FDA Pulmonary-Allergy Advisory Committee Meeting
Overview of the Clinical Program

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

Robert Busch, MD, MMSc
Clinical Reviewer
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
U.S. Food and Drug Administration
August 31, 2020

Outline

- Overview of the Clinical Program
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Susan Duke, MS, MS
  - Biometrics Reviewer: DB3, OTS, CDER, FDA
- Clinical Considerations
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Charge to the Committee
  - Banu Karimi-Shah, MD
  - Deputy Division Director: DPACC, OII, OND, CDER, FDA

Terminology

Drug Classes

- ICS: inhaled corticosteroid
- LABA: long-acting beta-agonist
- LAMA: long-acting muscarinic antagonist

Subgroups (defined by pre-study therapy*)

- Pre-study triple therapy: ICS+LABA+LAMA as part of maintenance treatment
- Pre-study ICS: ICS as part of maintenance treatment
- ICS-naïve: No maintenance ICS

Other

- ICS Removal: Discontinuation of inhaled corticosteroid medications

*prior to study enrollment and/or study interventions

TRELEGY ELLIPTA

- Approved Product
  - Fluticasone furoate 100 mcg (FF, an ICS), umeclidinium 62.5 mcg (UMEC, a LAMA), and vilanterol 25 mcg (VI, a LABA) inhalation powder for oral inhalation

- Current Indication
  - *TRELEGY ELLIPTA is a combination of fluticasone furoate, an inhaled corticosteroid (ICS); umeclidinium, an anticholinergic; and vilanterol, a long-acting beta2-adrenergic agonist (LABA), indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).*
  - *Important limitations of use: Not indicated for relief of acute bronchospasm or the treatment of asthma.*

Proposed Labeling Claim

- 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.
- **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 #)**.
- **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.

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

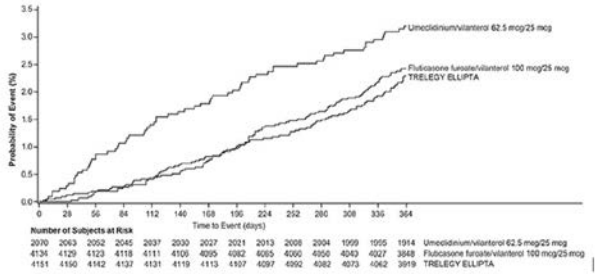


Table #. Reduction in All-Cause Mortality (Trial 3)

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.

Revised Proposed Labeling Claim

- *Revision 04/23/2020*
- *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.

ICS Comparisons

- Comparisons that inform the ICS efficacy question
  - ICS/LABA/LAMA versus LABA/LAMA
  - ICS/LABA versus LABA
  - ICS versus placebo

- From IMPACT
  - FF/UMEC/VI versus UMEC/VI
- From SUMMIT
  - FF/VI versus VI
  - FF versus placebo
- From TORCH
  - Fluticasone Propionate (FP)/Salmeterol (SAL) versus SAL
  - FP versus placebo

Overview of the Clinical Program

Overview of the Clinical Program

All-cause Mortality in COPD

ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

All-cause Mortality in COPD

ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

All-cause Mortality in COPD

- Limited interventions that affect all-cause mortality (ACM) in COPD
  - Smoking cessation
  - Supplemental oxygen for resting hypoxemia
  - Lung Volume Reduction Surgery (upper lobe predominant emphysema)

- Association of severe acute exacerbations of COPD with mortality

- No FDA-approved therapy has been shown to reduce ACM

References:

1. U.S. Department of Health and Human Services. The Health Benefits of Smoking Cessation. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publication No. (CDC) 90-8416, 1990..
2. Anthonisen NR, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: The Lung Health Study. JAMA, 1994.
3. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med, 1980.
4. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema: a report of the Medical Research Council Working Party. Lancet, 1981.
5. Fishman A, et al. A randomized trial comparing lung-volume reduction surgery with medical therapy for severe emphysema. NEJM, 2003.

ACM Trials in COPD

Mortality as a primary endpoint

- TORCH
  - Randomized (R), double blind (DB), placebo controlled (PC), 3-year factorial design trial of FP/SAL vs SAL vs FP vs Pbo
  - Primary analysis of FP/SAL vs. Pbo failed to show a statistically significant effect on ACM

- SUMMIT
  - R, DB, PC, event-driven duration factorial design trial of FF/VI vs VI vs FF vs Pbo
  - Primary analysis of FF/VI vs. Pbo failed to show a statistically significant effect on ACM

Other trials assessing mortality

- ISOLDE
  - Tested FP (ICS) versus placebo in a 1-year trial
- INSPIRE
  - Tested FP/SAL (ICS/LABA) versus tiotropium (LAMA) in a 2-year trial
- UPLIFT
  - Tested tiotropium (LAMA) versus placebo in a 4-year trial

Abbreviations: Pbo = placebo

References:
1. Calverley PMA, et al. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. NEJM, 2007.
2. Vestbo, J, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. The Lancet, 2016.
3. Burge PS, et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ, 2000.
4. Wedzicha JA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. AJRCCM, 2007.
5. Tashkin DP, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. NEJM, 2008.

All-cause Mortality in COPD

ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

ICS in COPD

- Benefit versus Risk
  - Efficacy on moderate to severe (ModSev) acute exacerbations of COPD (AECOPD)
  - Adverse events including pneumonia

- Still controversy surrounding initiation and removal in clinical practice
  - ICS initiation
    - Appropriate population to maximize benefit-risk ratio
  - ICS removal effects
    - Lung function and patient-reported outcome declines
    - AECOPD effects may be dependent on patient population
    - No trial designed to detect effect of ICS removal on ACM

All-cause Mortality in COPD

ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

Regulatory History

- 2017: TRELEGY ELLIPTA initial approval
  - Indication limited to COPD patients on FF/VI or taking UMEC and FF/VI in separate inhalers
- IMPACT protocol design
  - Primary endpoint of moderate-to-severe exacerbations
  - Agency agreed with comparators, duration, patients population, run-in period
- 2018: Labeling amended based on IMPACT results
- 2019: Revised to current labeling

Regulatory History

- No discussion of the appropriate timeframe or clinical design elements to support an all-cause mortality assessment

- Neither the Sponsor nor the Division discussed the potential risks of protocol-mandated ICS removal among symptomatic COPD patients

All-cause Mortality in COPD

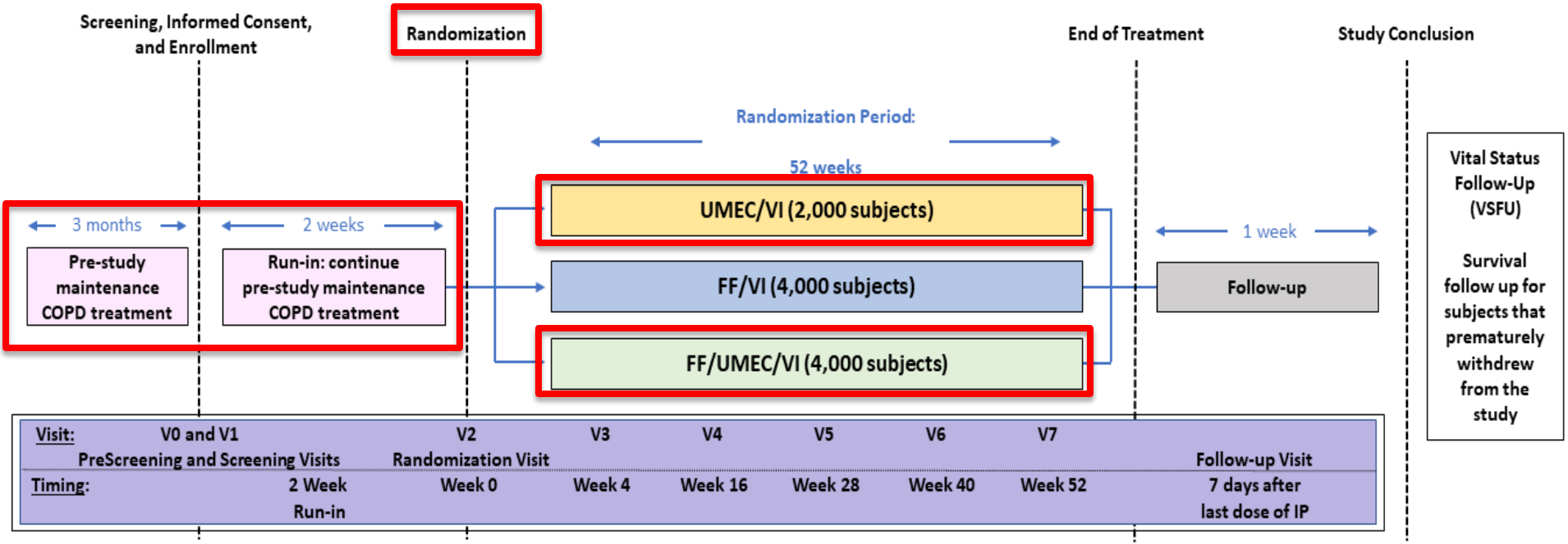
ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

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

IMPACT: Patient Selection

- Inclusion:
  - Outpatient male or female subjects ≥40 years of age
  - Current or former tobacco smoker with ≥10 pack-year history
  - Post-bronchodilator FEV_1/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)
  - Score of ≥10 on the COPD Assessment Test (CAT) at screening
  - Daily maintenance medication for the treatment of COPD for at least 3 months prior to screening (pre-study medication)
- Exclusion:
  - Systemic corticosteroids within 30 days

Abbreviations: FEV1 = forced expiratory volume in one second; FVC = forced vital capacity

IMPACT: Endpoints

- Primary
  - Annual Rate of on-treatment ModSev AECOPD
    - FF/UMEC/VI versus UMEC/VI
    - FF/UMEC/VI versus FF/VI
- Secondary
  - Change from baseline in trough FEV1 at Week 52
  - Change from baseline in SGRQ Total Score at Week 52
  - Time-to-first on-treatment ModSev AECOPD
    - FF/UMEC/VI versus FF/VI
    - FF/UMEC/VI versus UMEC/VI
- Other
  - All-cause mortality included as one of many exploratory endpoints

Abbreviations: SGRQ: St. George's Respiratory Questionnaire

IMPACT: Design

Study	IMPACT N = 10,355
Fluticasone Comparison	**FF/UMEC/VI vs UMEC/VI**
Number of Patients in Comparison	6221
Study Design Characteristics	
Duration	1 year
Enrollment Criteria	**FEV1**: Moderate to very severe COPD
	Medications: 3 months pre-study maintenance medications
	Exacerbations: Prior history of exacerbations despite COPD maintenance medications
	Symptoms: CAT ≥10
Run-in	Pre-study medication continued until randomization

Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; UMEC: umeclidinium 62.5mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test

