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.

<table>
<thead>
<tr>
<th>Table 2: Reduction in All-Cause Mortality (Trial 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>TRELEGY ELLIPTA</td>
</tr>
<tr>
<td>UMEC/Vi</td>
</tr>
</tbody>
</table>

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 (\( \geq 1 \) 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:
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:
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

www.fda.gov
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: FEV$_1$ = 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

<table>
<thead>
<tr>
<th>Study</th>
<th>IMPACT N = 10,355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone Comparison</td>
<td>FF/UMEC/VI vs UMEC/VI</td>
</tr>
<tr>
<td>Number of Patients in Comparison</td>
<td>6221</td>
</tr>
</tbody>
</table>

## Study Design Characteristics

<table>
<thead>
<tr>
<th>Duration</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Criteria</td>
<td>FEV1: Moderate to very severe COPD</td>
</tr>
<tr>
<td></td>
<td>Medications: 3 months pre-study maintenance medications</td>
</tr>
<tr>
<td></td>
<td>Exacerbations: Prior history of exacerbations despite COPD maintenance medications</td>
</tr>
<tr>
<td></td>
<td>Symptoms: CAT ≥10</td>
</tr>
<tr>
<td>Run-in</td>
<td>Pre-study medication continued until randomization</td>
</tr>
</tbody>
</table>

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

Discontinuation of maintenance ICS, LABA, or ICS/LABA medications by healthcare provider required for enrollment

At least 7 Days

Discontinuation of maintenance LAMA medications by healthcare provider required for enrollment

At least 2 Days

Randomization Period: Event Driven Duration 40 to 185 weeks

Common End Date (CED): After 1,000 death events

Study Conclusion

Run-in: only short-acting bronchodilators allowed

4 to 10 Days

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

Visit:
- V0: Screening Visit
- V1: Baseline Visit
- V2, V3, V4, V5, V6+: Weekly visits
- V6+: Every 12 weeks until CED
- V6+: Follow-up Visit

Timing:
- V0: 4 to 10 days
- V1: Week 0
- V2: Week 4
- V3: Week 12
- V4: Week 24
- V5: Week 36
- V6+: Every 12 weeks until CED
- V6+: 2 weeks after last dose of IP

Randomization Period:
Event Driven Duration
40 to 185 weeks

- FF/VI (4,000 subjects)*
- FF (4,000 subjects)
- VI (4,000 subjects)*
- Placebo (4,000 subjects)

At least 7 Days
Discontinuation of maintenance Laba or ICS/LABA medications by healthcare provider required for enrollment

At least 7 Days
Discontinuation of maintenance LAMA medications by healthcare provider required for enrollment

Run-in: only short-acting bronchodilators allowed

Follow-up

Common End Date (CED):
After 1,000 death events

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

<table>
<thead>
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<th>Study</th>
<th>IMPACT N = 10,355</th>
<th>SUMMIT N = 16,485</th>
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</thead>
<tbody>
<tr>
<td>Fluticasone Comparison</td>
<td>FF/UMEC/VI vs UMEC/VI</td>
<td>FF/VI vs VI</td>
</tr>
<tr>
<td>Number of Patients in Comparison</td>
<td>6221</td>
<td>8239</td>
</tr>
</tbody>
</table>

## Study Design Characteristics

<table>
<thead>
<tr>
<th>Enroll Criteria</th>
<th>IMPACT</th>
<th>SUMMIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>1 year</td>
<td>Event-driven (median 1.8 years)</td>
</tr>
<tr>
<td><strong>Enrollment Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1:</td>
<td>Moderate to very severe COPD</td>
<td>Moderate COPD</td>
</tr>
<tr>
<td>Medications:</td>
<td>3 months pre-study maintenance medications</td>
<td>no requirement</td>
</tr>
<tr>
<td>Exacerbations:</td>
<td>Prior history of exacerbations despite COPD maintenance medications</td>
<td>No requirement for prior history of exacerbations</td>
</tr>
<tr>
<td>Symptoms:</td>
<td>CAT ≥10</td>
<td>mMRC ≥2</td>
</tr>
<tr>
<td>Run-in</td>
<td>Pre-study medication continued until randomization</td>
<td>Discontinue ICS, LABA, and LAMA prior to enrollment; 4 to 10-day run-in on short-acting medications alone prior to randomization</td>
</tr>
</tbody>
</table>

