease (COPD)

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Office of New Drugs
U.S. Food and Drug Administration
August 31, 2020

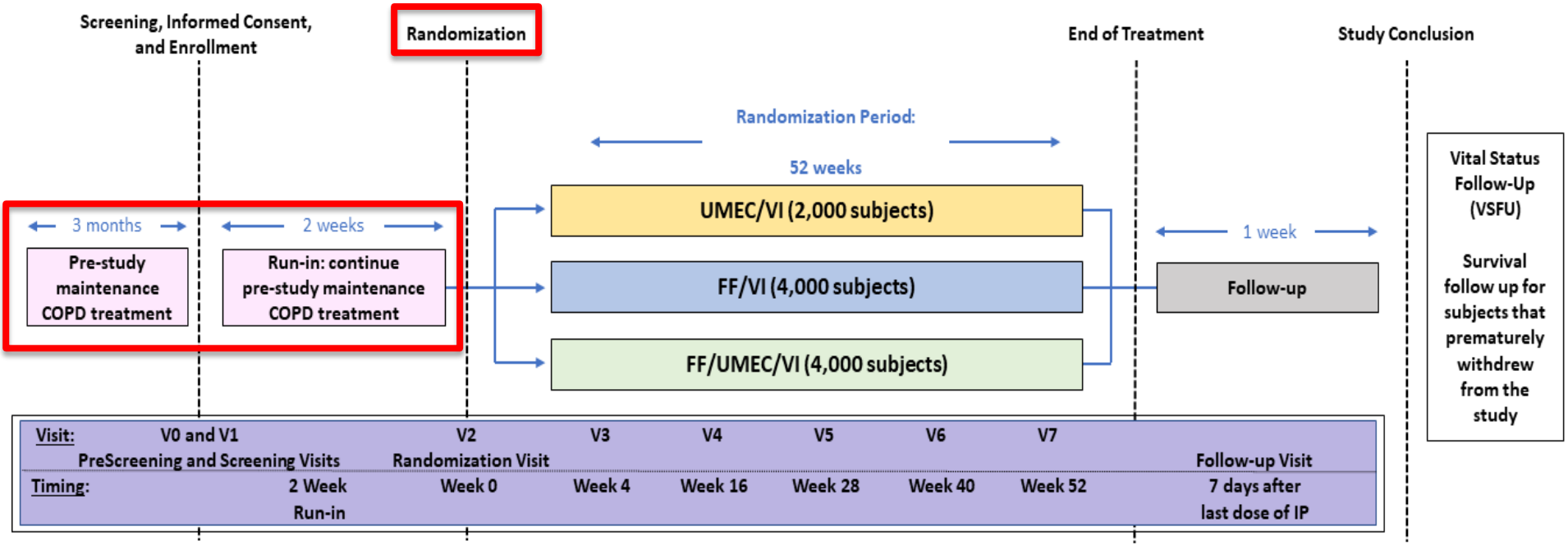
Proposed Labeling Claim

- *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.

Overview of the Clinical Program

Pivotal Efficacy Trial: IMPACT



Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; UMEC: umeclidinium 62.5mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; IP: Investigational Product; V: visit; VSFU: vital status follow-up

Design and Population of the 3 Studies

Study	IMPACT N = 10,355	SUMMIT N = 16,485		TORCH N = 6,112	
Fluticasone Comparison	**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	3058
Study Design Characteristics					
Duration	1 year	Event-driven (median 1.8 years)		3 years	
Enrollment Criteria	**FEV1**: Moderate to very severe COPD	**FEV1**: Moderate COPD		**FEV1**: Moderate to very severe COPD	
	Medications: 3 months pre-study maintenance medications	**Medications**: no requirement		**Medications**: no requirement	
	Exacerbations: Prior history of exacerbations despite COPD maintenance medications	**Exacerbations**: No requirement for prior history of exacerbations		**Exacerbations**: No requirement for prior history of exacerbations	
	Symptoms: CAT ≥10	**Symptoms**: mMRC ≥2		**Symptoms**: no requirement	
Run-in	Pre-study medication continued until randomization	Discontinue ICS, LABA, and LAMA prior to enrollment; 4 to 10-day run-in on short-acting medications alone prior to randomization		Discontinue ICS, LABA, and LAMA for 14-day run-in on short-acting medications alone prior to randomization	
Population Characteristics					
Pre-study Triple Therapy	38%	9%		<1%	
Pre-study ICS	71%	33%		49%	
Frequent Exacerbators in Prior Year	70%	21%		36%	
St. George's Respiratory Questionnaire Total Score	50.6	46.6		49.3	

Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; UMEC: umeclidinium 62.5mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; FF: fluticasone furoate 100mcg; VI: vilanterol 25mcg; Pbo: placebo; FP: fluticasone propionate 500 mcg; SAL: salmeterol 50 mcg; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council score; ; Triple Therapy: inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist

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Statistical Review of Efficacy

IMPACT Design Features

- Designed to understand contribution of FF and UMEC to FF/UMEC/VI with respect to exacerbations
- Not designed to assess ACM as primary or secondary objective
  - Primary endpoint: annual rate of moderate/severe exacerbations
  - Secondary endpoints: FEV_1, SGRQ, time to first exacerbation
  - **Exploratory 'Other' endpoints: All-cause mortality** (one of many)
- Not powered for mortality
- Only one-year duration; trials evaluating ACM have utilized a longer duration

FEV_1: forced expiratory volume in 1 second
SGRQ: St. George's Respiratory Questionnaire