All-cause Mortality in COPD

ICS in COPD

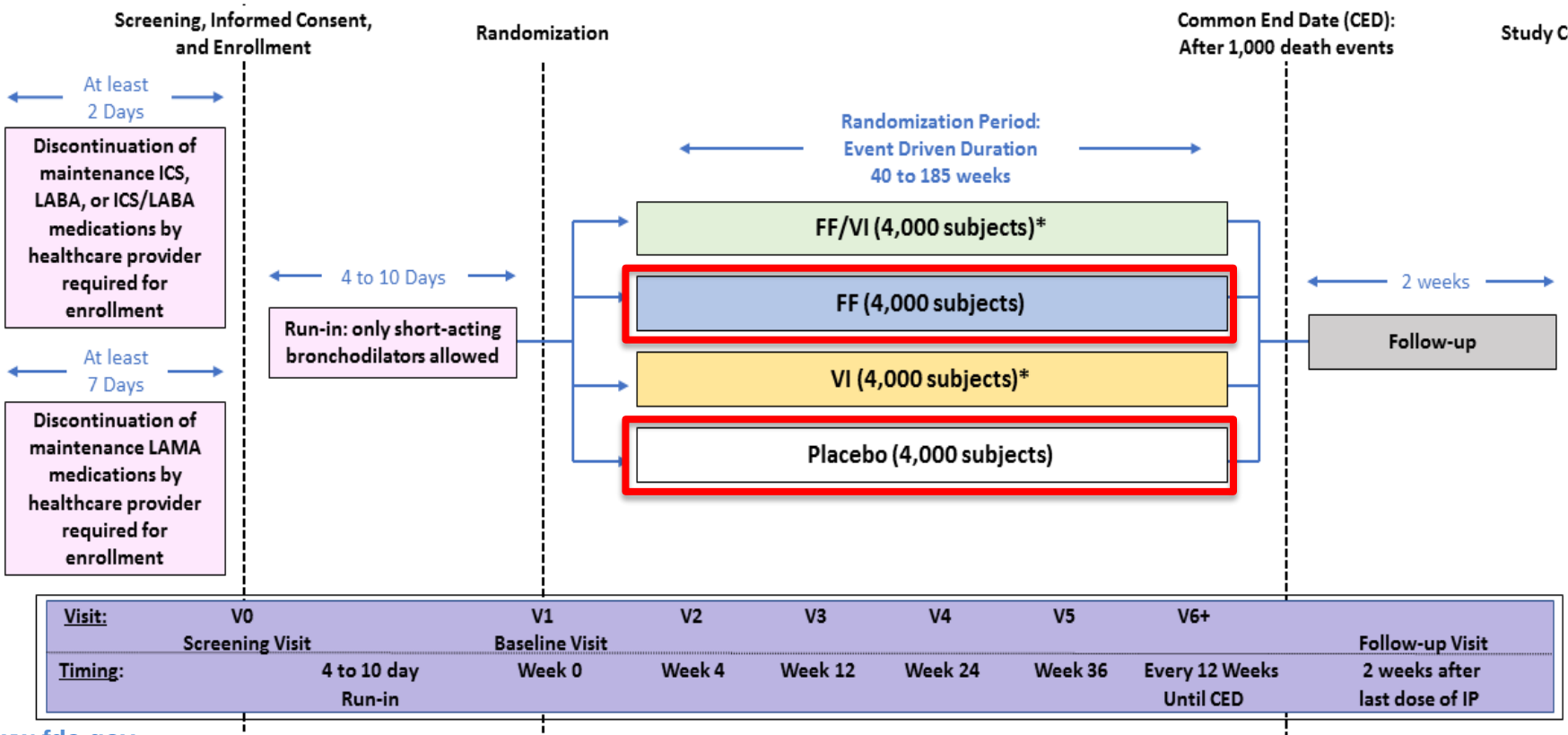
TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

- **Comparison to SUMMIT**
- **Comparison to TORCH**

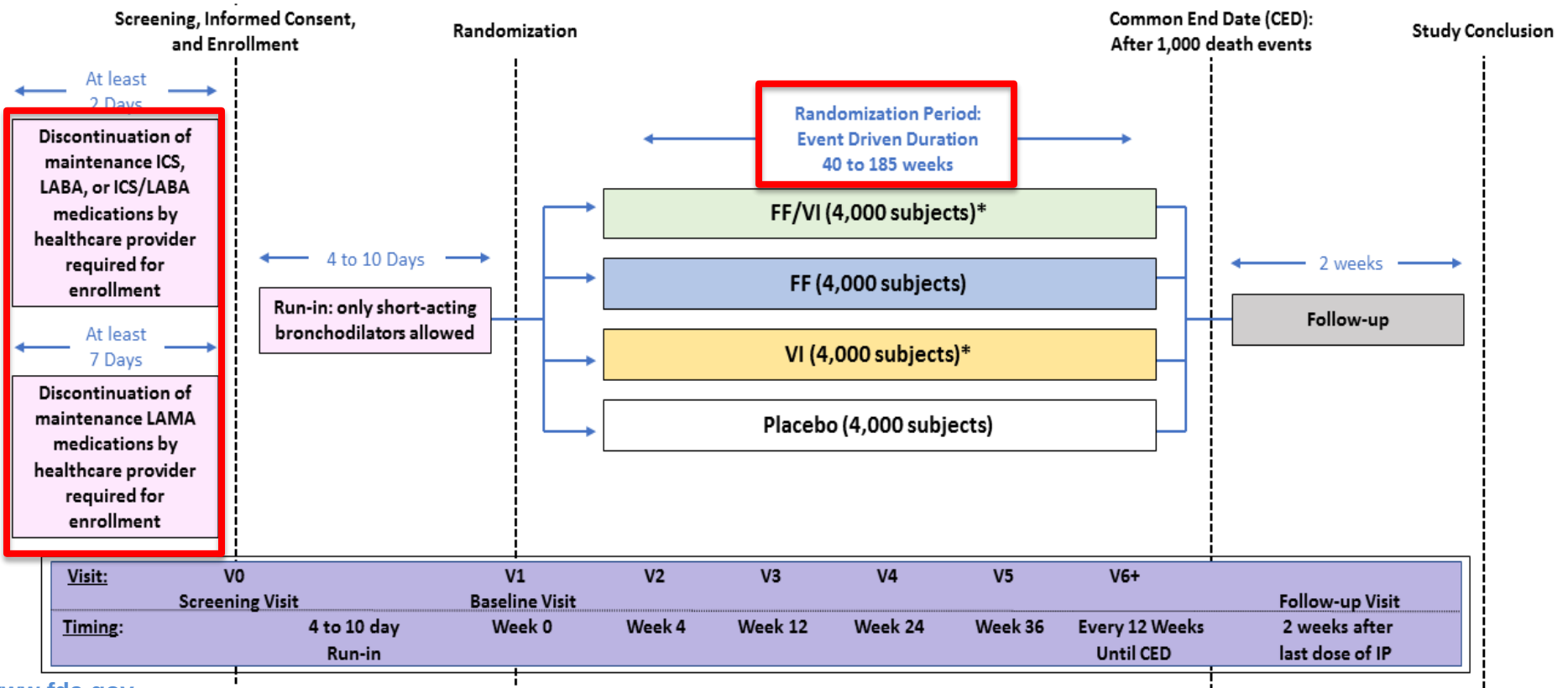
Patient Population Considerations

Supplementary Efficacy Trial: SUMMIT



Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; IP: investigational product; V: visit; ICS: inhaled corticosteroids: LABA: long-acting beta-agonist: LAMA: long-acting muscarinic antagonist

Supplementary Efficacy Trial: SUMMIT



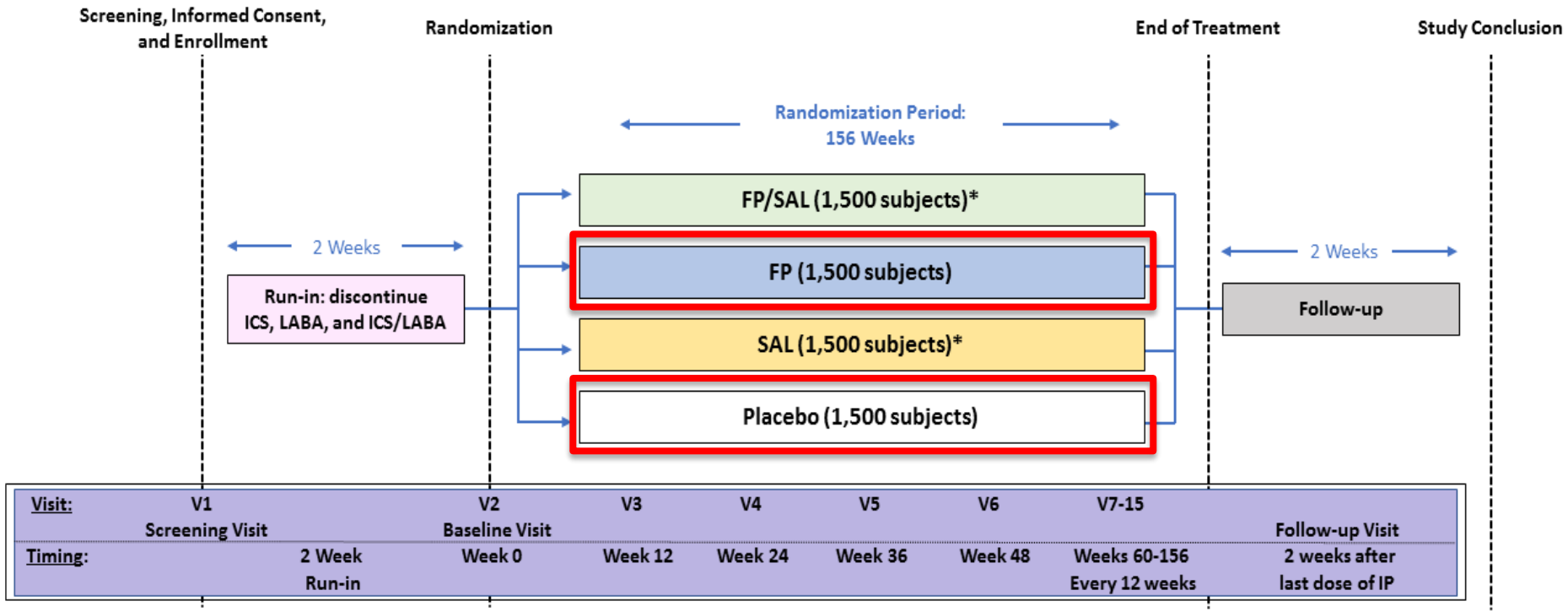
Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; IP: investigational product; V: visit; ICS: inhaled corticosteroids: LABA: long-acting beta-agonist: LAMA: long-acting muscarinic antagonist

SUMMIT: Design

Study	IMPACT N = 10,355	SUMMIT N = 16,485	
Fluticasone Comparison	**FF/UMEC/VI vs UMEC/VI**	**FF/VI vs VI**	**FF vs Pbo**
Number of Patients in Comparison	6221	8239	8246
Study Design Characteristics			
Duration	1 year	Event-driven (median 1.8 years)	
Enrollment Criteria	**FEV1**: Moderate to very severe COPD	**FEV1**: Moderate COPD	
	Medications: 3 months pre-study maintenance medications	**Medications**: no requirement	
	Exacerbations: Prior history of exacerbations despite COPD maintenance medications	**Exacerbations**: No requirement for prior history of exacerbations	
	Symptoms: CAT ≥10	**Symptoms**: mMRC ≥2	
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	