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

Screening, Informed Consent, and Enrollment

Randomization

End of Treatment

Study Conclusion

Run-in: discontinue ICS, LABA, and ICS/LABA

Randomization Period: 156 Weeks

FP/SAL (1,500 subjects)*

FP (1,500 subjects)

SAL (1,500 subjects)*

Placebo (1,500 subjects)

Visit: V1 Screening Visit V2 Baseline Visit V3 V4 V5 V6 V7-15 Follow-up Visit

Timing: 2 Week Run-in Week 0 Week 12 Week 24 Week 36 Week 48 Weeks 60-155 Every 12 weeks 2 weeks after last dose of IP

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>IMPACT N = 10,355</th>
<th>SUMMIT N = 16,485</th>
<th>TORCH N = 6,112</th>
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<tr>
<td>Fluticasone Comparison</td>
<td>FF/UMEC/VI vs UMEC/VI</td>
<td>FF/VI vs VI</td>
<td>FF vs Pbo</td>
</tr>
<tr>
<td>Number of Patients in Comparison</td>
<td>6221</td>
<td>8239</td>
<td>8246</td>
</tr>
<tr>
<td>Study Design Characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Duration</td>
<td>1 year</td>
<td>Event-driven (median 1.8 years)</td>
<td>3 years</td>
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<tr>
<td>Enrollment Criteria</td>
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<td></td>
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<tr>
<td><strong>FEV1:</strong> Moderate to very severe COPD</td>
<td><strong>FEV1:</strong> Moderate COPD</td>
<td><strong>FEV1:</strong> Moderate to very severe COPD</td>
<td></td>
</tr>
<tr>
<td><strong>Medications:</strong> 3 months pre-study maintenance medications</td>
<td><strong>Medications:</strong> no requirement</td>
<td><strong>Medications:</strong> no requirement</td>
<td></td>
</tr>
<tr>
<td><strong>Exacerbations:</strong> Prior history of exacerbations despite COPD maintenance medications</td>
<td><strong>Exacerbations:</strong> No requirement for prior history of exacerbations</td>
<td><strong>Exacerbations:</strong> No requirement for prior history of exacerbations</td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms:</strong> CAT ≥10</td>
<td><strong>Symptoms:</strong> mMRC ≥2</td>
<td><strong>Symptoms:</strong> no requirement</td>
<td></td>
</tr>
<tr>
<td>Run-in</td>
<td>Pre-study medication continued until randomization</td>
<td>Discontinue ICS, LABA, and LAMA prior to enrollment; 4 to 10-day run-in on short-acting medications alone prior to randomization</td>
<td>Discontinue ICS, LABA, and LAMA for 14-day run-in on short-acting medications alone prior to randomization</td>
</tr>
</tbody>
</table>

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

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

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/UMECD VI: fluticasone furoate 100 µg / umecilidium 62.5 µg / vilanterol 25 µg; FF/VI: fluticasone furoate 100 µg / vilanterol 25 µg; UMEC/VI: umecilidium 62.5 µg / vilanterol 25 µg.
# IMPACT: Pre-study Medications

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>IMPACT N = 10,355</th>
</tr>
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<tbody>
<tr>
<td>Fluticasone Comparison</td>
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<tr>
<td>Number of Patients in Comparison</td>
<td>6221</td>
</tr>
<tr>
<td>Population Characteristics</td>
<td></td>
</tr>
<tr>
<td>Pre-study Triple Therapy</td>
<td>38%</td>
</tr>
<tr>
<td>Pre-study ICS</td>
<td>71%</td>
</tr>
<tr>
<td>Frequent Exacerbators in Prior Year</td>
<td>70%</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire Total Score</td>
<td>50.6</td>
</tr>
</tbody>
</table>
Baseline Disease Characteristics Across Trials

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

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

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

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
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:
## IMPACT, SUMMIT, and TORCH: Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>IMPACT N = 10,355</th>
<th>SUMMIT N = 16,485</th>
<th>TORCH N = 6,112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone Comparison</td>
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<td></td>
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<td>33%</td>
<td>49%</td>
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<td>70%</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>St. George’s Respiratory Questionnaire Total Score</td>
<td>50.6</td>
<td>46.6</td>
<td>49.3</td>
</tr>
</tbody>
</table>

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.)