IMPACT Analysis Plan

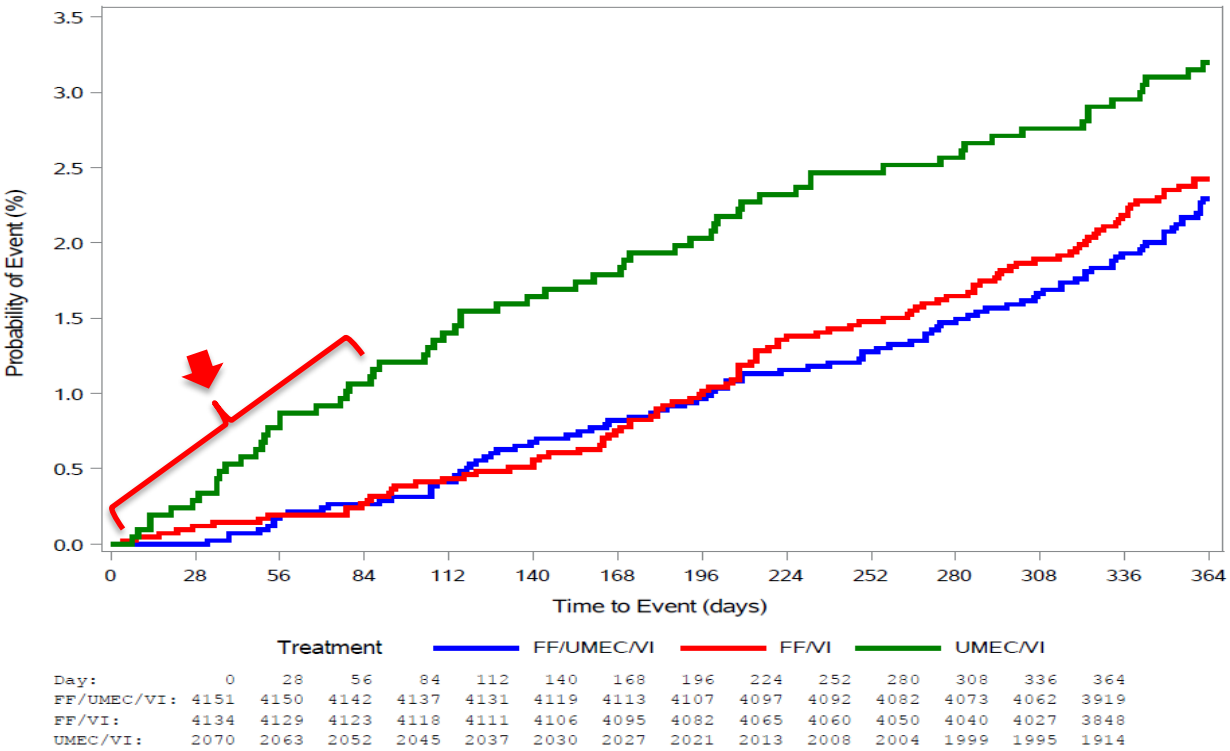
- **ACM one of roughly 30 exploratory 'Other' endpoints (most with two pairwise comparisons) not under Type I error control**
  - **Interpreting results challenging**
- ACM analyzed with Cox proportional hazards model, with covariates of gender and age, comparing:
  - FF/UMEC/VI to FF/VI (effect of UMEC)
  - FF/UMEC/VI to UMEC/VI (effect of FF)

IMPACT ACM Overall Results

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Subjects with event n (%)	98 (2.4)	109 (2.6)	66 (3.2)
ACM analysis of FF/UMEC/VI vs comparator			
HR for ACM 95% CI p-value		0.89 0.67, 1.16 0.387	0.72 0.53, 0.99 0.042

CI: confidence interval
HR: hazard ratio

IMPACT ACM Over 52 Weeks



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: Reviewer

SUMMIT and TORCH Objectives

- Primary objective: All-cause mortality evaluation
  - Primary analysis: ACM for ICS/LABA vs. placebo
  - Powered to detect differences in ACM
  - Longer durations
    - SUMMIT: Event-driven; median: 1.8 years, maximum: 46 months
    - TORCH: 3 years
- Neither study showed effect of ICS/LABA vs. placebo
- Our primary focus: fluticasone contribution
  - ICS/LABA vs LABA
  - ICS vs placebo

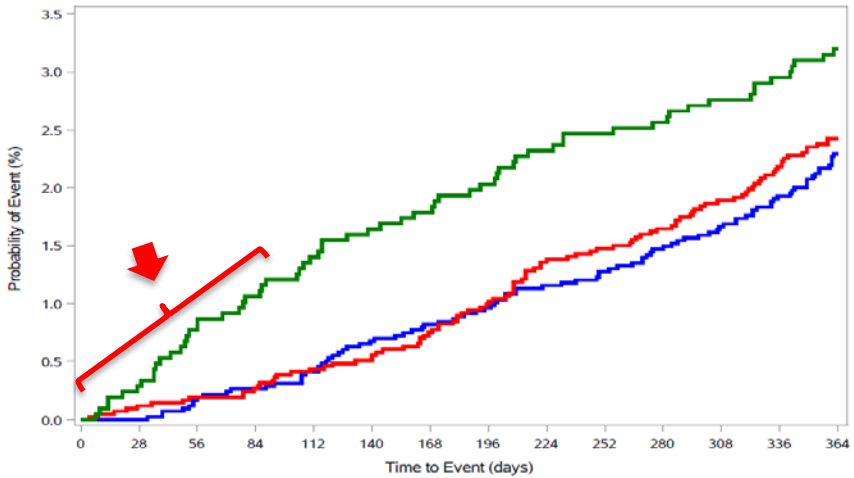
IMPACT, SUMMIT and TORCH ACM Results

	IMPACT N=10,355	SUMMIT N=16,485		TORCH N=6,112	
	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	3,058
Mortality events in comparison	164	511	526	398	477
ACM analyses Hazard ratio 95% CI	0.72 0.53 - 0.99	0.91 0.77 - 1.09	0.91 0.77 - 1.08	0.95 0.78 - 1.15	1.06 0.88 – 1.26