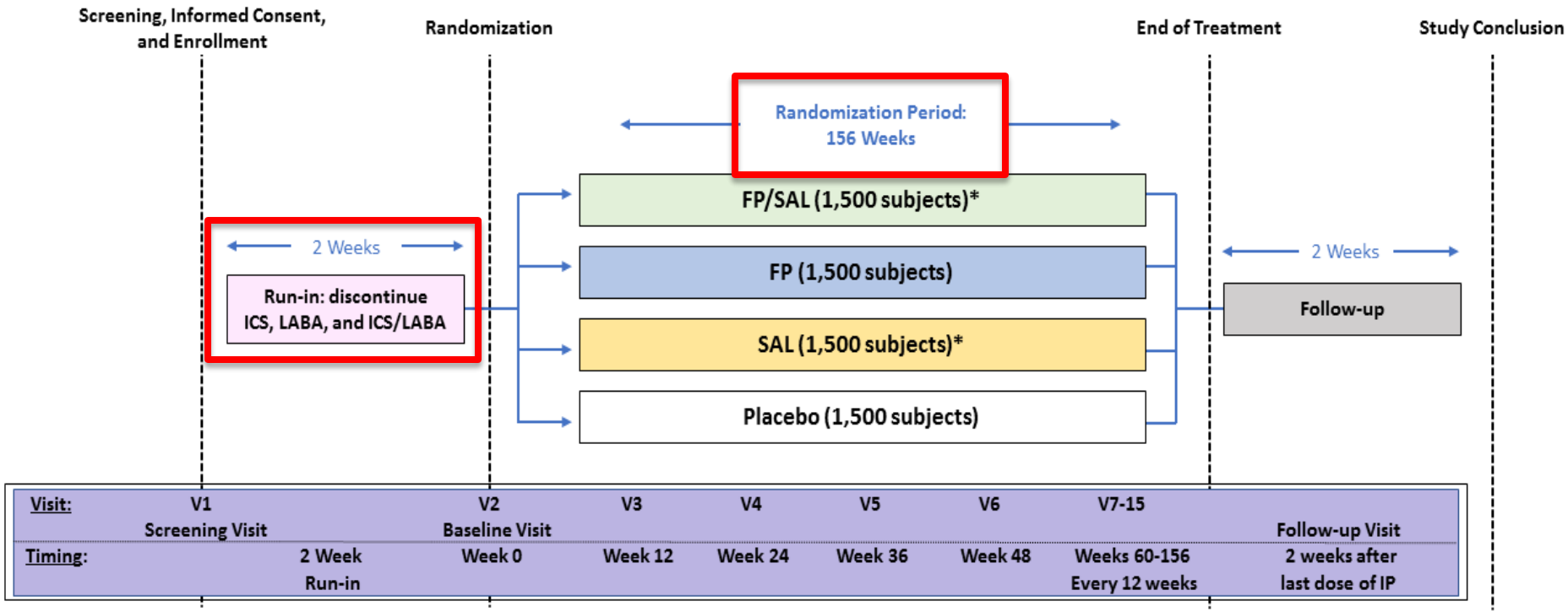
Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; UMEC: umeclidinium 62.5mcg; VI: vilanterol 25mcg; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; FF: fluticasone furoate 100mcg; VI: vilanterol 25mcg; Pbo: placebo; ICS: inhaled corticosteroids: LABA: long-acting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

Supplementary Efficacy Trial: TORCH



Source: Reviewer. Abbreviations: FP: fluticasone propionate 500 mcg; SAL: salmeterol 50 mcg; COPD: chronic obstructive pulmonary disease; IP: investigational product; V: visit; ICS: inhaled corticosteroids: LABA: long-acting beta-agonist

Supplementary Efficacy Trial: TORCH



Source: Reviewer

Source: Reviewer. Abbreviations: FP: fluticasone propionate 500 mcg; SAL: salmeterol 50 mcg; COPD: chronic obstructive pulmonary disease; IP: investigational product; V: visit; ICS: inhaled corticosteroids: LABA: long-acting beta-agonist

TORCH: Design

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	

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

All-cause Mortality in COPD

ICS in COPD

TRELEGY ELLIPTA COPD Development Program

IMPACT Trial Design and Endpoints

Patient Population Considerations

IMPACT: Baseline Disease Characteristics

	FF/UMEC/VI N (%)	FF/VI N (%)	UMEC/VI N (%)	Total N (%)
Total	4151	4134	2070	10355
Screening post-bronchodilator FEV1				
N with available data	4145	4133	2069	10347
Mean FEV1%p (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)
Screening Severe AECOPD History in Prior 12 Months				
N with available data	4151	4134	2070	10355
0	3064 (74)	3065 (74)	1555 (75)	7684 (74)
≥1	1087 (26)	1069 (26)	515 (25)	2671 (26)
Screening Moderate to Severe AECOPD Category				
N with available data	4151	4134	2070	10355
<2 moderate and no severe	1198 (29)	1242 (30)	616 (30)	3056 (30)
≥2 moderate or ≥1 severe	2953 (71)	2892 (70)	1454 (70)	7299 (70)
St. George's Respiratory Questionnaire Total Score				
N with analyzable data	4108	4092	2050	10250
Mean (SD)	50.8 (16.8)	50.7 (17.0)	50.2 (16.7)	50.7 (16.9)

Source: Reviewer. Adapted from Applicant's clinical study report and submitted materials for the IMPACT trial.
ITT: intention to treat; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: forced expiratory volume in one second; %p: percent predicted; 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

IMPACT: Pre-study Medications

	FF/UMEC/VI N (%)	FF/VI N (%)	UMEC/VI N (%)	Total N (%)
Total	4151	4134	2070	10355
ICS/LABA/LAMA-containing regimen				
Yes	1581 (38)	1563 (38)	826 (40)	3970 (38)
No	2570 (62)	2571 (62)	1244 (60)	6385 (62)
ICS-containing regimen				
Yes	2971 (72)	2908 (70)	1481 (72)	7360 (71)
No	1180 (28)	1226 (30)	589 (28)	2995 (29)

Source: Adapted from Applicant's clinical study report and submitted materials for the IMPACT trial.
ITT: intention to treat; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; 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: Population Results

Study	IMPACT N = 10,355
Fluticasone Comparison	**FF/UMEC/VI vs UMEC/VI**
Number of Patients in Comparison	6221
Population Characteristics	
Pre-study Triple Therapy	38%
Pre-study ICS	71%
Frequent Exacerbators in Prior Year	70%
St. George's Respiratory Questionnaire Total Score	50.6

Source: Reviewer. Abbreviations: FF: fluticasone furoate 100mcg; UMEC: umeclidinium 62.5mcg; VI: vilanterol 25mcg; ICS: inhaled corticosteroid; Triple Therapy: inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist

Baseline Disease Characteristics Across Trials

	IMPACT N (%)	SUMMIT N (%)	TORCH N (%)
Total	10355	16485	6112
Screening post-bronchodilator FEV1			
N with available data	10347	16483	6111
Mean FEV1%p (SD)	45.5 (14.8)	59.7 (6.1)	44.0 (12.4)
Screening severe AECOPD history in prior 12 months			
N with available data	10355	16485	6112
0	7684 (74)	14280 (87)	5005 (82)
≥1	2671 (26)	2205 (13)	1107 (18)
Screening moderate to severe AECOPD category			
N with available data	10355	16485	6112
<2 moderate and no severe	3056 (30)	13057 (79)	3914 (64)
≥2 moderate or ≥1 severe	7299 (70)	3428 (21)	2198 (36)
St. George's Respiratory Questionnaire total score			
N with analyzable data	10250	4433	4752
Mean (SD)	50.7 (16.9)	46.3 (16.0)	49.3 (17.1)

Source: Reviewer, adapted from CSR and IR Responses of IMPACT, SUMMIT, and TORCH trials. Abbreviations: AECOPD: acute exacerbation of COPD; SD: standard deviation: FEV1: forced expiratory volume in one second; %p: percent predicted. CSR: clinical study report; IR: information request

Pre-study Medication Across Trials

	IMPACT N (%)	SUMMIT N (%)	TORCH N (%)
Total	10355	16485	6112
Pre-study ICS, LABA, and LAMA-containing regimen (triple therapy)			
Yes	3970 (38)	1433 (9)	1 (<1)
No	6385 (62)	15052 (91)	6111 (99)
Pre-study ICS-containing regimen			
Yes	7360 (71)	5486 (33)	2976 (49)
No	2995 (29)	10999 (67)	2984 (49)
Pre-study medication not reported*			
Yes	0	0	152 (2)

Source: Reviewer, adapted from CSR and IR Responses of IMPACT, SUMMIT, and TORCH trials. Abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; CSR: clinical study report; IR: information request

Source: Reviewer

Pre-study Therapy Considerations

- Suissa, et al. 2008
  - Pre-study medications
    - What does it mean to be in a trial of a drug while already on that drug class?
  - Different trial interventions: example of ICS
    - In ICS naïve subjects (add-on trial)
    - In pre-study ICS subjects (removal trial)
  - Pre-study medications and trial outcomes
    - Proportion of patients on pre-study ICS associated with relative risk difference
  - Mixing different pre-study medication groups may not be interpretable

References:
1. Suissa S, et al. Methodological issues in therapeutic trials of COPD. ERJ, 2008

IMPACT, SUMMIT, and TORCH: Subjects

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
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; Triple Therapy: inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic antagonist

Summary

- All-cause Mortality in COPD
  - No approved therapies reduce ACM in COPD
  - Previous trials of ICS/LABA versus placebo failed to demonstrate a difference

- ICS in COPD
  - Exacerbation benefit established; concerns regarding increased risk of pneumonia
  - No established benefit on COPD mortality

- TRELEGY ELLIPTA COPD Development Program
  - IMPACT trial designed for specific purpose and indication
  - Neither Sponsor nor FDA raised ICS removal concerns during development

Summary (cont.)

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

Outline

- Overview of the Clinical Program
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Susan Duke, MS, MS
  - Biometrics Reviewer: DB3, OTS, CDER, FDA
- Clinical Considerations
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Charge to the Committee
  - Banu Karimi-Shah, MD
  - Deputy Division Director: DPACC, OII, OND, CDER, FDA

FDA Pulmonary-Allergy Advisory Committee Meeting
Statistical Review of Efficacy

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

Susan Duke, MS, MS
Statistical Reviewer
Division of Biometrics III
Office of Biostatistics
Office of Translational Sciences
U.S. Food and Drug Administration
August 31, 2020

Outline

1. IMPACT and all-cause mortality
    a. Study design features
    b. Analysis plan
    c. Follow-up for mortality
    d. Overall results
2. Independent supportive evidence
    a. SUMMIT and TORCH objectives and results
3. Exploratory analyses of IMPACT
    a. Timeframe of effects
    b. Pre-study ICS subgroup analysis
4. Summary

Outline

1. IMPACT and all-cause mortality
   a. Study design features
   b. Analysis plan
   c. Follow-up for mortality
   d. Overall results
2. Independent supportive evidence
   a. SUMMIT and TORCH objectives and results
3. Exploratory analyses of IMPACT
   a. Timeframe of effects
   b. Pre-study ICS subgroup analysis
4. Summary

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 Follow-Up for ACM

- Different analyses include different degrees of ACM follow-up
  - *On-treatment*: all deaths and follow-up after treatment discontinuation excluded
  - *On-study*: all deaths and follow-up after study withdrawal excluded
  - *All vital status follow-up*: includes additional follow-up after study withdrawal
- FDA focus: *all vital status follow-up (*"ITT + VS + VSFU")
  - Interest in evaluating difference in survival regardless of adherence and use of other therapy
  - Analysis including all vital status follow-up provides most reliable results

IMPACT Follow-Up for ACM

Percent of Patients with Complete Vital Status Information included in Analysis

	FF/UMEC/VI	FF/VI	UMEC/VI	Total
On-treatment	87.7%	76.6%	74.4%	79.2%
On-study	95.4%	94.0%	93.5%	94.5%
All vital status follow-up	99.8%	99.6%	99.3%	99.6%

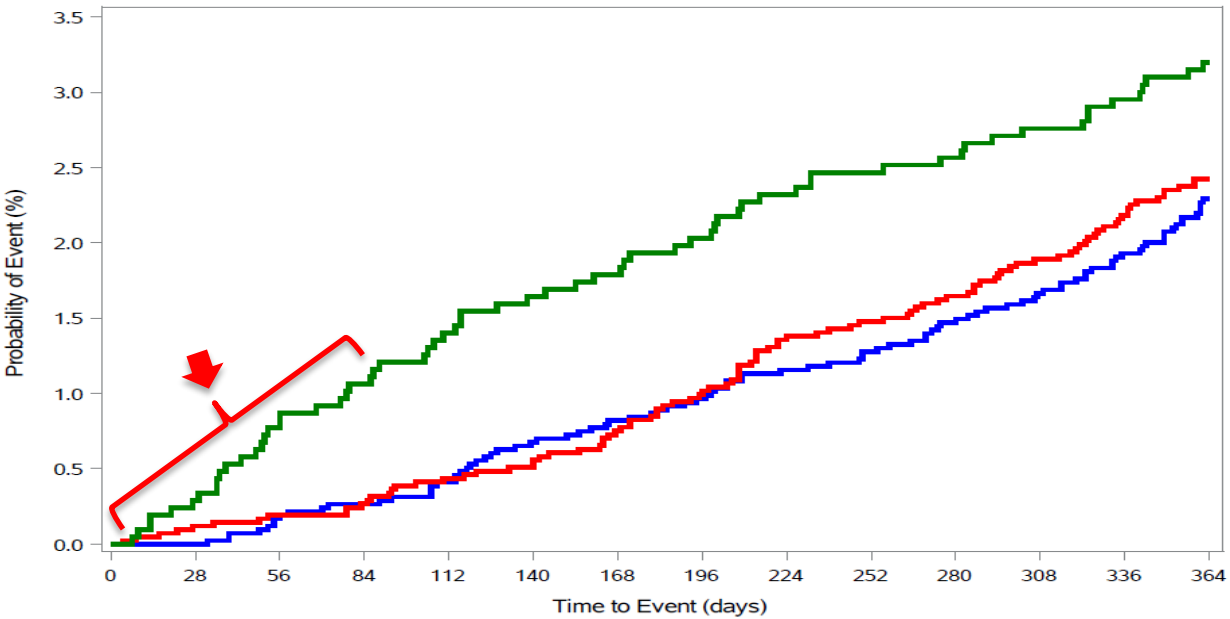
Source: Reviewer
FF/UMEC/VI: fluticasone furoate 100 µg / umeclidinium 62.5 µg / vilanterol 25 µg
FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg
UMEC/VI: umeclidinium 62.5 µg / vilanterol 25 µg