<table>
<thead>
<tr>
<th>Study</th>
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<thead>
<tr>
<th>Duration</th>
<th>Event-driven (median 1.8 years)</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Criteria</td>
<td><strong>FEV1</strong>: Moderate to very severe COPD</td>
<td><strong>FEV1</strong>: Moderate COPD</td>
</tr>
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<td>Medications:</td>
<td>3 months pre-study maintenance medications</td>
<td>Medications: no requirement</td>
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<td>Exacerbations:</td>
<td>Prior history of exacerbations despite COPD maintenance medications</td>
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Source: Reviewer. Abbreviations: FF: fluticasone furoate 100 mcg; UMEC: umeclidinium 62.5 mcg; VI: vilanterol 25 mcg; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; FF: fluticasone furoate 100 mcg; VI: vilanterol 25 mcg; 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
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
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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: FEV₁, 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

FEV₁: 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

<table>
<thead>
<tr>
<th></th>
<th>FF/UMEC/VI</th>
<th>FF/VI</th>
<th>UMEC/VI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-treatment</strong></td>
<td>87.7%</td>
<td>76.6%</td>
<td>74.4%</td>
<td>79.2%</td>
</tr>
<tr>
<td><strong>On-study</strong></td>
<td>95.4%</td>
<td>94.0%</td>
<td>93.5%</td>
<td>94.5%</td>
</tr>
<tr>
<td><strong>All vital status follow-up</strong></td>
<td>99.8%</td>
<td>99.6%</td>
<td>99.3%</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

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

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

CI: confidence interval  
HR: hazard ratio
IMPACT ACM Over 52 Weeks

Source: Reviewer
Outline

1. IMPACT and all-cause mortality
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   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 |
<table>
<thead>
<tr>
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<td>6221</td>
<td>8239</td>
<td>8246</td>
</tr>
<tr>
<td></td>
<td>Event-driven (median 1.8 years)</td>
<td>3054</td>
<td>3058</td>
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</table>

**Study Design Characteristics**

<table>
<thead>
<tr>
<th>Duration</th>
<th>1 year</th>
<th>Event-driven (median 1.8 years)</th>
<th>3 years</th>
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</thead>
<tbody>
<tr>
<td>Enrollment Criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1: Moderate to very severe COPD</td>
<td></td>
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<td></td>
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<td>Symptoms: CAT ≥10</td>
<td></td>
<td>Symptoms: mMRC ≥2</td>
<td></td>
</tr>
<tr>
<td>Run-in</td>
<td></td>
<td>Discontinue ICS, LABA, and LAMA prior to enrollment; 4 to 10-day run-in on short-acting medications alone prior to randomization</td>
<td></td>
</tr>
<tr>
<td>Pre-study medication continued until randomization</td>
<td></td>
<td>Discontinue ICS, LABA, and LAMA for 14-day run-in on short-acting medications alone prior to randomization</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>IMPACT N=10,355</th>
<th>SUMMIT N=16,485</th>
<th>TORCH N=6,112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in ICS comparison</td>
<td>FF/UMEC/VI vs UMEC/VI</td>
<td>FF/VI vs VI</td>
<td>FF vs Pbo</td>
</tr>
<tr>
<td></td>
<td>6,221</td>
<td>8,239</td>
<td>8,246</td>
</tr>
<tr>
<td>Mortality events in comparison</td>
<td>164</td>
<td>511</td>
<td>526</td>
</tr>
<tr>
<td>ACM analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.72</td>
<td>0.91</td>
<td>0.91</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.53 - 0.99</td>
<td>0.77 - 1.09</td>
<td>0.77 - 1.08</td>
</tr>
</tbody>
</table>