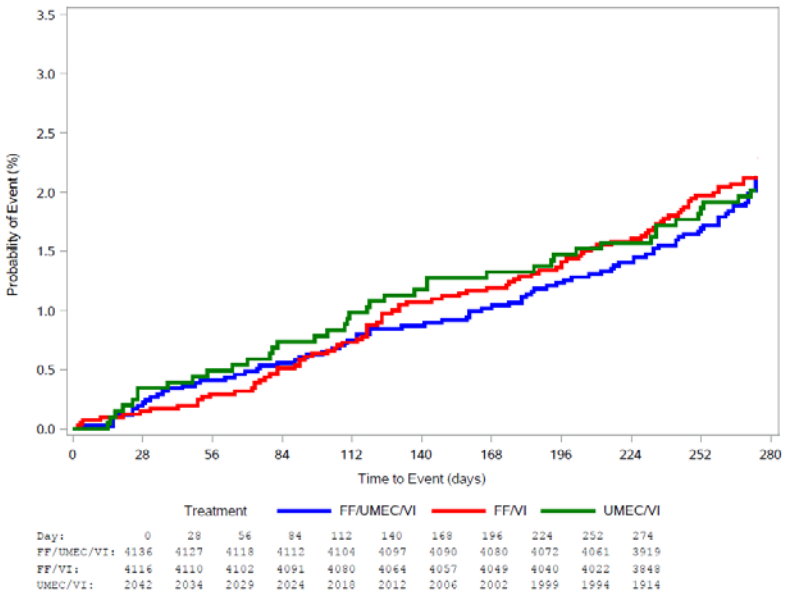
Source: Reviewer

IMPACT ACM: Early Separation

All Mortality Data



Mortality Data after Day 90



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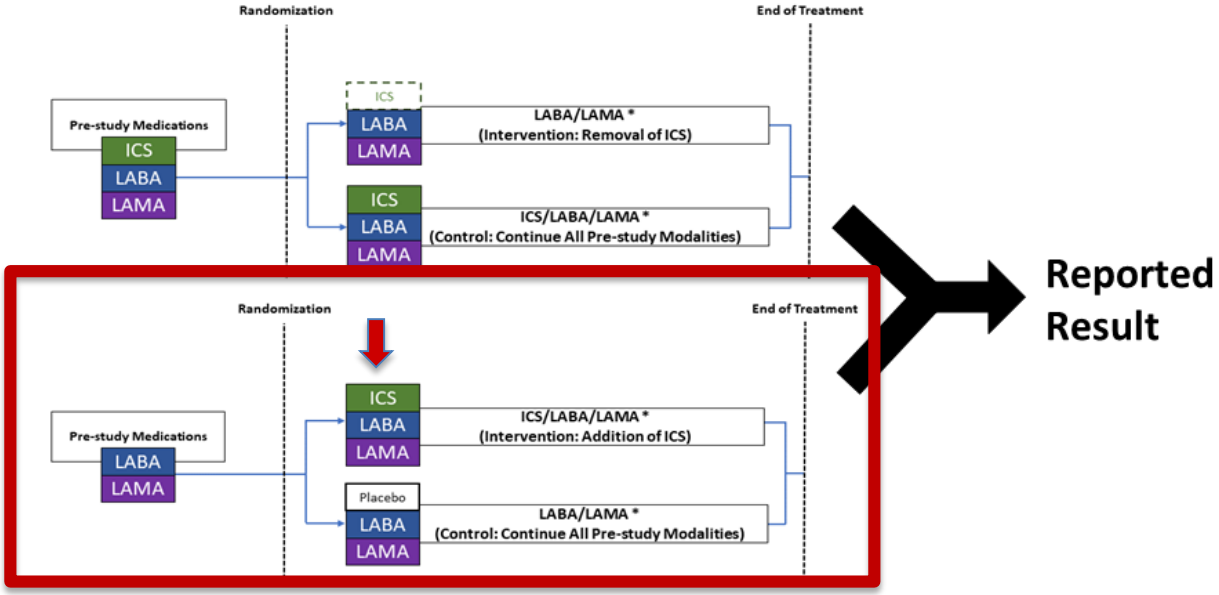
Clinical Considerations

ICS Removal in COPD Trials

- ICS removal versus ICS-addition
  - Suissa et al



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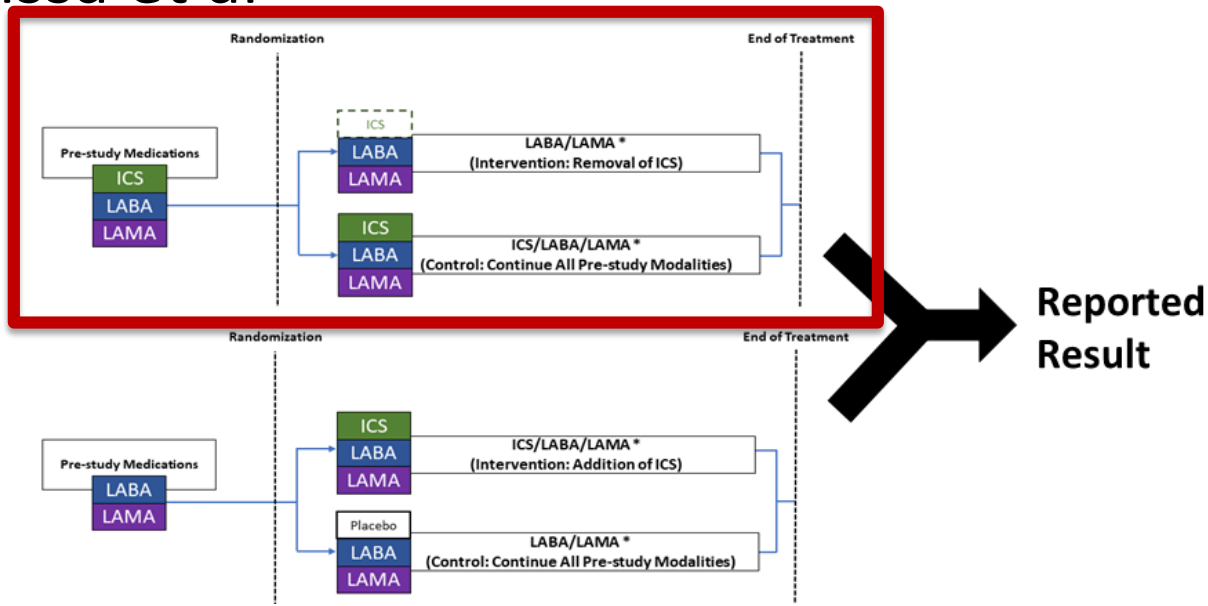