IMPACT ACM 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

Outline

1. IMPACT and all-cause mortality
   a. Study design features
   b. Analysis plan
   c. Follow-up for mortality
   d. Overall results
2. Independent supportive evidence
   a. SUMMIT and TORCH objectives and results
3. Exploratory analyses of IMPACT
   a. Timeframe of effects
   b. Pre-study ICS subgroup analysis
4. Summary

Design Characteristics 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	

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

SUMMIT and TORCH Objectives

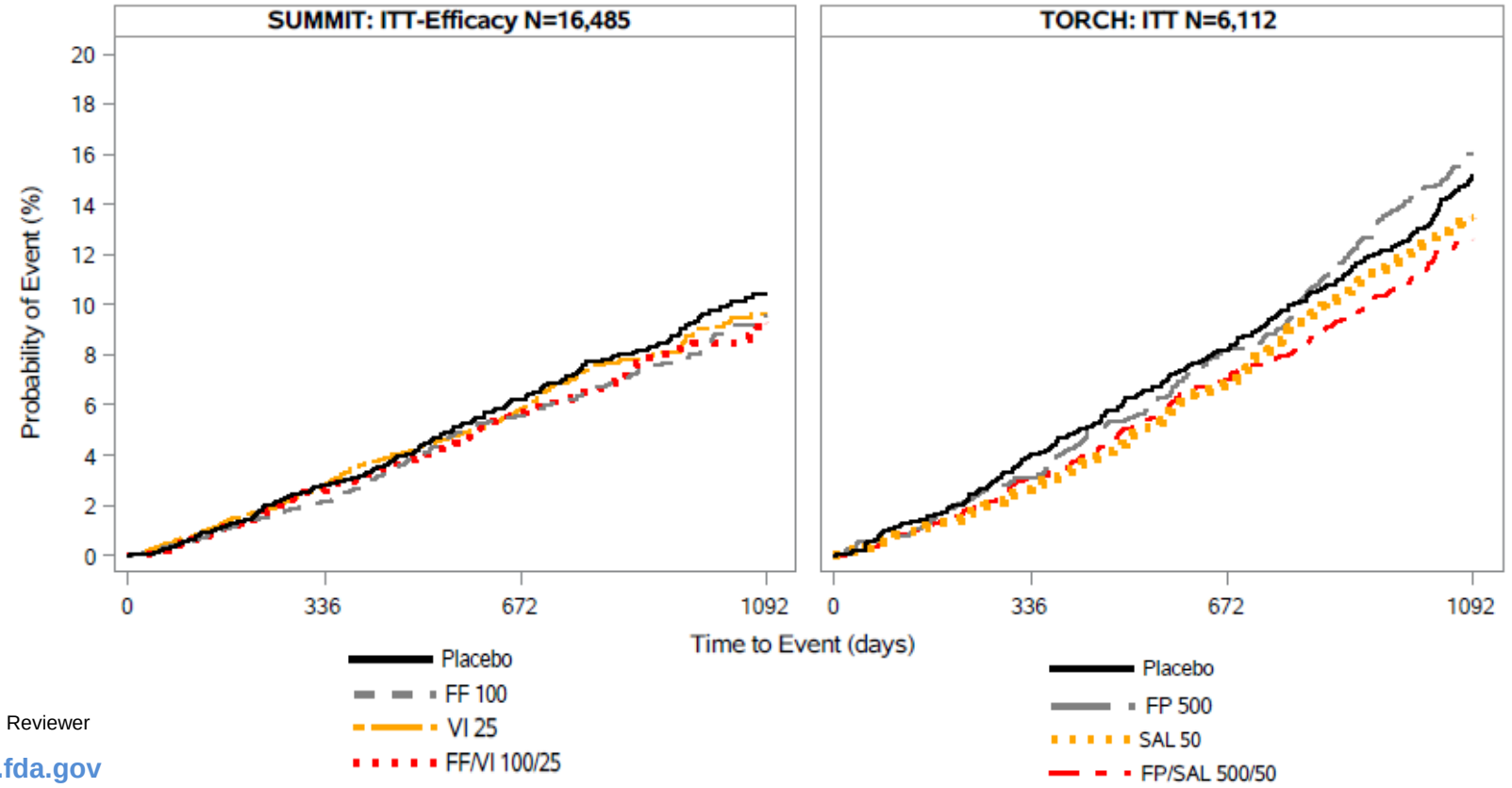
- Primary objective: All-cause mortality evaluation
  - Primary analysis: ACM for ICS/LABA vs. placebo
  - Powered to detect differences in ACM
  - Longer durations
    - SUMMIT: Event-driven; median: 1.8 years, maximum: 46 months
    - TORCH: 3 years
- Neither study showed effect of ICS/LABA vs. placebo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

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

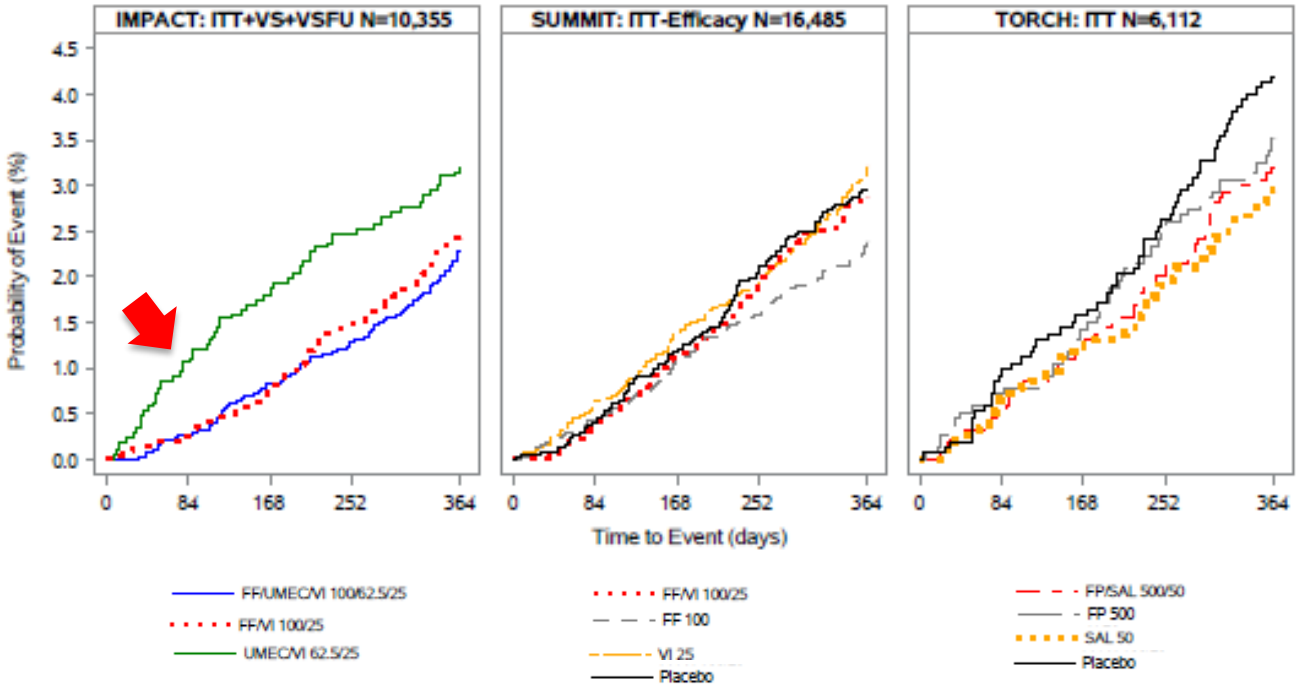
Source: Reviewer

SUMMIT and TORCH ACM Over 3 Years



Source: Reviewer

IMPACT, SUMMIT and TORCH ACM Over 52 Weeks



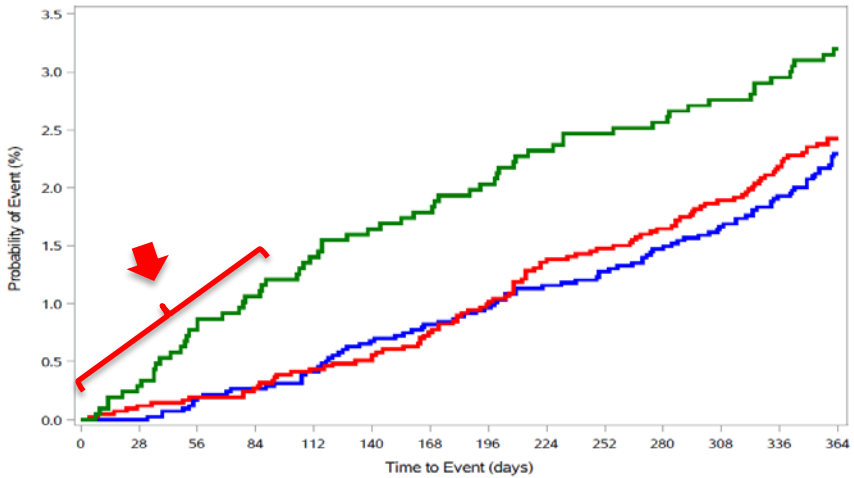
Source: Reviewer

Outline

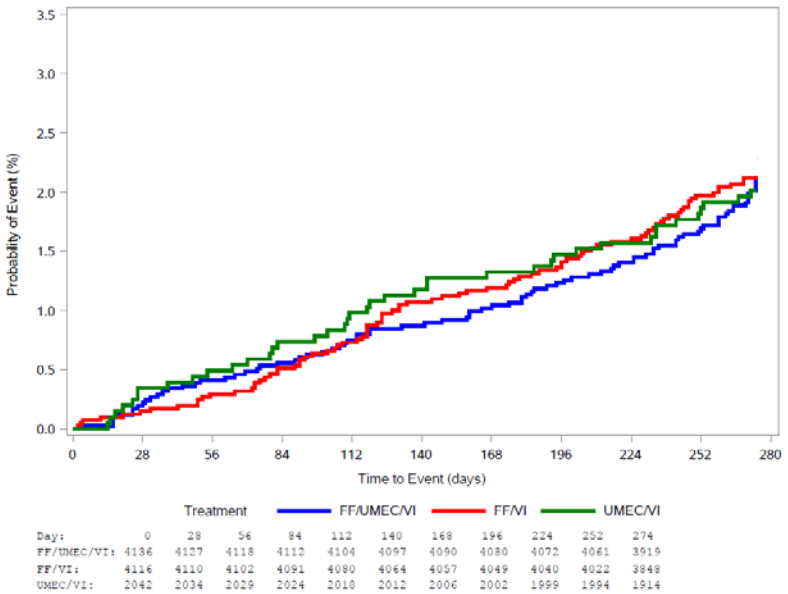
1. IMPACT and all-cause mortality
   a. Study design features
   b. Analysis plan
   c. Follow-up for mortality
   d. Overall results
2. Independent supportive evidence
   a. SUMMIT and TORCH objectives and results
3. Exploratory analyses of IMPACT
   a. Timeframe of effects
   b. Pre-study ICS subgroup analysis
4. Summary