Source: Reviewer
SUMMIT and TORCH ACM Over 3 Years

Source: Reviewer

www.fda.gov
IMPACT, SUMMIT and TORCH ACM Over 52 Weeks

Source: Reviewer
Outline

1. IMPACT and all-cause mortality
   a. Study design features
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   d. Overall results
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   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

www.fda.gov
IMPACT ACM by Pre-Study ICS Subgroup

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

Source: Reviewer
www.fda.gov
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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 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
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- 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:
ICS Removal in COPD

- Magnussen et al. (WISDOM)

- Trend towards increased severe AECOPD after ICS removal

References:
ICS Removal in COPD

- **Rossi et al (INSTEAD)**
  - Pre-study: ICS/LABA
  - Run-in: ICS/LABA (i.e., FP/SAL)
  - Randomization
  - Randomization Period: 26 Weeks
  - LABA (Intervention: ICS Removal)
  - ICS/LABA (Control: Continue All Pre-study modalities)

- **Chapman et al (SUNSET)**
  - Pre-study: Triple therapy with ICS, LABA, and LAMA
  - Run-in: ICS/LABA/LAMA (i.e., FP/SAL + Tiotropium)
  - Randomization
  - Randomization Period: 26 Weeks
  - LABA/LAMA (Intervention: ICS-removal)
  - ICS/LABA/LAMA (Control: Continue All Pre-study Modalities)

References:
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:

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

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Timeframe of Efficacy in IMPACT

Interpretations Under ICS Removal Paradigm

Generalizability of IMPACT Results to Clinical Practice

Efficacy Results in Context
**IMPACT: ICS Removal**

- **Pre-study:** ICS/LABA/LAMA
- **Run-in:** continue ICS/LABA/LAMA
- **Randomization Period:** 52 weeks
- **End of Treatment**

- **LABA/LAMA**: (Intervention: Removal of ICS)
- **ICS/LABA**
- **ICS/LABA/LAMA**: (Control: Continue Pre-study Modalities)

*In this analysis stratified by pre-study triple therapy, comparison of the ICS/LABA/LAMA arm versus the LABA/LAMA arm may provide data on the effect of ICS removal among patients with a history of COPD exacerbations and uncontrolled symptoms.*

Source: Reviewer

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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)

Some subjects still had pre-study ICS

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

* In this analysis stratified by pre-study ICS use, comparison of the ICS/LABA/LAMA arm versus the LABA/LAMA arm may provide data on the effect of ICS removal among patients with a history of COPD exacerbations and uncontrolled symptoms, potentially influenced by the addition of other COPD therapeutic modalities
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)

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)

<table>
<thead>
<tr>
<th>Week 52: All-cause Mortality Analysis</th>
<th>FF/UMEC/VI N=2971</th>
<th>FF/VI N=2908</th>
<th>UMEC/VI N=1481</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with event, n (%)</td>
<td>65 (2.2)</td>
<td>79 (2.7)</td>
<td>52 (3.5)</td>
</tr>
<tr>
<td>Hazard Ratio for ACM</td>
<td></td>
<td>1.25</td>
<td>1.64</td>
</tr>
<tr>
<td>95% CI (Comparator versus FF/UMEC/VI)</td>
<td>0.90, 1.75</td>
<td></td>
<td>1.15, 2.38</td>
</tr>
</tbody>
</table>

**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 | 0.89 | 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)

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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)

<table>
<thead>
<tr>
<th>Week 52: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator</th>
<th>FF/UMEC/VI N=1180</th>
<th>FF/VI N=1226</th>
<th>UMEC/VI N=589</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with event, n (%)</td>
<td>33 (2.8)</td>
<td>30 (2.5)</td>
<td>14 (2.4)</td>
</tr>
<tr>
<td>Hazard Ratio for ACM (95% CI)</td>
<td>1.13 (0.69, 1.86)</td>
<td><strong>1.16 (0.62, 2.16)</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator

<table>
<thead>
<tr>
<th>Number of subjects with event at Day 90, n (%)</th>
<th>FF/UMEC/VI N=1177</th>
<th>FF/VI N=1219</th>
<th>UMEC/VI N=584</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio for ACM (95% CI)</td>
<td>1.03 (0.21, 5.10)</td>
<td><strong>0.50 (0.10, 2.50)</strong></td>
<td></td>
</tr>
</tbody>
</table>

### After Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator Excluding first 90 Days

<table>
<thead>
<tr>
<th>Number of subjects with available data after Day 90</th>
<th>1177</th>
<th>1219</th>
<th>584</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with event after Day 90, n (%)</td>
<td>30 (2.6)</td>
<td>27 (2.2)</td>
<td>11 (1.9)</td>
</tr>
<tr>
<td>Hazard Ratio for ACM (95% CI)</td>
<td><strong>1.35 (0.67, 2.79)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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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

**Pre-study:** ICS-containing

- Discontinuation of maintenance ICS, LABA, or ICS/LABA medications by healthcare provider required for enrollment

**Screening, Informed Consent, and Enrollment**
- At least 2 Days

**Randomization**
- 4 to 10 Days
- Run-in: only short-acting bronchodilators allowed

**Randomization Period:** Event Driven Duration 40 to 185 weeks

**Common End Date (CED):** After 1,000 death events

**Study Conclusion**
- 2 weeks

**Follow-up**

- VI
- Placebo (ICS Removal)*
- FF/VI
- FF (Continue ICS)*
TORCH: ICS Removal

Screening, Informed Consent, and Enrollment

Pre-study: ICS-containing

Run-in: discontinue ICS, LABA, and ICS/LABA

Randomization

Randomization Period: 156 Weeks

2 Weeks

End of Treatment

Placebo (ICS Removal)*

FP (Continue ICS)*

FP/SAL

SAL

2 Weeks

Study Conclusion

Follow-up
# ICS Removal and Addition Across Trials

## All-cause Mortality Analyses in Pre-study ICS Subgroup at Day 90

<table>
<thead>
<tr>
<th>ICS Removal Comparison</th>
<th>IMPACT N = 10,355</th>
<th>SUMMIT N = 16,485</th>
<th>TORCH N = 6,112</th>
</tr>
</thead>
<tbody>
<tr>
<td>UMEC/VI vs FF/UMEC/VI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI vs FF/VI</td>
<td>5.00 (2.27, 11.11)</td>
<td>3.85 (1.08, 14.3)</td>
<td>1.35 (0.50, 3.85)</td>
</tr>
<tr>
<td>Pbo vs FF</td>
<td>1.35 (0.50, 3.85)</td>
<td>3.03 (0.31, 33.33)</td>
<td>1.92 (0.56, 6.67)</td>
</tr>
<tr>
<td>SAL vs FP/SAL</td>
<td>1.92 (0.56, 6.67)</td>
<td>1.92 (0.56, 6.67)</td>
<td>1.92 (0.56, 6.67)</td>
</tr>
<tr>
<td>Pbo vs FP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## All-cause Mortality Analyses in ICS-naïve Subgroup at Study End

<table>
<thead>
<tr>
<th>ICS Addition Comparison</th>
<th>IMPACT N = 10,355</th>
<th>SUMMIT N = 16,485</th>
<th>TORCH N = 6,112</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF/UMEC/VI vs UMEC/VI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF/VI vs FF</td>
<td>1.16 (0.62, 2.16)</td>
<td>0.99 (0.80, 1.23)</td>
<td>0.96 (0.77, 1.19)</td>
</tr>
<tr>
<td>FF vs Pbo</td>
<td>0.96 (0.77, 1.19)</td>
<td>0.98 (0.75, 1.29)</td>
<td>1.13 (0.87, 1.45)</td>
</tr>
<tr>
<td>FP/SAL vs SAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP vs Pbo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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; 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
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Uncertainties in the Interpretation of the All-cause Mortality Results

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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

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**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

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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
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
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.”
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
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
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?