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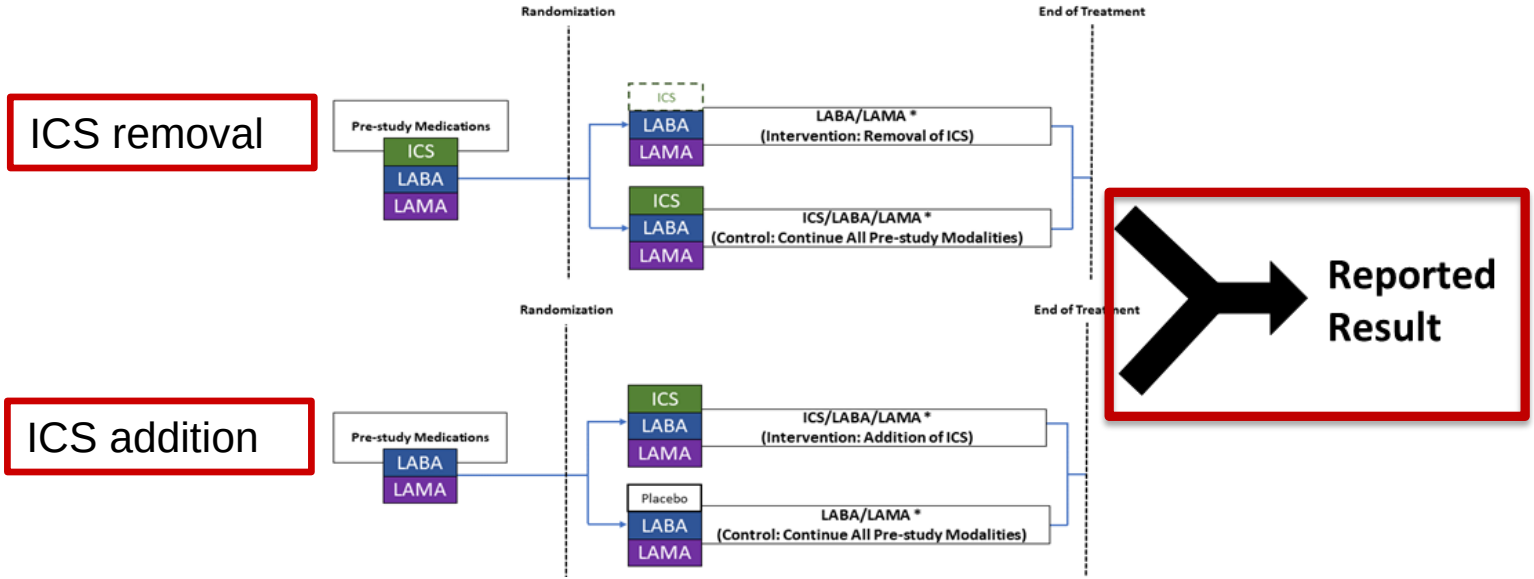

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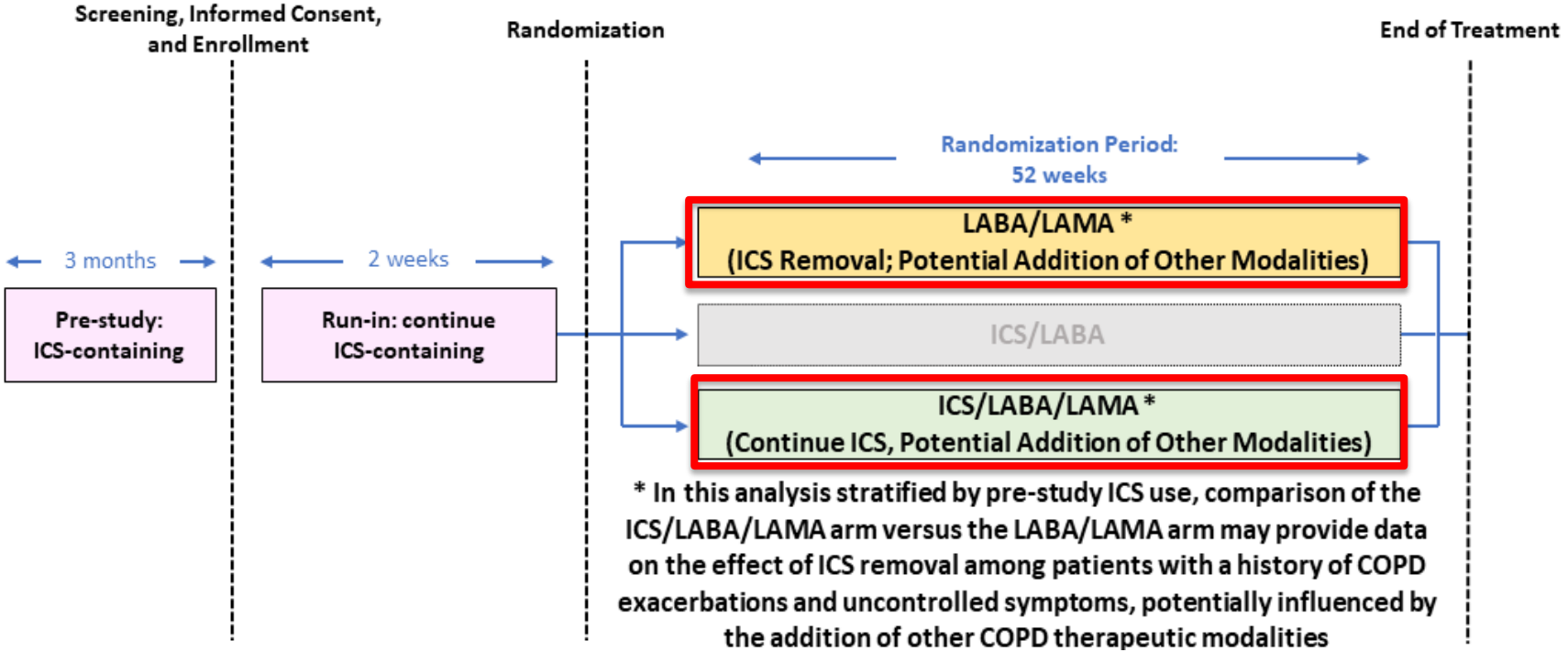
IMPACT: ICS Removal