IMPACT ACM: Early Separation

All Mortality Data

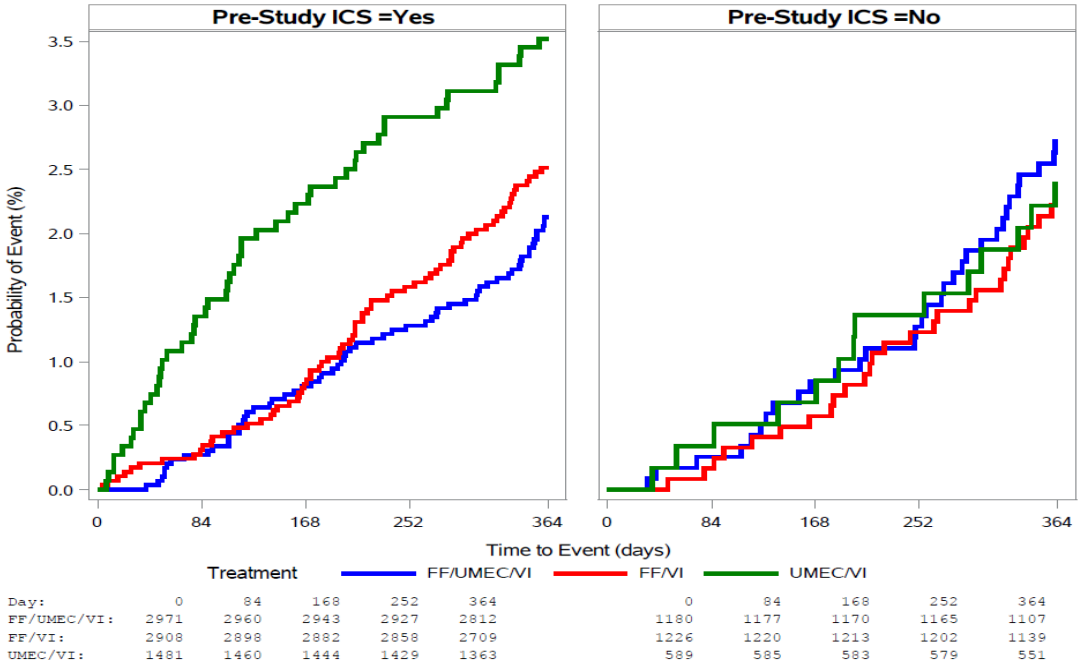


Mortality Data after Day 90



Source: Reviewer

IMPACT ACM by Pre-Study ICS Subgroup



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

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

Source: Reviewer

Outline

1. IMPACT and all-cause mortality
   a. Study design features
   b. Analysis plan
   c. Follow-up for mortality
   d. Overall results
2. Independent supportive evidence
   a. SUMMIT and TORCH objectives and results
3. Exploratory analyses of IMPACT
   a. Timeframe of effects
   b. Pre-study ICS subgroup analysis
4. Summary

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

Statistical Summary

- Persuasiveness of IMPACT ACM Results
  - IMPACT not designed to evaluate ACM, only 1-year duration
  - ACM one of many exploratory endpoints, with no Type I error control
  - Questions about strength of evidence (p-value=0.042 from single study)
- Degree of support from TORCH and SUMMIT
  - Designed for ACM, longer duration, roughly 3-fold more events
  - Lack of evidence of ACM effects for fluticasone products
- Exploratory analyses add additional uncertainty
  - Efficacy timeframe and pre-study ICS subgroup findings


FDA
U.S. FOOD & DRUG
ADMINISTRATION

FDA Pulmonary-Allergy Advisory Committee Meeting Clinical Considerations

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

Robert Busch, MD, MMSc
Clinical Reviewer
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
U.S. Food and Drug Administration
August 31, 2020

Clinical Considerations and Interpretation

- Pre-study Medication Considerations
  - ICS Removal in COPD
  - Subgroup Analyses by Pre-study Medication
  - ICS Removal in IMPACT
  - ICS Removal in SUMMIT and TORCH
- Uncertainties in the Interpretation of the All-cause Mortality Results
  - Statistical Persuasiveness of IMPACT
  - Evidence Across IMPACT, SUMMIT, and TORCH
  - Timeframe of Efficacy in IMPACT
  - Interpretations Under ICS Removal Paradigm
  - Generalizability of IMPACT Results to Clinical Practice
- Efficacy Results in Context

Pre-study Medication Considerations

- **ICS Removal in COPD**
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

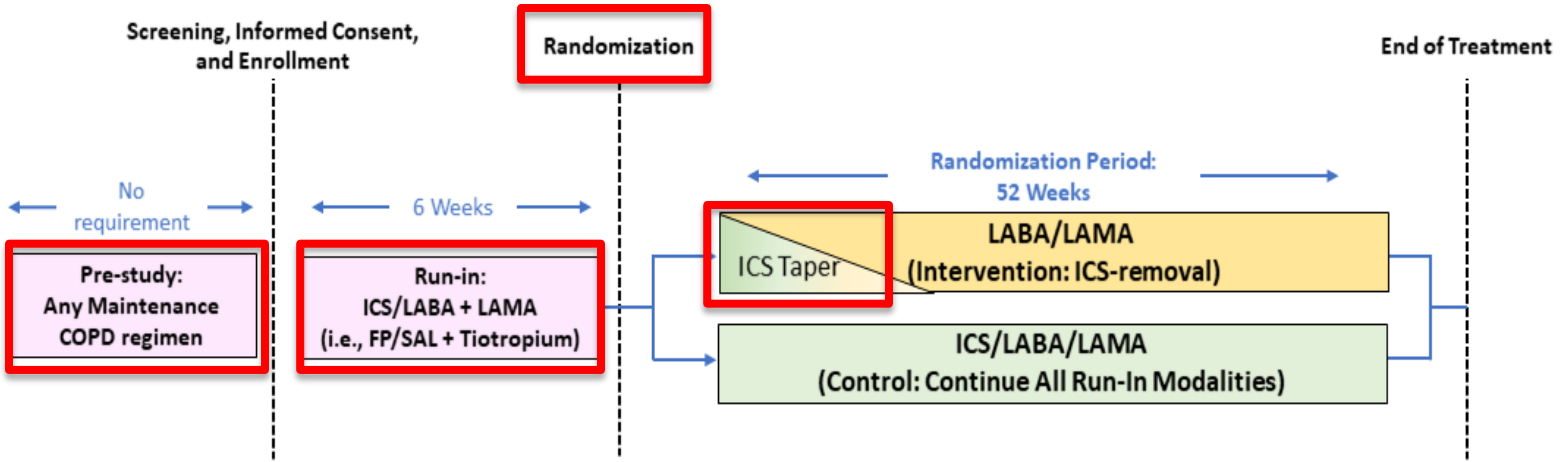
ICS Removal in COPD

- Early Studies and Trials
  - Jarad et al
    - Long-acting medication removal during run-in of ISOLDE trial
    - Higher proportion of pre-study ICS subjects experienced AECOPD during observation period than ICS-naïve subjects
  - Wouters et al
    - 3 months ICS/LABA followed by randomized removal of ICS
    - ICS removal led to immediate and sustained deterioration in lung function and symptom scores
  - Van der Valk et al, Choudhury et al

References:
1. Jarad NA, et al. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. Respiratory Medicine, 1999.
2. Wouters EFM, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax, 2005
3. Van der Valk P, et al. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. AJRCCM, 2002
4. Choudhury AB, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res, 2007.

ICS Removal in COPD

- Magnussen et al. (WISDOM)



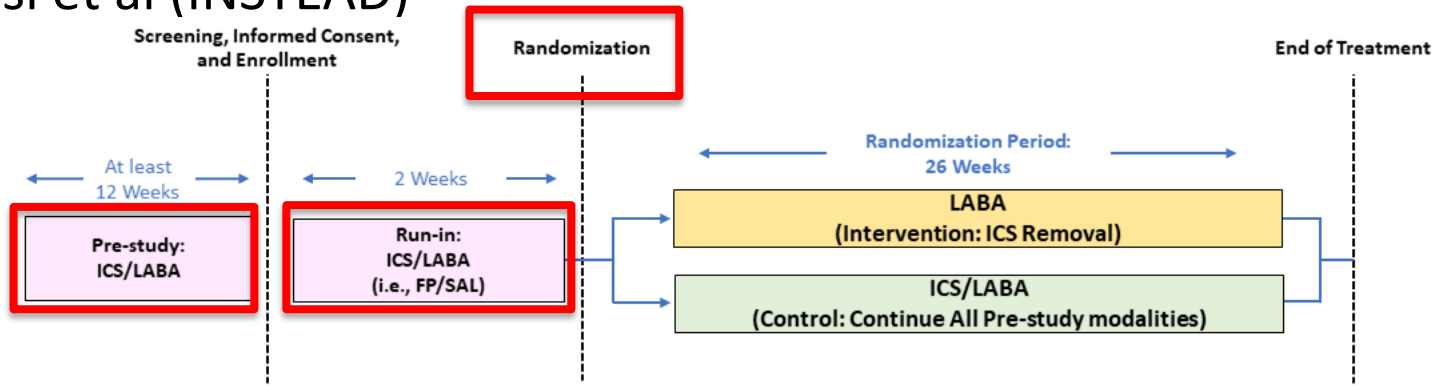
- Trend towards increased severe AECOPD after ICS removal

References:

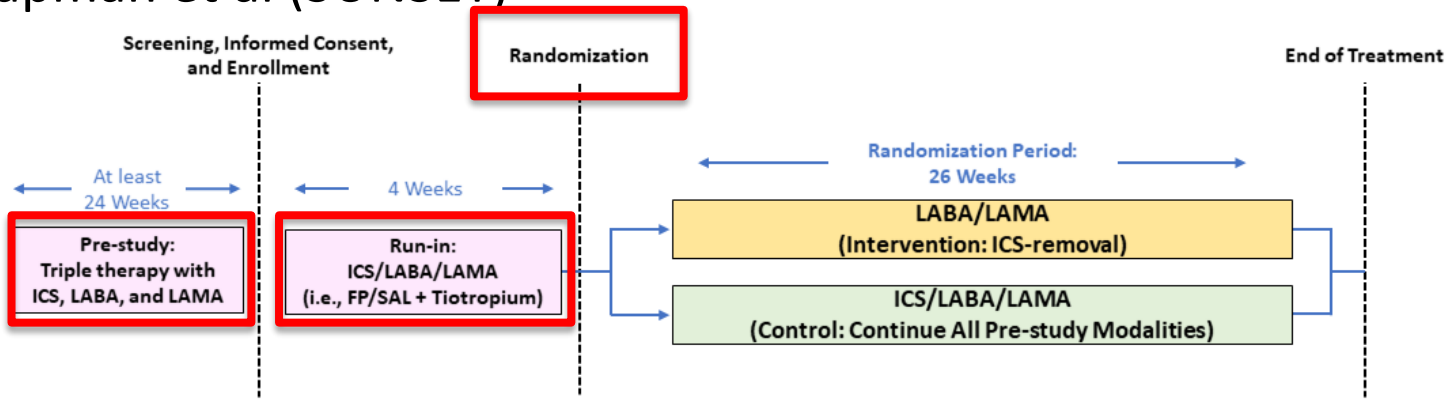
1. Magnussen H, et al. Withdrawal of Inhaled Glucocorticoids and Exacerbations of COPD. NEJM, 2014.
2. Magnussen H, Tetzlaff K, Bateman ED, et al. Lung function changes over time following withdrawal of inhaled corticosteroids in patients with severe COPD. Eur Respir J 2016;47:651-4.
3. Cosio M, Baraldo S, Saetta M. Inhaled glucocorticoids and COPD exacerbations. N Engl J Med 2015;372:92.
4. Subgabayagan A, Johnston SL, Mallia P. Inhaled glucocorticoids and COPD exacerbations. N Engl J Med 2015;372:92.
5. Magnussen H, Tetzlaff K, Calverley PM. Inhaled glucocorticoids and COPD exacerbations. N Engl J Med 2015;372:92.
6. Yawn BP, Suissa S, Rossi A. Appropriate use of inhaled corticosteroids in COPD: the candidates for safe withdrawal. NPJ Prim Care Respir Med 2016;26 16068.
7. Calverley PMA, Tetzlaff K, Vogelmeier C, et al. Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2017;196:1219-21
8. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med 2016;4:390-8.

ICS Removal in COPD

- Rossi et al (INSTEAD)



- Chapman et al (SUNSET)



References:
1. Rossi A, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. ERJ, 2014.
2. Chapman KR, et al. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. AJRCCM, 2018.

ICS Removal in COPD

- Data suggests symptomatic decline after ICS removal in COPD
  - Lung function and patient-reported outcomes
  - Unclear effect on exacerbations
  - Controlled COPD versus frequent exacerbators

- Interpretation
  - WISDOM, SUNSET, INSTEAD: safety of ICS removal in select patients
  - ICS removal data applicable to decision-making for ICS addition?

Pre-study Medication Considerations

- ICS Removal in COPD
- **Subgroup Analyses by Pre-study Medication**
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

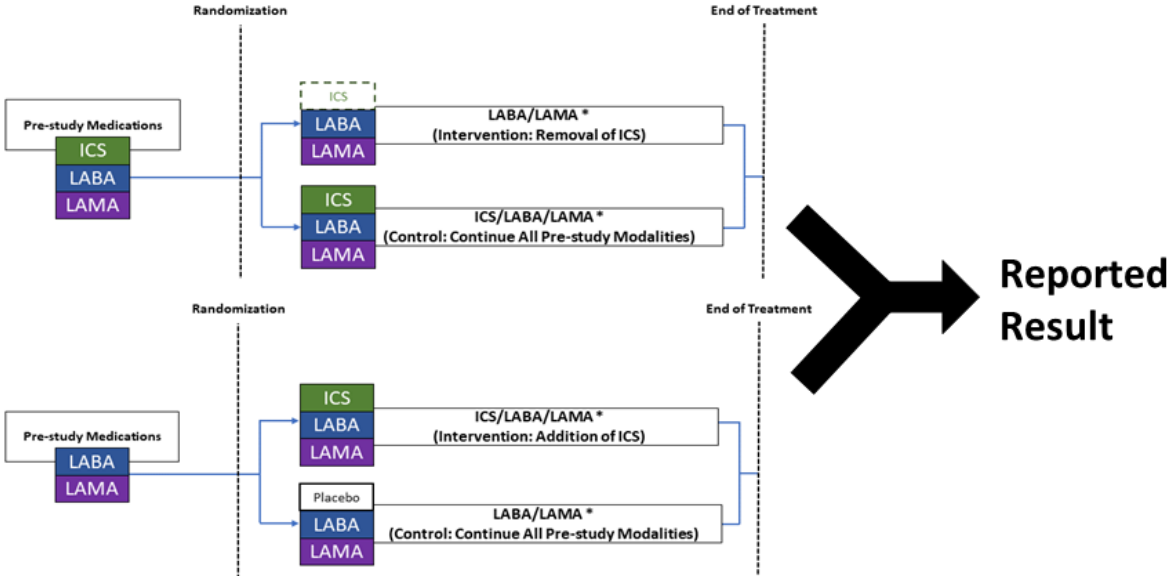
Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

ICS Removal in COPD Trials

- ICS removal versus ICS-addition
  - Suissa et al



References:
1. Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. Eur Respir J 2008;31:927-33.

Source: Reviewer

Pre-study Medication Considerations

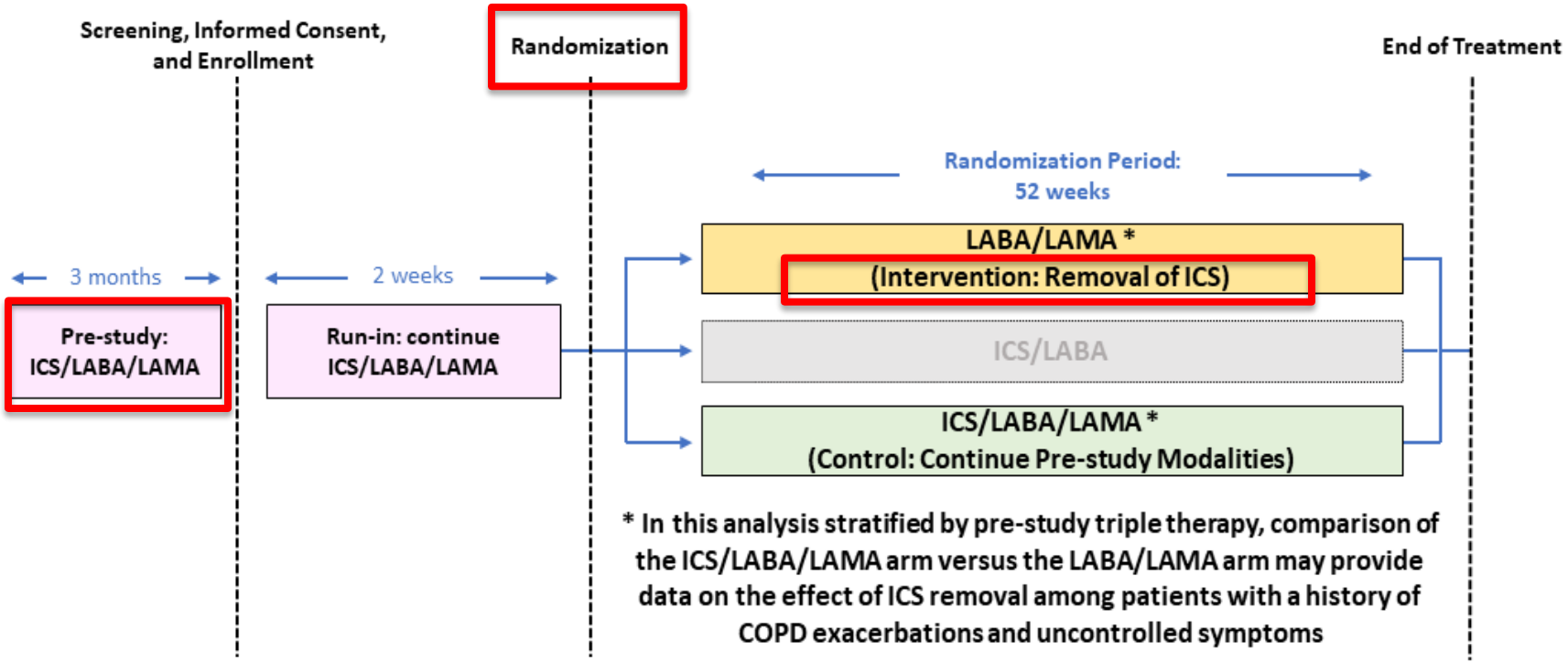
- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- **ICS Removal in IMPACT**
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