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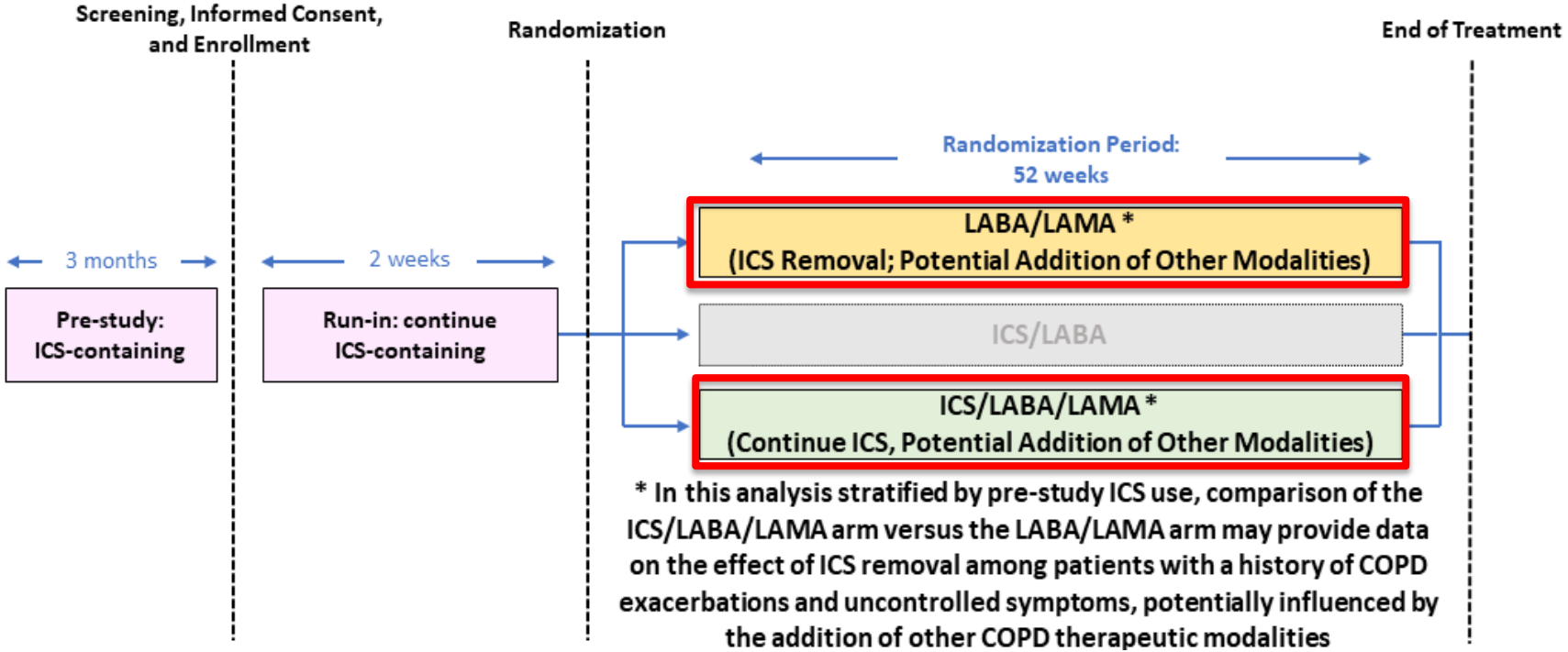
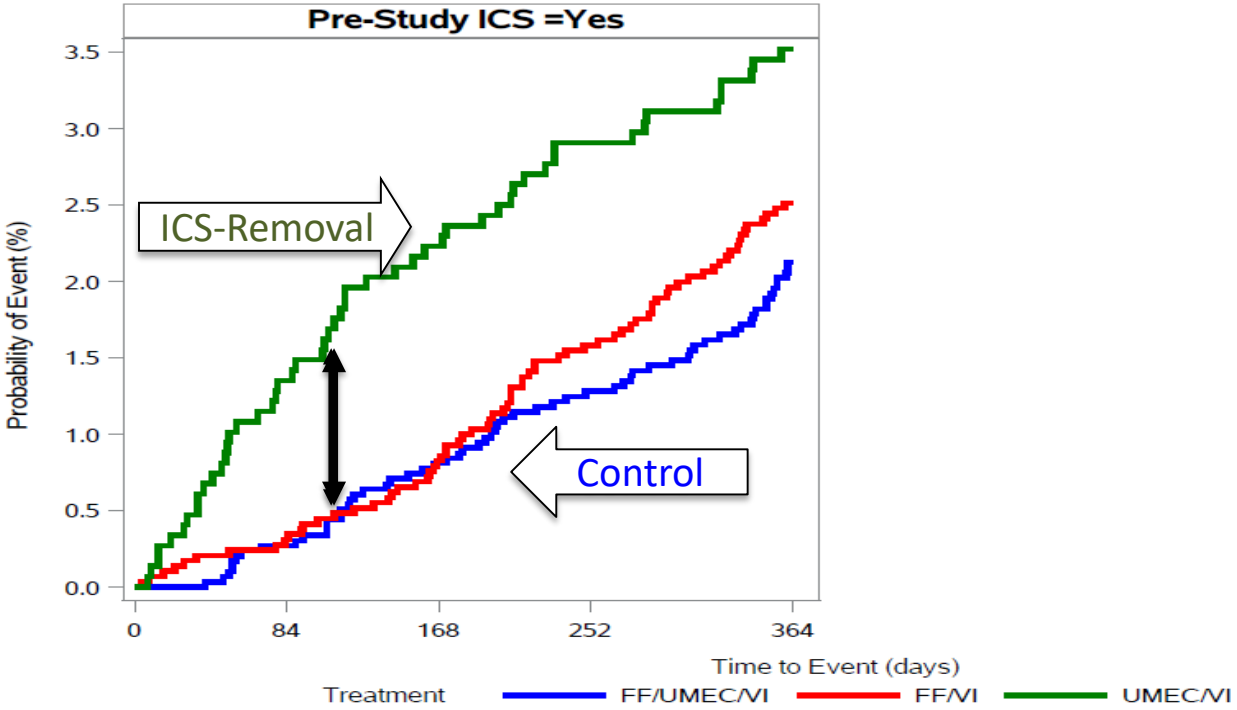


Pre-study ICS subgroup: over 7,000 subjects; 1491 randomized to ICS removal

Source: Reviewer

IMPACT: Pre-study ICS Therapy and ACM

Pre-study ICS Subgroups: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



Day:	0	84	168	252	364
FF/UMEC/VI:	2971	2960	2943	2927	2812
FF/VI:	2908	2898	2882	2858	2709
UMEC/VI:	1481	1460	1444	1429	1363

Source: Reviewer. Abbreviations: ITT: intention to treat; VS: vital status assessment, 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; CI: confidence interval. Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA

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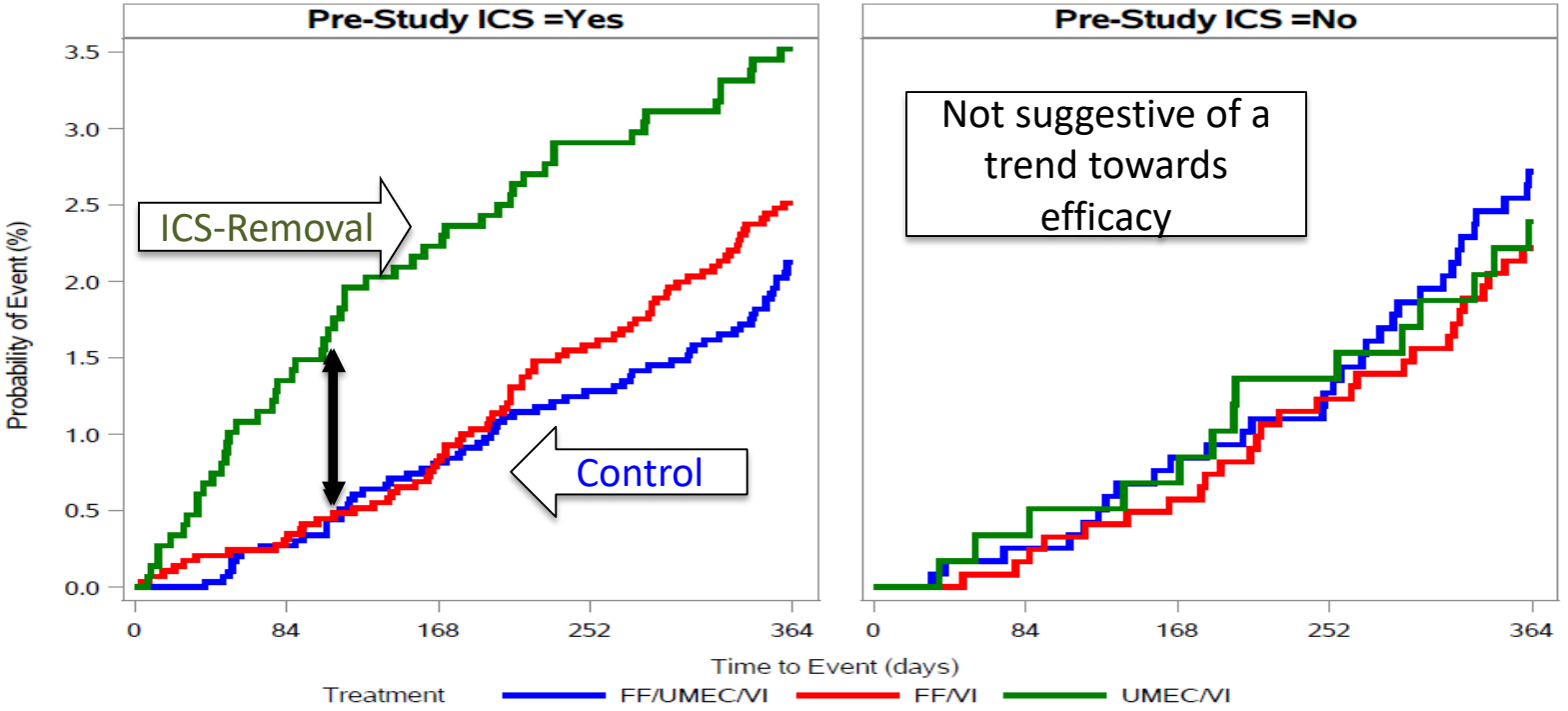

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FF/VI:	2908	2898	2882	2858	2709	1226	1220	1213	1202	1139
UMEC/VI:	1481	1460	1444	1429	1363	589	585	583	579	551