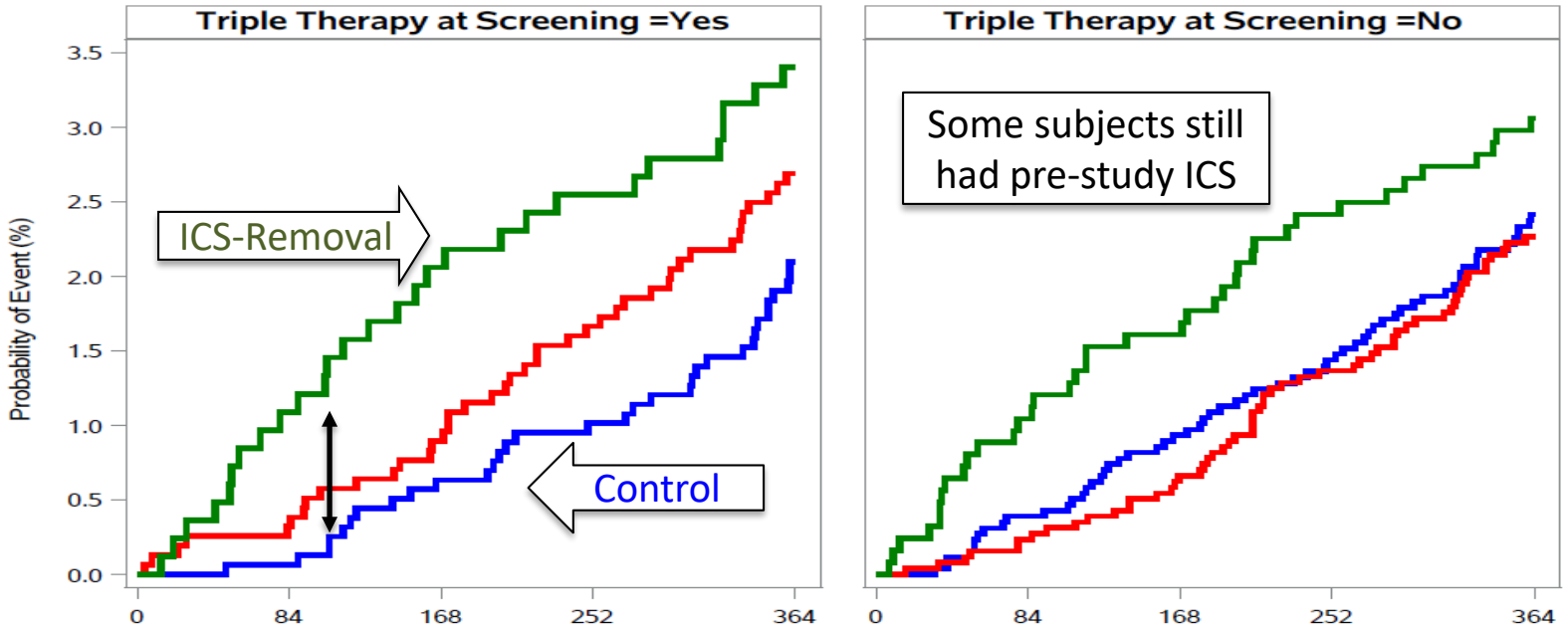
IMPACT: ICS Removal



Source: Reviewer

IMPACT: Pre-study Triple Therapy and ACM

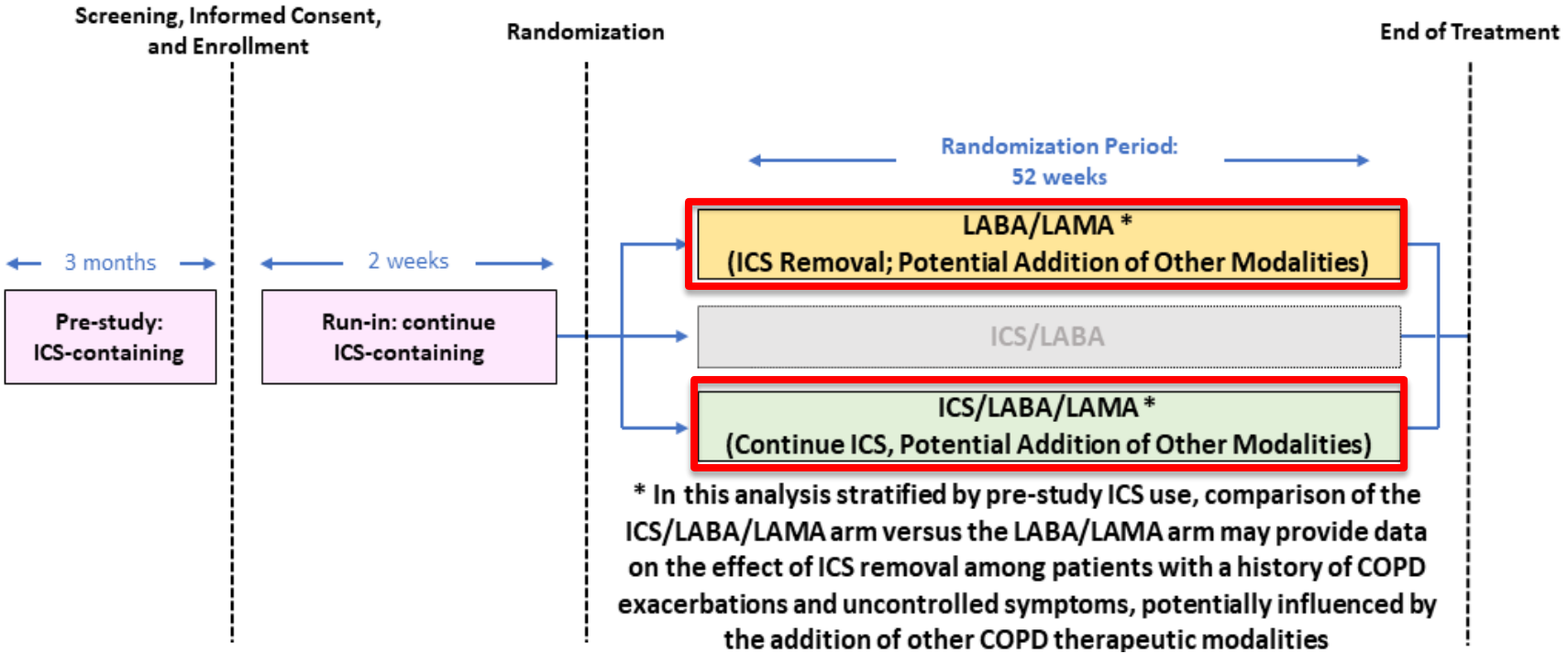
Pre-study Triple Therapy Subgroups: Probability of All-cause Mortality over 52 Weeks by Treatment Arm (ITT+VS+VSFU)



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: 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 Triple Therapy: subjects with pre-study ICS, LABA, and LAMA therapy

IMPACT: ICS Removal

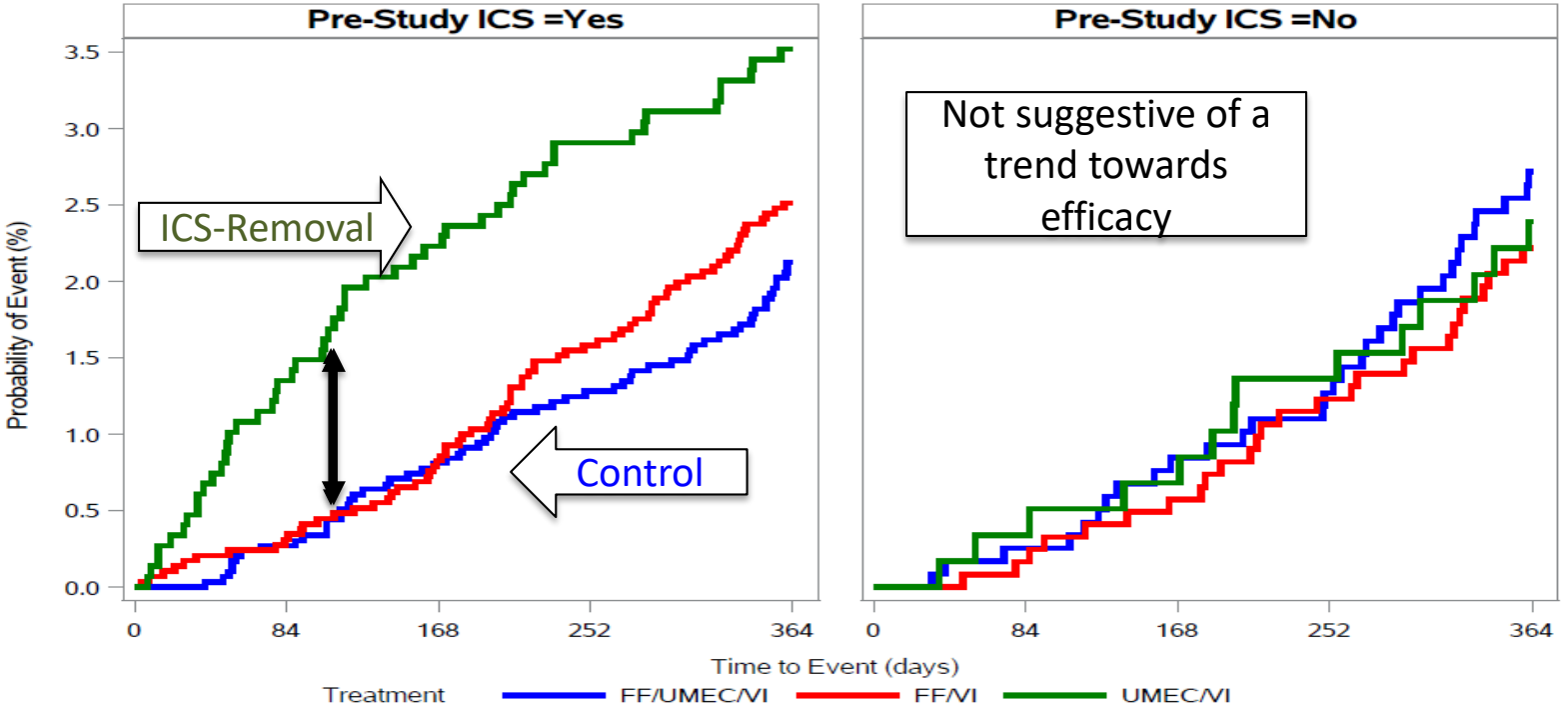


Pre-study ICS subgroup: over 7,000 subjects; 1491 randomized to ICS removal

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	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: 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

IMPACT: ICS Removal and ACM

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

	FF/UMEC/VI N=2971	FF/VI N=2908	UMEC/VI N=1481
Week 52: All-cause Mortality Analysis			
Number of subjects with event, n (%)	65 (2.2)	79 (2.7)	52 (3.5)
Hazard Ratio for ACM		1.25	**1.64**
95% CI (Comparator versus FF/UMEC/VI)		0.90, 1.75	**1.15, 2.38**
Day 90: All-cause Mortality Analysis			
Number of subjects with event at Day 90, n (%)	9 (0.3)	10 (0.3)	22 (1.5)
Hazard Ratio for ACM		1.14	**5.00**
95% CI (Comparator versus FF/UMEC/VI)		0.46, 2.78	**2.27, 11.11**
After Day 90: All-cause Mortality Analysis Excluding first 90 Days			
Number of subjects with available data after Day 90	2959	2897	1458
Number of subjects with event after Day 90, n (%)	56 (1.9)	69 (2.4)	30 (2.1)
Hazard Ratio for ACM		1.30	**1.11**
95% CI (Comparator versus FF/UMEC/VI)		0.89, 1.89	**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.
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

ICS Removal in COPD

- Meeting minutes from the Independent Data Monitoring Committee
  - Concern for early mortality and ICS removal

    The DMC was particularly concerned with the number of deaths that appear to have occurred either on the same day as first dose of [sic] 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.

  - Assessment of enrollment criteria

    The protocol was reviewed [sic] the DMC found that inhaled steroid use is prohibited 30 days prior to screening and during the study

  - Lack of available data on prior history of exacerbations

    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.

IMPACT: ICS Addition and ACM

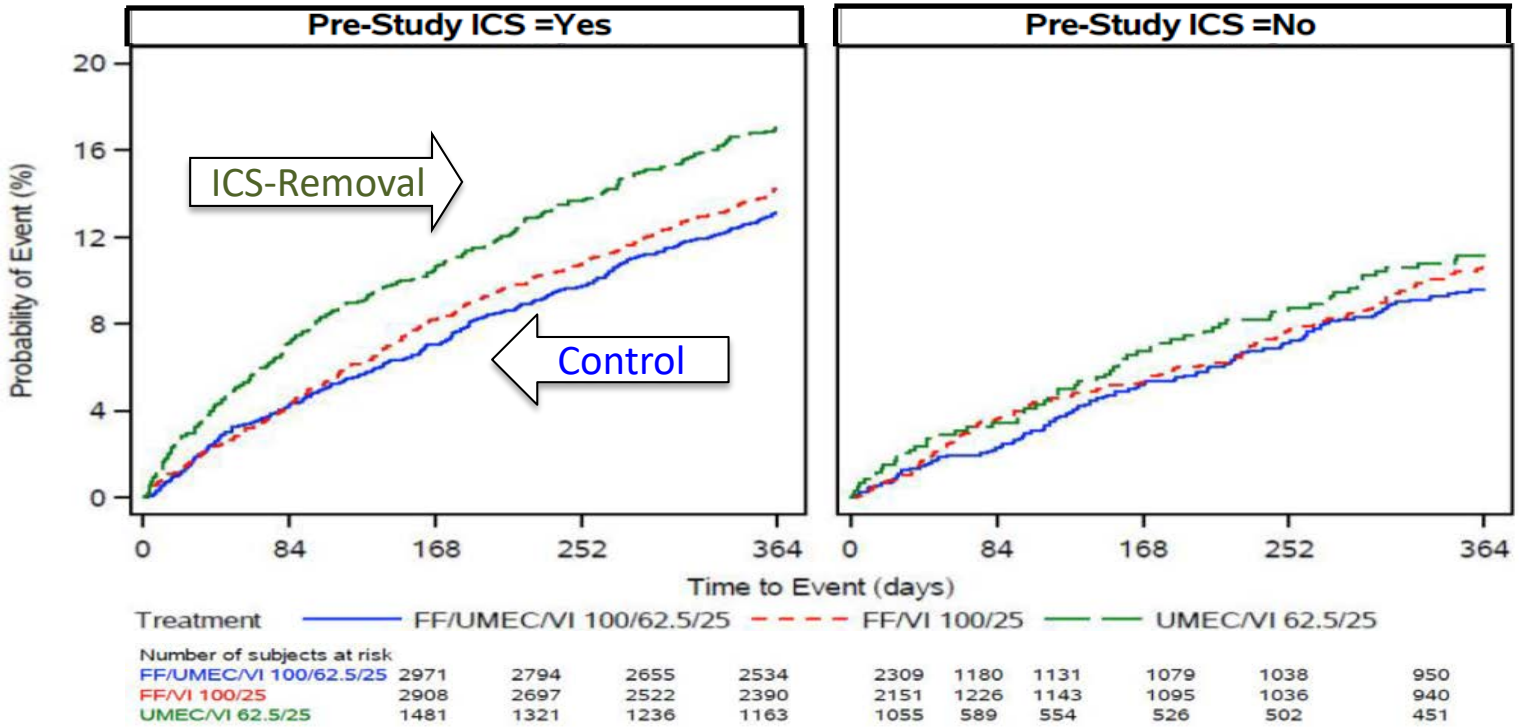
Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Various Timepoints (ITT+VS+VSFU)

	FF/UMEC/VI N=1180	FF/VI N=1226	UMEC/VI N=589
Week 52: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator			
Number of subjects with event, n (%)	33 (2.8)	30 (2.5)	14 (2.4)
Hazard Ratio for ACM 95% CI		1.13 0.69, 1.86	**1.16** **0.62, 2.16**
Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator			
Number of subjects with event at Day 90, n (%)	3 (0.3)	3 (0.2)	3 (0.5)
Hazard Ratio for ACM 95% CI		1.03 0.21, 5.10	**0.50** **0.10, 2.50**
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	1177	1219	584
Number of subjects with event after Day 90, n (%)	30 (2.6)	27 (2.2)	11 (1.9)
Hazard Ratio for ACM 95% CI			**1.35** **0.67, 2.79**