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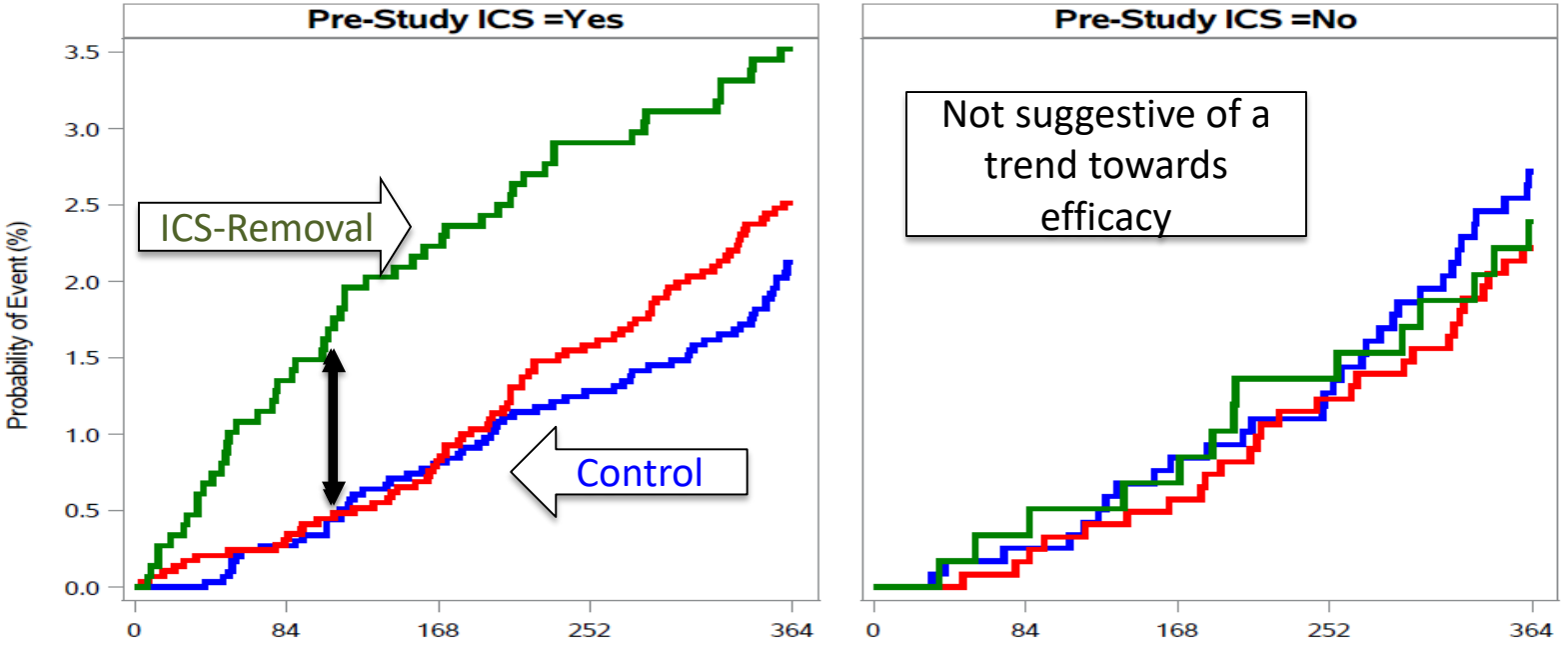

P-value=0.08 for interaction between pre-study ICS and treatment (FF/UMEC/VI vs UMEC/VI comparison)

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ICS Removal and Addition Across Trials

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All-cause Mortality Analyses in Pre-study ICS Subgroup at Day 90					
ICS Removal Comparison	UMEC/VI vs FF/UMEC/VI	VI vs FF/VI	Pbo vs FF	SAL vs FP/SAL	Pbo vs FP
Number of Patients in Comparison	4,452	2,768	2,718	1,441	1,535
Hazard Ratio for ICS Removal Comparison at Day 90	**5.00 (2.27, 11.11)**	**3.85 (1.08, 14.3)**	**1.35 (0.50, 3.85)**	**3.03 (0.31, 33.33)**	**1.92 (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 IMPACT, SUMMIT, and TORCH studies 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 fluticasone products on ACM endpoints. Abbreviations: ITT-E: intention to treat, efficacy; CI: confidence interval; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo; Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

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All-cause Mortality Analyses in ICS-naïve Subgroup at Study End					
ICS Addition Comparison	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	1,769	5,471	5,528	1,537	1,447
Hazard Ratio for ICS Addition Comparison at Study End	**1.16 (0.62, 2.16)**	**0.99 (0.80, 1.23)**	**0.96 (0.77, 1.19)**	**0.98 (0.75, 1.29)**	**1.13 (0.87, 1.45)**

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 IMPACT, SUMMIT, and TORCH studies 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 fluticasone products on ACM endpoints. Abbreviations: ITT-E: intention to treat, efficacy; CI: confidence interval; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo; Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

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ICS Addition Comparison	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	1,769	5,471	5,528	1,537	1,447
Hazard Ratio for ICS Addition Comparison at Study End	**1.16 (0.62, 2.16)**	**0.99 (0.80, 1.23)**	**0.96 (0.77, 1.19)**	**0.98 (0.75, 1.29)**	**1.13 (0.87, 1.45)**

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 IMPACT, SUMMIT, and TORCH studies 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 fluticasone products on ACM endpoints. Abbreviations: ITT-E: intention to treat, efficacy; CI: confidence interval; FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg; FF/ VI: fluticasone furoate 100 µg / vilanterol 25 µg; FF: fluticasone furoate 100 µg; VI: vilanterol 25 µg; Pbo: placebo; FP/SAL: fluticasone propionate 500 µg / salmeterol 50 µg; FP: fluticasone propionate 500 µg; SAL: salmeterol 50 µg; Pbo: placebo; Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