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.
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; ACM: all-cause mortality; CI: confidence interval; Pre-Study ICS = No: subjects without pre-study ICS-containing therapy

IMPACT: Pre-Study ICS and Severe AECOPD

IMPACT: Pre-Study ICS Subgroups: Probability of First Severe AECOPD Through Week 52 by Treatment Arm
(ITT including on- and off-treatment data)



Source: Adapted from Applicant's submitted materials. 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

Pre-study Medication Considerations

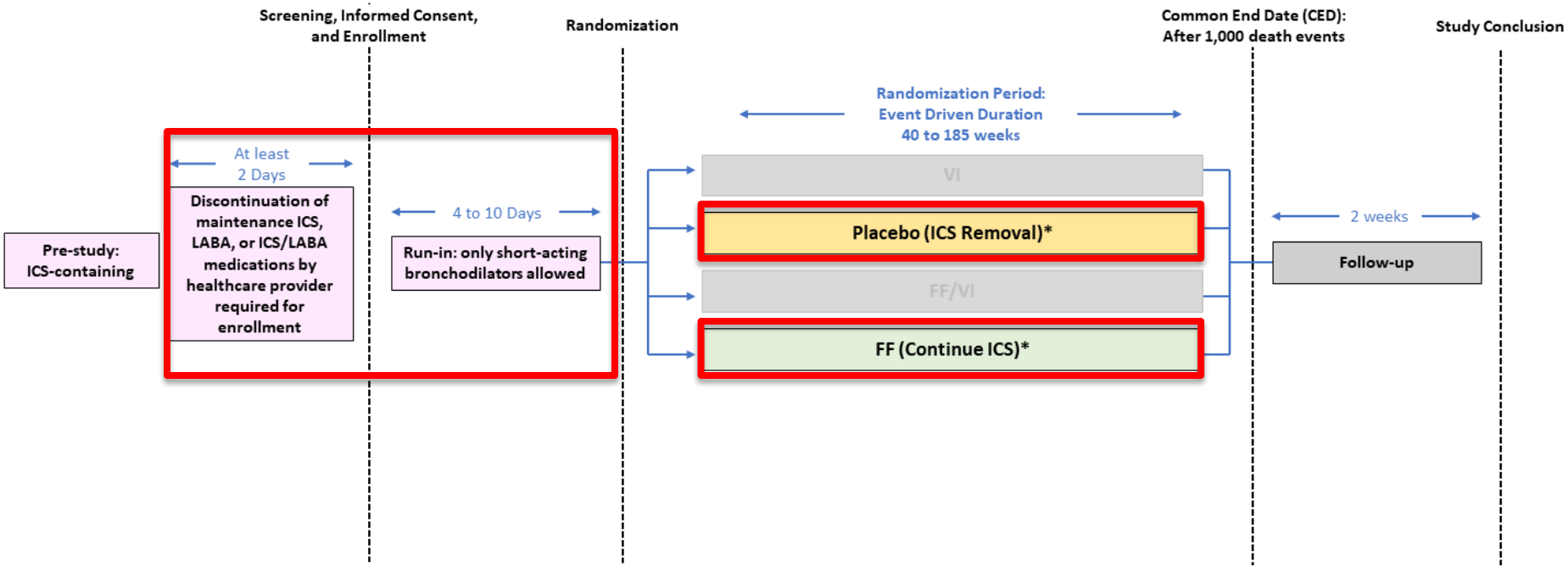
- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- **ICS Removal in SUMMIT and TORCH**

Uncertainties in the Interpretation of the All-cause Mortality Results

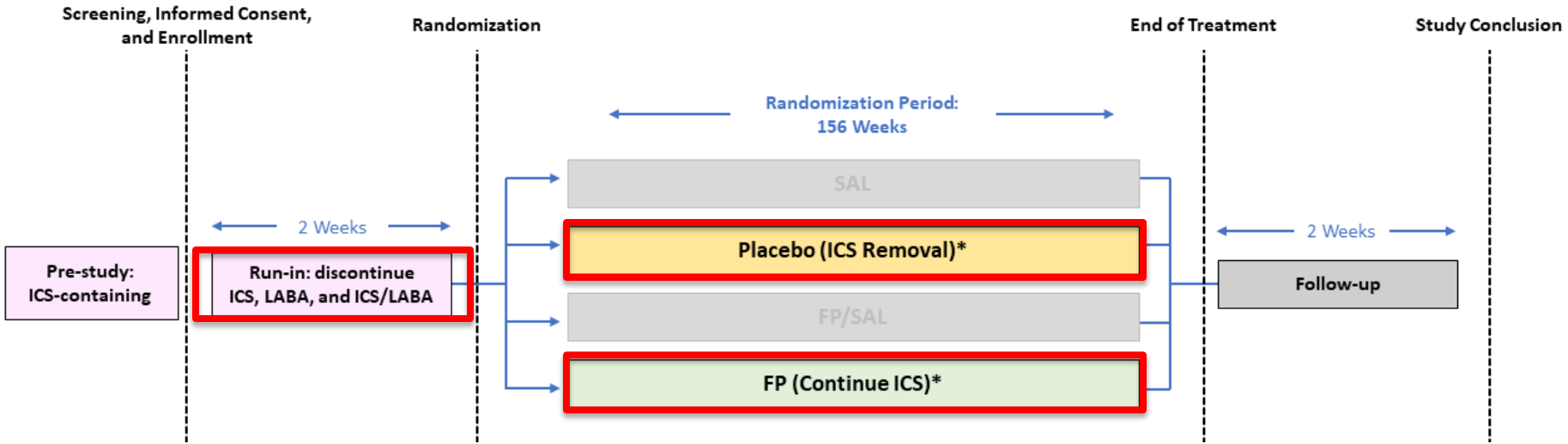
- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

SUMMIT: ICS Removal



TORCH: ICS Removal



ICS Removal and Addition Across Trials

	IMPACT N = 10,355	SUMMIT N = 16,485		TORCH N = 6,112	
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)**
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: 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

Pre-study Medication Considerations

- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- **Statistical Persuasiveness of IMPACT**
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

Statistical Persuasiveness of IMPACT

- Overall Result
  - FF/UMEC/VI versus UMEC/VI: HR 0.72 (95% CI of 0.53, 0.99) attributable to fluticasone component

- Uncertainties
  - Single trial
  - Lack of Type 1 Error Control
  - ACM one of multiple “other” endpoints
  - Unexpected results for fluticasone furoate

Pre-study Medication Considerations

- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- **Evidence Across IMPACT, SUMMIT, and TORCH**
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

Evidence Across Trials

- SUMMIT and TORCH
  - Longer trial duration
  - Designed to assess mortality
  - Higher statistical power
  - Lack of supportive evidence from ICS comparisons

  - Differences in study design and patient population

Pre-study Medication Considerations

- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- **Timeframe of Efficacy in IMPACT**
- Interpretations Under ICS Removal Paradigm
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

Timeframe of Efficacy

- Early timeframe of mortality difference in IMPACT
  - Unexpected results for fluticasone furoate
  - Likelihood that this early difference represents
    - Mortality benefit attributable to fluticasone furoate?
    - Harm attributable to ICS removal?

Pre-study Medication Considerations

- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- **Interpretations Under ICS Removal Paradigm**
- Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

ACM and ICS Removal

- IMPACT ACM results driven by events observed among subjects in the pre-study ICS subgroup

- IMPACT ACM data suggest increased risk for ACM in pre-study ICS subgroup
  - UMEC/VI versus FF/UMEC/VI comparison at Week 52
  - Increased risk for ACM attributable to ICS removal events in Day 90 analyses
  - Similar early trends in SUMMIT and TORCH comparisons despite run-in periods
  - Increased early risk period for severe AECOPD in IMPACT

- No mortality benefit attributable to ICS addition in ICS-naïve subgroups
  - Similar trends observed in SUMMIT and TORCH comparisons despite longer durations

Pre-study Medication Considerations

- ICS Removal in COPD
- Subgroup Analyses by Pre-study Medication
- ICS Removal in IMPACT
- ICS Removal in SUMMIT and TORCH

Uncertainties in the Interpretation of the All-cause Mortality Results

- Statistical Persuasiveness of IMPACT
- Evidence Across IMPACT, SUMMIT, and TORCH
- Timeframe of Efficacy in IMPACT
- Interpretations Under ICS Removal Paradigm
- **Generalizability of IMPACT Results to Clinical Practice**

Efficacy Results in Context

Generalizability: Clinical Interpretation

- How will the proposed claim influence clinical decisions?

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.

- Clinical Questions: Does the addition of fluticasone furoate (as part of TRELEGY ELLIPTA) improve survival?

- 71% of patients in IMPACT could not have had ICS added as part of the IMPACT trial

Generalizability: Clinical Interpretation

- Data from ICS-naïve subjects do not suggest an ACM benefit attributable to ICS addition

- Additional data from SUMMIT and TORCH also do not suggest a benefit of ICS addition
  - Despite longer durations
  - Despite higher numbers of events

- Pre-study Medication Considerations
  - ICS Removal in COPD
  - Subgroup Analyses by Pre-study Medication
  - ICS Removal in IMPACT
  - ICS Removal in SUMMIT and TORCH
- Uncertainties in the Interpretation of the All-cause Mortality Results
  - Statistical Persuasiveness of IMPACT
  - Evidence Across IMPACT, SUMMIT, and TORCH
  - Timeframe of Efficacy in IMPACT
  - Interpretations Under ICS Removal Paradigm
  - Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context

Outline

- Overview of the Clinical Program
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Statistical Review of Efficacy
  - Susan Duke, MS, MS
  - Biometrics Reviewer: DB3, OTS, CDER, FDA
- Clinical Considerations
  - Robert Busch, MD, MMSC
  - Medical Officer: DPACC, OII, OND, CDER, FDA
- Charge to the Committee
  - Banu Karimi-Shah, MD
  - Deputy Division Director: DPACC, OII, OND, CDER, FDA

FDA Pulmonary-Allergy Advisory Committee Meeting
Charge to the Committee

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

Banu A. Karimi-Shah, MD
Deputy Director
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
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.

Efficacy Considerations (1)

- Statistical uncertainty of all-cause mortality (ACM) results in IMPACT
  - Single Trial
  - No control for Type 1 error
- Totality of Evidence (SUMMIT and TORCH)
  - Primary objective was to evaluate mortality
  - Longer trial durations, more death events
  - Comparisons did not support the effect of fluticasone on ACM
- Early Timeframe of ACM Signal
  - KM curves (FF/UMEC/VI vs. UMEC/VI) separate within 90 days
  - Not consistent with previous ACM trials in COPD
  - Potentially consistent with inhaled corticosteroid (ICS) removal effect among pre-study ICS subgroup
    - No such early signal among ICS-naïve subgroup

Efficacy Considerations (2)

- ICS Removal Across Studies
  - Stratified analyses suggest that Pre-study ICS = YES subjects with ICS removal experience a higher rate of death events compared to ICS-continuation controls
    - Similar trend observed for severe COPD exacerbations
  - Stratified analyses suggest that ICS-naïve subjects that start ICS may not receive a mortality benefit
- Generalizability to Clinical Practice
  - Labeling claim may be misleading regarding ACM efficacy for clinical practice decisions of adding fluticasone furoate to UMEC/VI
  - Majority of patients entered on pre-study ICS, and were randomized to either ICS removal or continuation
  - Ability of the IMPACT trial to answer whether addition of FF reduced ACM in COPD?

Approval of an Application
21 CFR 314.105 (c)

- “FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling.”

Efficacy Standard
21 CFR 314.125
Refusal to Approve an Application

- (b)(5) "…substantial evidence consisting of adequate and well-controlled investigations…that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

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

Safety Standard
21 CFR 314.125
Refusal to Approve an Application

(b)(2) "…do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

(b)(3) "The results of the test show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions."

(b)(4) "There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling."

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?


FDA
U.S. FOOD & DRUG
ADMINISTRATION