Charge to the Committee

Effectiveness Standards

- **Gold standard:** substantial evidence from 2 adequate, well-controlled studies
- Otherwise, “one adequate and well-controlled clinical investigation plus confirmatory evidence”[1,2]
  - Key factors include “persuasiveness of evidence from a single study” and “robustness of confirmatory evidence” [1]
  - A single study should “be limited to situations in which the trial has demonstrated a clinically meaningful and statistically *very persuasive effect* on mortality…” [2]

From: [1]Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products guidance, 1998 and [2]Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products draft guidance, 2019

Efficacy Considerations

- Statistical uncertainty of all-cause mortality (ACM) results in IMPACT
- Totality of Evidence (SUMMIT and TORCH)
- Early Timeframe of ACM Signal
- Effect of ICS Removal Across Studies
- Generalizability to Clinical Practice

Discussion Points and Voting Questions (1)

1. **DISCUSSION:** 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

Discussion Points and Voting Questions (2)

2. **DISCUSSION:** 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

Discussion Points and Voting Questions (3)

3. **DISCUSSION:** Discuss the generalizability of the IMPACT 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

Discussion Points and Voting Questions (4)

4. **VOTE:** Do the data from the IMPACT trial provide substantial evidence of efficacy to support the claim that TRELEGY ELLIPTA improves all-cause mortality in patients with COPD?

   a. If no, what further data are needed?


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BACKUP SLIDES SHOWN

IMPACT, Baseline **Across** Subgroups

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

Treatment	Total N (%)	
Pre-Study ICS	**Yes**	**No**
Total	7360	2995
Smoking History		
Current	2408 (33)	1179 (39)
Former	4952 (67)	1816 (61)
Screening post-bronchodilator FEV1*		
Mean FEV1%p (SD)	44.7 (14.7)	47.7 (15.1)
Screening Moderate to Severe AECOPD Category**		
<2 Mod and no Sev	2141 (29)	915 (31)
≥2 Mod or ≥1 Sev	5219 (71)	2080 (69)

Source: Reviewer, adapted from Applicant's submitted materials.
*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: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up; FEV1: forced expiratory volume in one second; %p: percent predicted; SD: standard deviation; AECOPD: acute exacerbation of COPD; ICS: inhaled corticosteroid; 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

IMPACT, Baseline **Within** Subgroups

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

Treatment	FF/UMEC/VI N (%)		FF/VI N (%)		UMEC/VI N (%)	
Pre-Study ICS	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Total	2971	1180	2908	1226	1481	589
Smoking History						
Current	978 (33)	458 (39)	937 (32)	486 (40)	493 (33)	235 (40)
Former	1993 (67)	722 (61)	1971 (68)	740 (60)	988 (67)	354 (60)
Screening post-bronchodilator FEV1*						
Mean FEV1%p (SD)	44.7 (14.7)	48.3 (15.3)	44.6 (14.6)	47.6 (15)	44.8 (14.7)	46.9 (14.6)
Screening Moderate to Severe AECOPD Category**						
<2 Mod and no Sev	862 (29)	336 (28)	858 (30)	384 (31)	421 (28)	589 (33)
≥2 Mod or ≥1 Sev	2109 (71)	844 (72)	2050 (70)	842 (69)	1060 (72)	394 (67)

Source: Reviewer, adapted from Applicant's submitted materials.
*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: ITT: intention to treat; VSFU: vital status follow-up; FEV1: forced expiratory volume in one second; %p: percent predicted; SD: standard deviation; AECOPD: acute exacerbation of COPD; 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;

IMPACT, Pre-study Triple Therapy Subgroup Death by Day 365

IMPACT: Pre-study Triple Therapy = Yes Subgroup: All-cause Mortality Subgroup Results at Day 365 (ITT+VS+VSFU)

	FF/UMEC/VI N=1581	FF/VI N=1563	UMEC/VI N=826
Week 52: All-cause Mortality Analysis			
Number of subjects with event, n (%)	34 (2.2)	47 (3.0)	28 (3.4)
Hazard Ratio for ACM 95% CI (FF/UMEC/VI versus Comparator)		0.71 (0.45, 1.10)	0.63 (0.38, 1.04)
Hazard Ratio for ACM **95% CI (Comparator versus FF/UMEC/VI)**			**1.6** **(0.96, 2.63)**

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.
Abbreviations: ITT: intention to treat; 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 vilanterol 25 µg; CI: confidence interval. Pre-Study ICS = Yes: subjects with pre-study ICS therapy (such as ICS/LABA/LAMA or ICS/LABA

IMPACT, Death Narratives, Pre-study ICS

IMPACT: Pre-Study ICS Subgroup: Death Narrative Information for Death Events by Day 90 in FF/UMEC/VI and UMEC/VI Arms

Pre-study ICS = YES	FF/UMEC/VI	UMEC/VI
Death by Day 90: Death Narratives, Cause of Death Verbatim Terms		
Number of subjects with death narrative	11	25
Cause of death includes COPD Exacerbation	0 (0)	5 (20)
Cause of death includes COPD Exacerbation, Acute Respiratory Failure, Respiratory Failure, or Respiratory Arrest	2 (18)	6 (24)
Cause of death includes COPD Exacerbation, Acute Respiratory Failure, Respiratory Failure, Respiratory Arrest, Cardiorespiratory Arrest, or Cardiopulmonary Arrest	3 (27)	10 (40)
Cause of death lists pneumonia	2 (18)	2* (8)

NOTE: These data are derived from the Clinical Study Report from the IMPACT trial, Section 15.1 Serious and Fatal Adverse Events. These death narratives do not include all subjects with death events in the ITT+VS+VSFU, because subjects who withdrew from the study would not have death narratives recorded. *includes one case of pulmonary tuberculosis.

Abbreviations: FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg; UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg.