Errata to the FDA Briefing Document

PADAC Advisory Committee Meeting

August 31, 2020

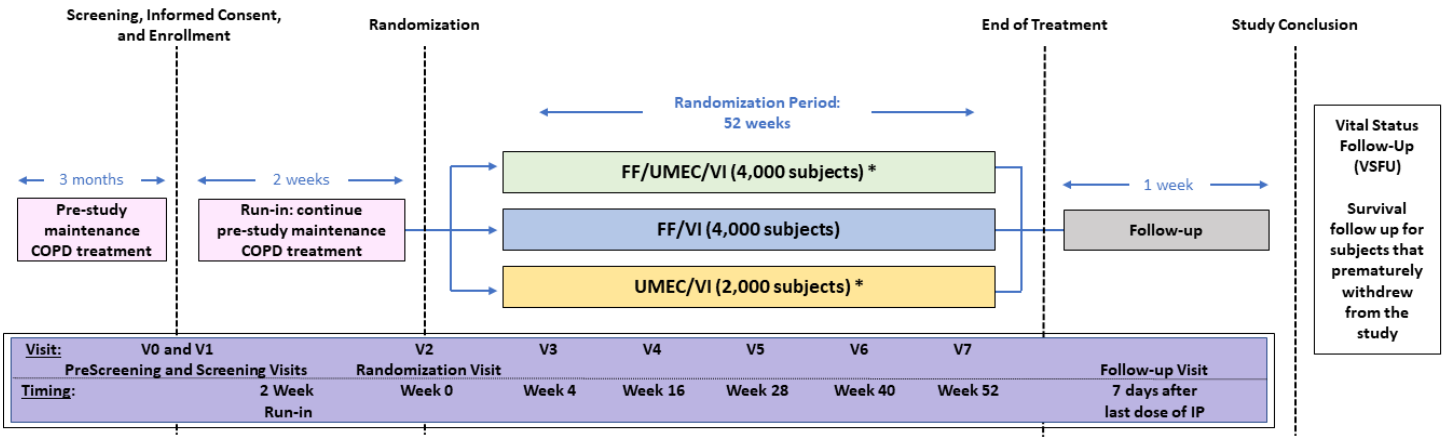
Page numbers refer to PDF page number. Paragraph numbering begins with the first new paragraph on the page unless otherwise noted.

Where these data appear in the Division's pre-recorded presentations, these errata should be applied as well.

Division Memorandum

1. On page 7, Figure A. IMPACT: Trial Schematic, wording on the figure should be modified in the following way: the blue text above the treatment arm rectangles should read "Randomization Period: ~~Event Driven Duration~~ 52 Weeks". The figure should be replaced with the following figure:

Figure A. IMPACT: Trial Schematic



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

2. On page 8, Table A. IMPACT: All-cause Mortality Results at 52 Weeks (ITT+VS+VSFU)
    - In the category "All-cause Mortality Analysis of FF/UMEC/VI versus Comparator (column)"
        i. Row "95% CI", 2nd column "FF/VI", should read "~~0.68, 1.17~~ **0.67, 1.16**"
3. On page 10, Table B. IMPACT: All-cause Mortality Results at Various Timepoints (ITT+VS+VSFU)

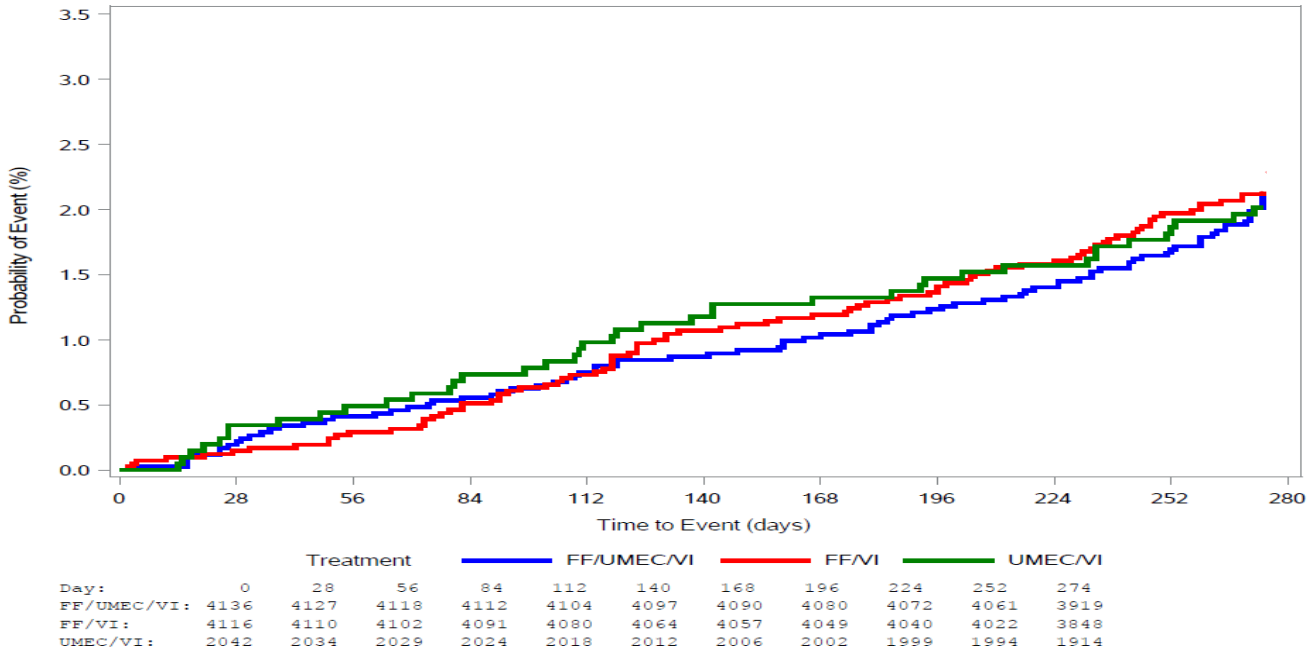
- In the category "After Day 90: All-cause Mortality Analysis of FF/UMEC/VI versus Comparator Excluding first 90 Days"
    i. Row "Number of subjects with available data after Day 90", 1st column "FF/UMEC/VI", should read "~~4135~~ **4136**"

4. On page 11, Figure C. IMPACT: Probability of All-cause Mortality After Day 90 by Treatment Arm (ITT+VS+VSFU), the figure should be modified in the following way:

- The number of days on the x-axis of the figure should be truncated at day ~~280~~ **274**.
- In the final column of numbers in the table of numbers beneath the figure:
    i. Row "Day" should read "~~280~~ **274"**
    ii. Row "FF/UMEC/VI" should read ~~2997~~ **3919**
    iii. Row "FF/VI" should read ~~2846~~ **3848**
    iv. Row "UMEC/VI" should read ~~1419~~ **1914**

The figure should be replaced with the following figure:

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



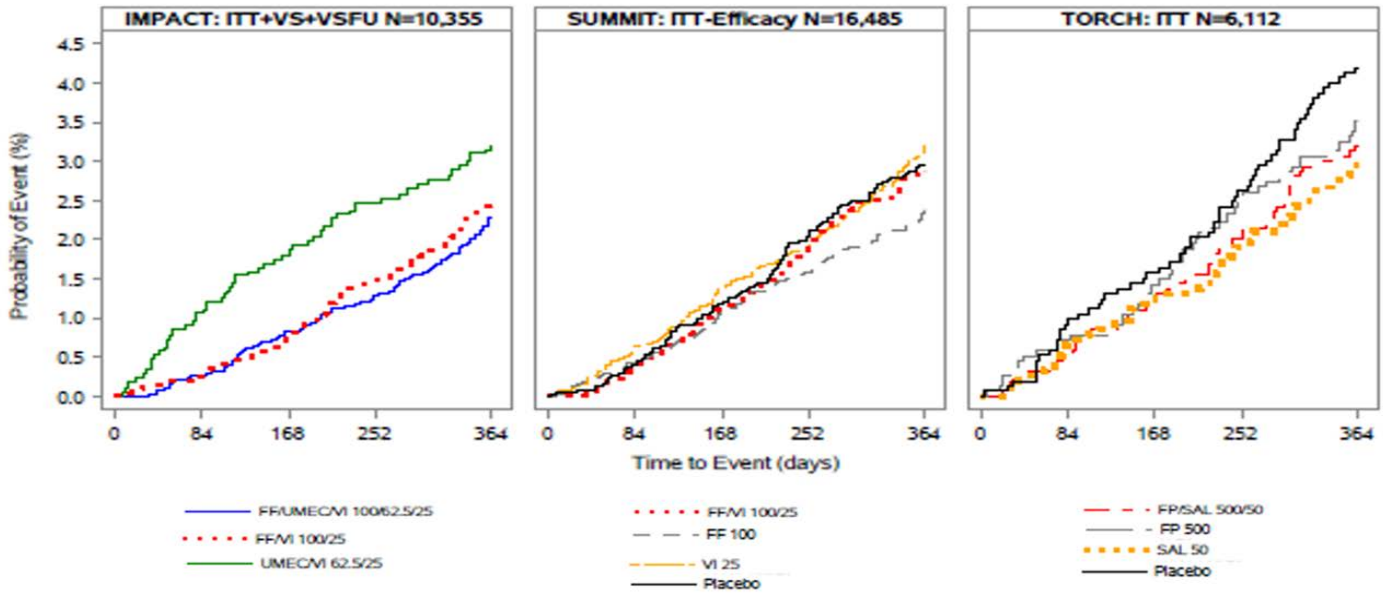
Source: Statistical reviewer. These analyses incorporate on- and off-treatment vital status data from the IMPACT study and available vital status follow-up data for subjects who withdrew from the study.
Abbreviations: ITT: intention to treat; VS: end of study vital status; VSFU: vital status follow-up;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

5. On page 13, Table C. All-cause Mortality Across Trials: Pairwise Treatment Comparisons That Isolate the Effect of ICS on ACM in IMPACT, SUMMIT, and TORCH

    - In the category "Data for Relevant All-cause Mortality Comparisons"
        i. Row "Number of Patients in Comparison", column "TORCH N=6,112" should read "~~3057~~ **3058**"
    - In the category "All-cause Mortality Analyses"
        i. Row "95% CI", column "TORCH N=6,112" should read "0.88 to ~~1.25~~ **1.26**"

6. On page 14, Figure D. All-cause Mortality Across Trials: Probability of All-cause Mortality over 52 Weeks by Treatment Arm in IMPACT, SUMMIT, and TORCH (Including On- and Off-treatment Data), the figure should be modified in the following way: separate legends should be added for each study. The figure should be replaced with the following figure:

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



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

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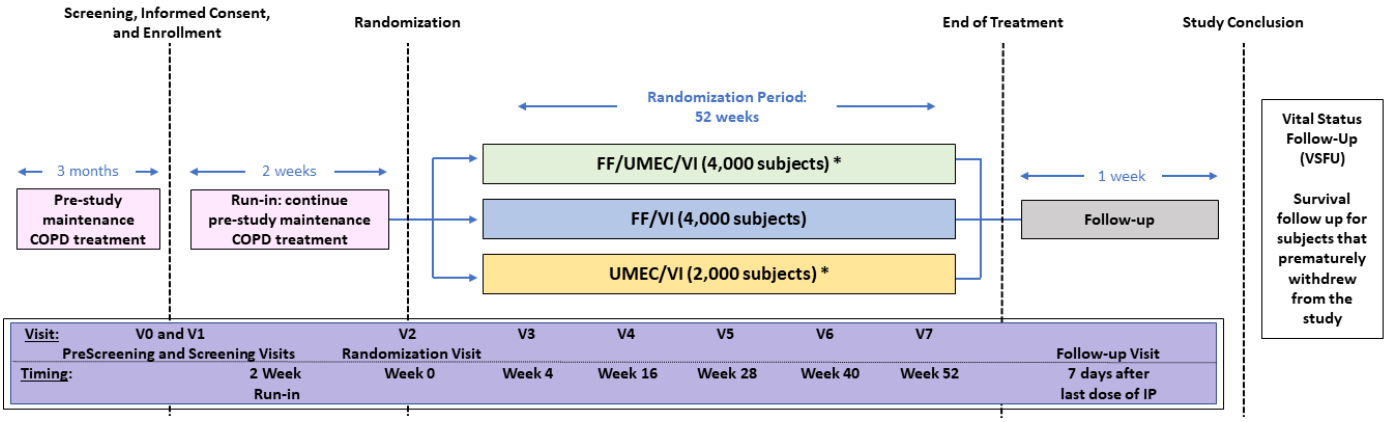
7. On page 31, paragraph 4, 1st sentence, should read "The indication for TRELEGY ELLIPTA was amended on April 24, 2018 after approval of an sNDA relying on data from trial ~~CTT116873~~ **CTT116855** (IMPACT).".
8. On page 42, Table 2. Clinical Trials of Fluticasone for All-cause Mortality in COPD
    - In section CTT116855 (IMPACT)
        i. Row corresponding to "FF/UMEC/VI" under column "Number (ITT)" should read "~~4,145~~ **4,151**"
        ii. Row corresponding to "FF/VI" under column "Number (ITT)" should read "~~4,133~~ **4,134**"
9. On page 47, Figure 1. IMPACT: Trial Schematic, the figure should be modified in the following way: the blue text above the treatment arm rectangles should read "Randomization Period: ~~Event Driven Duration~~ 52 Weeks". The figure should be replaced with the following figure:

Figure 1. IMPACT: Trial Schematic



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

10. On page 49, 4th bullet of "Exclusion Criteria" heading, 1st sub-bullet should read "Subjects with a current diagnosis of asthma were ~~included~~ **excluded**; subjects with a prior history of asthma were included if they had a current diagnosis of COPD"
11. On page 70, Table 3. Demographics Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH
    - In the category "Age Group"
        i. Row "≥75 years", column "IMPACT n(%)" should read "~~1,406 (13)~~ **1,406 (14)**"

12. On page 71, Table 4. IMPACT: Demographic Characteristics, ITT Population

- In the category Smoking History, the table should read:
    i. In Row "Current"
        1. Column "FF/UMEC/VI" should read "1,436 (35~~.0~~)"
        2. Column "FF/VI" should read "1,423 (34~~.0~~)"
        3. Column "Total" should read "3,587 (35~~.0~~)
    ii. In Row "Former"
        1. Column "FF/UMEC/VI" should read "2,715 (65~~.0~~)"
        2. Column "FF/VI" should read "2,711 (66~~.0~~)"
        3. Column "Total" should read "6,768 (65~~.0~~)

13. On page 72, Table 5. Baseline Disease Characteristics Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH

- In the category "Total"
    i. Row "Total", column "IMPACT", should read "~~10,355~~ **10,347**"
- In the category "GOLD spirometric severity grade*"
    i. Row "Mild", column "TORCH", should read "~~N/A~~ **28 (<1)**"
    ii. Row "Moderate", column "TORCH", should read "~~2,156~~ **2,128** (35)"
- In the category "SGRQ total score"
    i. Row "N with analyzable data"
        1. column "SUMMIT" should read "~~4,403~~ **4,433**"
        2. column "TORCH" should read "~~4,951~~ **4,752**"
    ii. Row "Mean (SD)"
        1. column "IMPACT", should read "~~50.6~~ **50.7** (16.9)"
        2. column "SUMMIT", should read "~~46.6~~ **46.3** (16.0)"

14. On page 74, Table 6. Pre-study COPD Medication Groups Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH

- In category "Total", Column "TORCH", should read "~~6,122~~ **6,112**"
- In category "Triple therapy*", Column "TORCH", should read "~~6,121~~ **6,111** (99)"
- The category heading "Medication not reported*" should read "**Medication not reported ****" with reference to the footnote "**For the purposes of subgroup analyses, subjects with no pre-study medication reported are included in the "pre-study triple therapy = No" and "pre-study ICS therapy = No" subgroups throughout the review."

15. On page 74, Table 7. IMPACT: Baseline Disease Characteristics, ITT Population

- In the category "Postbronchodilator FEV1"
    i. Row "N with available data", column "TOTAL" should read "~~10,345~~ **10,347**"
- In the category "SGRQ total score"
    i. Row "N with analyzable data", column "FF/UMEC/VI", should read "~~41,08~~ **4,108**"
    ii. Row "Mean (SD)", column "Total", should read "~~50.6~~ **50.7** (16.9)"
- The category heading "COPD assessment test score" should read "COPD Assessment Test score **at Screening**"

16. On page 77, Table 9. Disposition Across Trials: ITT Population of IMPACT, SUMMIT, and TORCH

- In the category "Study completion status"
    i. Row "Prematurely withdrawn", column "IMPACT N=10,355" should read "~~1,269~~ **1,268** (12.3)"

17. On page 78, Table 10. IMPACT: Subject Disposition, ITT Population

- In the category "Study completion status"
    i. Row "Prematurely withdrawn"
        1. Column "FF/VI" should read "~~537~~ **536** (13.0)"
        2. Column "Total" should read "~~1,269~~ **1,268** (12.3)"
    ii. Row "Investigator Discretion"
        1. Column "FF/UMEC/VI" should read "~~48~~ **47** (11.0)"
        2. Column "Total" should read "~~134~~ **132** (10.6)"

18. On page 79, Table 11. IMPACT: Follow-up for Mortality and Number of Deaths

- In category "Complete follow-up for mortality"
    i. Row "On-treatment follow-up (ITT)"
        1. Column "FF/UMEC/VI" should read "3,475 (~~87.7~~ **83.7**)
        2. Column "UMEC/VI" should read "1,561 (~~74.4~~ **75.4**)"

19. On page 79, section 4.3.4. TORCH: Disposition, 3rd sentence should read "More than ~~98%~~ **99%** of randomized subjects in TORCH had complete follow-up for mortality."

20. On page 80, Table 12. IMPACT: All-cause Mortality Results at 52 Weeks (ITT+VS+VSFU)

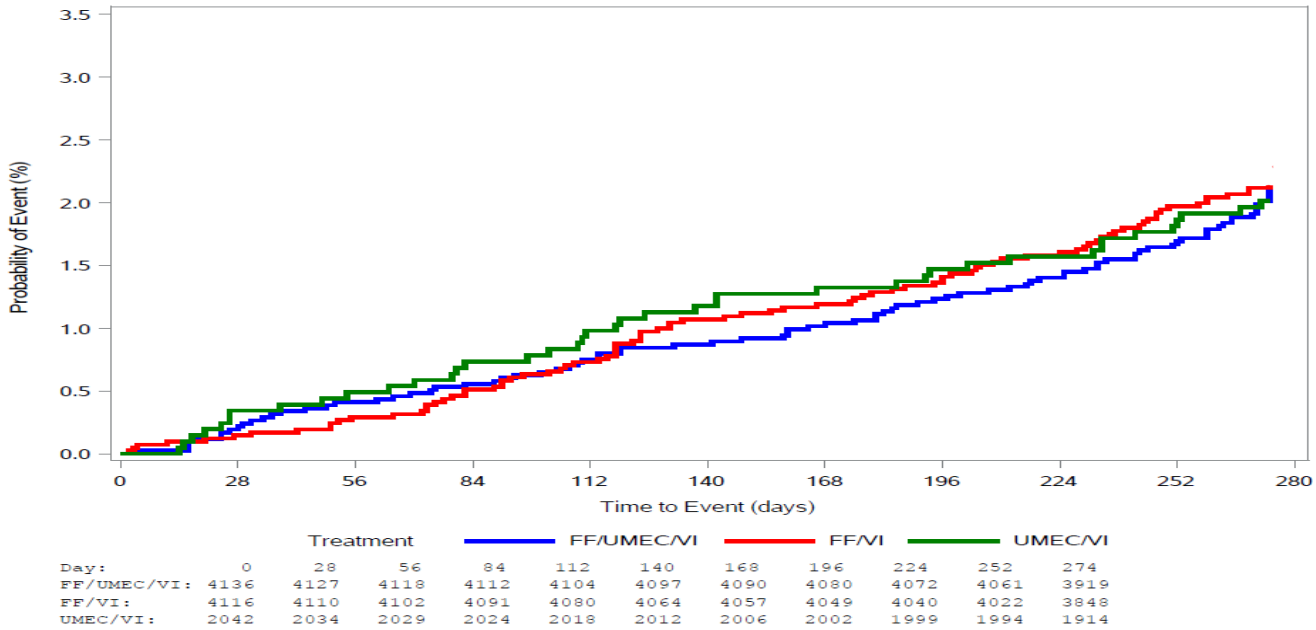
- In category ACM analysis of FF/UMEC/VI vs comp, row "95% CI", column "FF/VI" should read "~~0.68~~ **0.67**, ~~1.17~~ **1.16**"

21. On page 85, Figure 5. IMPACT: Probability of All-cause Mortality After Day 90 by Treatment Arm (ITT+VS+VSFU), the figure should be modified in the following way:

- The number of days with data (see x-axis of the figure) should be truncated at day ~~280~~ **274**.
- In the final column of numbers in the table of numbers beneath the figure:
  i. Row "Day" should read "~~280~~ **274"**
  ii. Row "FF/UMEC/VI" should read **"**~~2997~~ **3919"**
  iii. Row "FF/VI" should read "~~2846~~ **3848"**
  iv. Row "UMEC/VI" should read "~~1419~~ **1914**"

The figure should be replaced with the following figure:

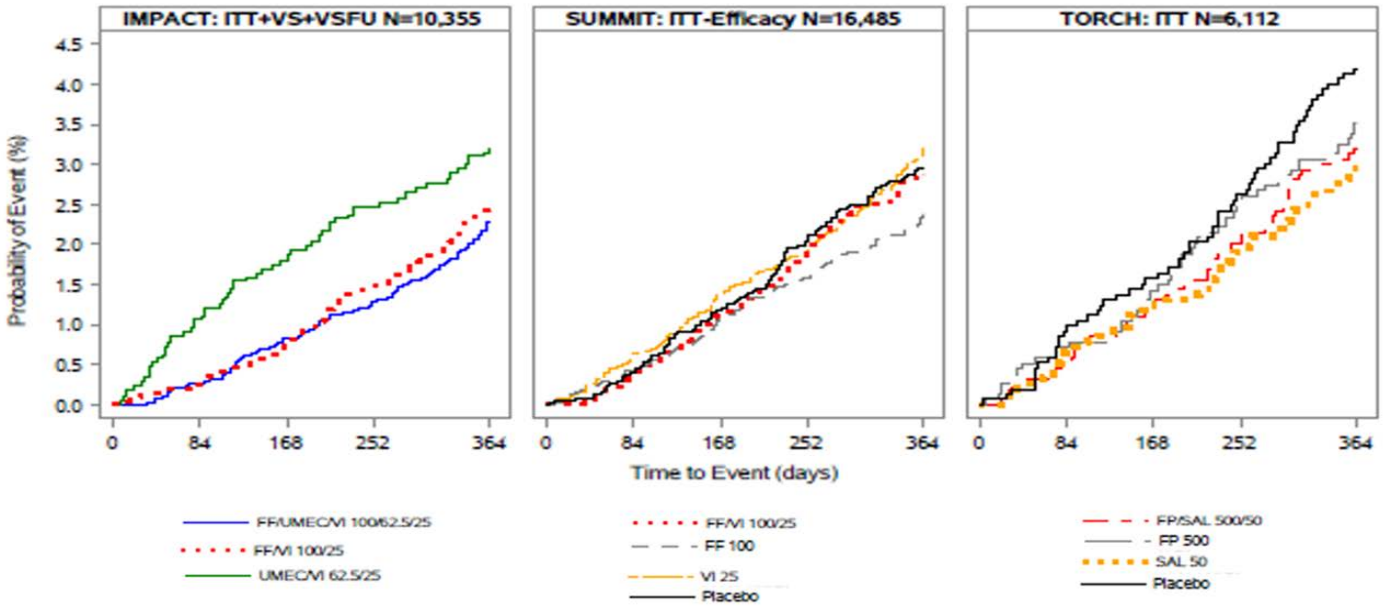
Figure 5. IMPACT: Probability of All-cause Mortality After Day 90 by Treatment Arm (ITT+VS+VSFU)



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

22. On page 92, Figure 10. All-cause Mortality Across Trials: Probability of All-cause Mortality over 52 Weeks by Treatment Arm in IMPACT, SUMMIT, and TORCH (Including On- and Off-treatment Data), the figure should be modified in the following way: **separate legends should be added for each study**. The figure should be replaced with the following figure:

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



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

23. On page 92, Table 16. All-cause Mortality Across Trials: Pairwise ICS Treatment Comparisons on ACM in IMPACT, SUMMIT, and TORCH

- In category "Patients in ICS comparison", column "FP vs Pbo" should read "~~3,057~~ **3,058**"
- In category "ACM analyses"
  i. Row "95% CI", column "FP vs Pbo" should read "0.88 to ~~1.25~~ **1.26**"

24. On page 106, Table 17. IMPACT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Various Timepoints (ITT+VS+VSFU)

- In category "After day 90 (excluding first 90 days)", the table should read

After day 90 (excluding first 90 days)			
Subjects with available data after day 90	~~2,933~~ **2,959**	~~2,856~~ **2,897**	~~1,435~~ **1,458**
Subjects with event after day 90, n (%)	~~49 (1.7)~~ **56 (1.9)**	~~51 (2.1)~~ **69 (2.4)**	~~26 (1.8)~~ **30 (2.1)**
ACM HR (95% CI, FF/UMEC/VI vs. comparator)		~~0.77 (0.53, 1.12)~~ **0.78 (0.55, 1.12)**	~~0.90 (0.56, 1.44)~~ **0.90 (0.58, 1.41)**
ACM HR (95% CI, comparator vs. FF/UMEC/VI)		~~1.30 (0.89, 1.89)~~ **1.28 (0.89, 1.81)**	~~1.11 (0.69, 1.79)~~ **1.11 (0.71, 1.72)**

25. On page 107, Table 18. IMPACT: Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Various Timepoints (ITT+VS+VSFU)

- In category "After day 90 (excluding first 90 days)", the table should read

After day 90 (excluding first 90 days)			
Subjects with available data after day 90	~~1,164~~ **1,177**	~~1,203~~ **1,219**	~~578~~ **584**
Subjects with event after day 90, n (%)	~~28 (2.4)~~ **30 (2.6)**	~~23 (1.9)~~ **27 (2.2)**	~~10 (1.7)~~ **11 (1.9)**
ACM HR (95% CI, FF/UMEC/VI vs. comparator)			~~1.35 (0.66, 2.78)~~ **1.35 (0.67, 2.79)**

26. On page 108, Table 19. IMPACT: Pre-study ICS Subgroups: Demographic and Baseline Disease Characteristics Across Subgroups (ITT+VS+VSFU)

- Footnote should read "*FEV1 data for ~~5~~ **8** subjects were missing from this analysis; calculated proportions incorporate this adjusted denominator"

27. On page 109, Table 20. IMPACT: Pre-study ICS Subgroups: Demographic and Baseline Disease Characteristics by Subgroup and Treatment Arm (ITT+VS+VSFU)

- In category "AECOPD category**"
    i. Row "<2 mod and no sev", Column "Pre-study ICS = No", subcolumn "UMEC/VI", should read "~~589~~ **195** (33)"
- Footnote should read "*FEV1 data for ~~5~~ **8** subjects were missing from this analysis; calculated proportions incorporate this adjusted denominator"

28. On page 112, Table 21. IMPACT: Probability of First Severe AECOPD Through Week 52, Pre-study ICS = YES (ITT Including Both On- and Off-treatment Data"

- Column Headings should read
    i. "FF/UMEC/VI N=~~1180~~ **2,971"**
    ii. "FF/VI N=~~1226~~ **2,908**"
    iii. "UMEC/VI N=~~589~~ **1,481**"
- Row "HR (95% CI for FF/UMEC/VI vs comparator)", column "UMEC/VI N=1,481" should read "0.72 (~~0.62~~ **0.61**, 0.85)
- Row "HR (95% CI for comparator vs FF/UMEC/VI)"
    i. Column "FF/VI N=2,908" should read "~~1.09~~ **1.10** (0.96, 1.27)"
    ii. Column "UMEC/VI N=1,481" should read "1.39 (1.18, ~~1.61~~ **1.64**)"

29. On page 113, Table 22, IMPACT: Time-to-First Severe AECOPD, Week 52, Pre-study ICS = No (ITT Including Both On- and Off-Treatment Data)

- Row "HR (95% CI for FF/UMEC/VI vs comparator)"
    i. Column "FF/VI" should read "0.93 (0.72, ~~1.21~~ **1.20**)
    ii. Column "UMEC/VI" should read "~~0.87~~ **0.89** (~~0.64~~ **0.65**, ~~1.19~~ **1.21**)"

30. On page 125, Table 23. ACM Across Trials: Totality of Evidence for Comparisons Evaluating ICS Effects Across IMPACT, SUMMIT, and TORCH

- In category "Patients in ICS comparison", Column "FP vs Pbo", should read "~~3,057~~ **3,058**"

31. On page 127, 2nd paragraph, 9th sentence, should read "Data from this subgroup should be interpreted cautiously, however, since only ~~30%~~ **29%** of the IMPACT trial population did not receive pre-study ICS, limiting the power to inform conclusions based on data from this subgroup alone."

32. On page 132, 3rd paragraph, starting at 4th sentence, should read "However, this interpretation would be incorrect, since ~~nearly 70%~~ **71%** of the subjects in IMPACT used pre-study ICS and could have added ICS to their COPD regimen. Even if we eliminate those ~~70%~~ **71%** of subjects with pre-study ICS and attempt to apply only the data that would inform **a** decision to add ICS, the subgroup comparison of FF/UMEC/VI versus UMEC/VI among the ~~30%~~ **29%** of ICS-naïve subjects in IMPACT was not able to demonstrate a mortality benefit for the FF component, increasing uncertainty in the validity of the clinical interpretation and of the proposed labeling claim."

33. Page 145, Table 25. IMPACT Data Appendix: List of Efficacy Analyses in IMPACT

- This table should read as follows:

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

Endpoints Controlled for Multiplicity			
Number of Comparisons	Endpoints	Data Included	Population
2 (primary)	Annual rate moderate/severe **COPD Exacerbations**	On-treatment	ITT
~~4 (secondary)~~	~~Moderate/severe4~~	~~On-treatment~~	~~≥150 eosinophils/µL~~ ~~<150 eosinophils/ µL~~
~~2 (secondary)~~	~~Severe4~~	~~On-treatment~~	~~ITT~~
~~4 (secondary)~~	~~Moderate/severe~~	~~On-treatment~~	~~≥150 eosinophils/ µL~~ ~~<150 eosinophils/ µL~~
1 (secondary)	**Trough FEV1**	**Week 52**	**ITT - FF/UMEC/VI vs FF/VI only**
1 (secondary)	**SGRQ Total score**	**Week 52**	**ITT - FF/UMEC/VI vs FF/VI only**
2 (secondary)	**Time to first moderate/severe COPD Exacerbation**	**On-treatment**	**ITT**
*Total number of comparisons for multiplicity-controlled endpoints: ~~1~~ **6***			
Other Secondary Endpoints Not Controlled for Multiplicity			
1	**Annual Rate Moderate/severe COPD Exacerbations**	**On-treatment**	**≥150 eosinophils/µL subgroup and FF/UMEC/VI vs UMEC/VI only**
2	**Annual Rate Severe COPD Exacerbations**	**On-treatment**	**ITT**
1	**Time to First Moderate/severe COPD Exacerbation**	**On-treatment**	**≥150 eosinophils/µL and FF/UMEC/VI vs UMEC/VI only**
Exploratory analyses			
COPD exacerbations			
~~2~~	~~Time to first moderate/severe~~	~~On-treatment~~	~~ITT~~

~~2~~	~~Annual rate moderate/severe~~	~~On- and off-treatment~~	~~ITT~~
4	**Annual Rate** Severe	On-treatment	≥150 eosinophils/µL <150 eosinophils/µL
3	**Annual Rate Moderate/Severe**	**On-treatment**	**≥150 eosinophils/µL (FF/UMEC/VI vs FF/VI only)** **<150 eosinophils/µL**
8	**Annual Rate** Mild/moderate/severe	On-treatment	ITT
	Annual Rate Moderate	On-treatment	ITT
	Annual Rate Moderate/severe requiring oral/systemic corticosteroids	On-treatment	ITT
	Annual Rate Moderate/severe requiring antibiotics	On-treatment	ITT
~~10~~ **5**	~~Time to first moderate/severe~~	~~On- and off-treatment~~	~~ITT~~
	~~Moderate/severe~~	~~On-treatment or premature discontinuation~~	~~ITT~~
	Time to first Moderate/severe	On-treatment	≥150 eosinophils/µL **(FF/UMEC/VI vs FF/VI only)** <150 eosinophils/µL
	Time to first Severe	On-treatment	ITT
6	**Time to first** Severe	On-treatment	≥150 eosinophils/µL <150 eosinophils/µL
	Time to first Mild/moderate/severe	On-treatment	ITT
6	**Time to first** Moderate	On-treatment	ITT
	Time to first Moderate/severe requiring oral/systemic corticosteroids	On-treatment	ITT
	Time to first Moderate/severe requiring antibiotics	On-treatment	ITT
4	**Time to each** moderate/severe	On-treatment	ITT
	Time to each Severe	On-treatment	ITT
Lung function			
1	**Trough FEV1**	**Week 52**	**ITT - FF/UMEC/VI vs UMEC/VI only**
4	Trough FEV1	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
2	100 mL increase FEV1	Week 52	ITT
4	100 mL increase FEV1	Week 52	≥150 eosinophils/µL <150 eosinophils/µL
8	Post-bronchodilator FEV_1	Week 52	ITT
	FEV_1 reversibility	Week 52	ITT
	Trough FVC	Week 52	ITT
	Post-bronchodilator FVC	Week 52	ITT

SGRQ			
1	**SGRQ Total score**	**Week 52**	**ITT - FF/UMEC/VI vs UMEC/VI only**
4	Total score	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
2	Responders	Week 52	ITT
4	Responders	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
2	Moderate/major responders	Week 52	ITT
2	Major responders	Week 52	ITT
Transition dyspnea index			
2	Focal score	Week 52	TDI
4	Focal score	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
2	Responders	Week 52	TDI
4	Responders	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
4	Moderate/major responders Major responders[10]	Week 52 Week 52	TDI TDI
COPD assessment test			
12	Score	Week 52	ITT
	Score	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
	Responders	Week 52	ITT
	Responders	Week 52	≥150 eosinophils/μL <150 eosinophils/μL
E-diary endpoints			
8	Subject global rating of activity limitation	Week 52	ITT
	Subject global rating of change in COPD severity	Week 52	ITT
	Occasions of rescue medication use per day by four weekly period	Weeks 49 to 52	ITT
	Percentage of rescue-free days by four weekly period	Weeks 49 to 52	ITT
2	Number of nighttime awakenings per night by four weekly period	Weeks 49 to 52	ITT
2	Percentage of days symptoms stopped usual activities by four weekly period	Weeks 49 to 52	ITT
All-cause mortality			
4	Time to all-cause mortality	On-treatment	ITT
	Time to all-cause mortality	On- and off-treatment	ITT
2	Time to all-cause mortality	On- and off-treatment plus vital status follow-up	ITT

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

34. Page 151, Table 26. SUMMIT Demographic Characteristics, ITT-E Population, final row of table should read:

Other	~~41 (1)~~ **30 (<1)**	~~32 (<1)~~ **25 (<1)**	~~32 (<1)~~ **28 (<1)**	~~42 (1)~~ **32 (<1)**	115 (<1)

35. On page 152, Table 27. SUMMIT: Baseline Disease Characteristics, ITT-E Population

- In category "Postbronchodilator FEV1"
  i. Row "N with available data"
    1. Column "FF/VI" should read "~~4,127~~ **4,120**"
    2. Column "FF" should read "~~4,141~~ **4,134**"
    3. Column "Pbo" should read "~~4,108~~ **4,111**"
- In category "GOLD spirometric severity grade*"
  i. Row "N with available data"
    1. Column "FF/VI" should read "~~4,121~~ **4,120**"
    2. Column "Pbo" should read "~~4,110~~ **4,111**"
  ii. Row "Mild"
    1. Column "FF/VI" should read "~~2 (<1)~~ **1 (<1)**"
    2. Column "Pbo" should read "~~1 (<1)~~ **2 (<1)**"

36. On page 156, Table 30. SUMMIT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Common End Date (ITT-E Including Both On- and Off-treatment Data)

- In category "FF/VI vs comparator"
  i. Row "ACM HR"
    1. Column "VI" should read "0.79 ~~(0.59, 1.06)~~"
    2. Column "Pbo" should read "0.70 ~~(0.52, 0.93)~~"
  ii. Row "95% CI"
    1. Column "VI" should read "~~0.30~~ **(0.59, 1.06)**"
    2. Column "Pbo" should read "~~0.14~~ **(0.52, 0.93)**"
- In category "FF vs. comparator"
  i. Row "ACM HR", Column "Pbo" should read "~~0.83~~ **0.84**"
  ii. Row "95% CI", Column "Pbo" should read "~~0.63, 1.10~~ **0.62, 1.13**"

37. On page 158, Table 32. SUMMIT: Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT-E Including Both On- and Off-Treatment Data)

- In category "Comparator vs FF"
    i. Row "95% CI", column "Pbo" should read "~~0.50~~ **0.47**, 3.85"

38. On page 160, Table 34. SUMMIT: Study Attrition Among Subjects Who Did Not Start Treatment by Pre-study ICS Subgroup

- Row "Run-in failure*", Column "Pre-study ICS Use", subcolumn "Yes" should read "~~90~~ **91** (30)"
- Category title "FAEs among subjects who dd not start treatment" should read "FAEs among subjects who ~~dd~~ **did** not start treatment"

39. On page 164, Table 36. TORCH: Baseline Disease Characteristics, ITT Population should read as follows to align with the data previously presented in Table 5. Baseline Disease Characteristics Across Trials: ITT Populations of IMPACT, SUMMIT, and TORCH:

Baseline Characteristics	FP/SAL	FP	SAL	Pbo	Total
Total	1,533	1,534	1,521	1,524	6,112
Postbronchodilator FEV1					
N with available data	1,524	1,529	1,516	1,515	6,084
Mean FEV1%p (SD)	44.7 (~~13.5~~**14.0**)	44.6 (13.3)	43.7 (13.3)	44.2 (13.1)	44.3 (13.5)
GOLD spirometric severity grade*					
N with available data	1,524 **1,533**	1,529 **1,534**	1,516 **1,524**	1,515 **1,524**	6,084 **6,112**
Mild	12 ~~(1)~~ **(<1)**	9 **5** ~~(1)~~ **(<1)**	2 (<1)	5 (<1)	28 (<1)
Moderate	~~549~~ **550** (36)	~~525 (34)~~ **530 (35)**	~~517~~ **520** (34)	~~527~~ **530** (35)	~~2,118~~ **2,128** (35)
Severe	~~722~~ **728** (47)	~~776~~ **775** (51)	~~738~~ **739** (49)	~~769~~ **775** (51)	~~3,005~~ **3,019** (49)
Very severe	~~241~~ **243** (16)	~~219~~ **214** (14)	~~259~~ **260** (17)	214 (14)	~~933~~ **937** (15)
Moderate AECOPD history**					
N with available data	1,533	1,534	1,521	1,524	6,112
<2	1,164 (~~75~~) **(76)**	1,144 (75)	1,131 (74)	1,126 (74)	~~4,645~~ **4,565** (75)
≥2	369 ~~(25)~~ (**24**)	390 (25)	390 (26)	398 (26)	~~1,467~~ **1,547** (25)

40. On page 165, Table 37. TORCH: Pre-study COPD Medication Groups, ITT-E Population

- In category "ICS-containing regimen"
    i. Row "Unknown or no data"
        1. Column "FP/SAL" should read "~~42 (3)~~ **32 (2)**"
        2. Column "FP" should read "~~44 (3)~~ **34 (2)**"
        3. Column "SAL" should read "~~34 (2)~~ **44 (3)**"
        4. Column "Pbo" should read "~~32 (2)~~ **42 (3)**"

41. On page 166, Table 38. TORCH: Subject Disposition, ITT Population should read:

Category	FP/SAL	FP	SAL	Pbo	Total
Total	1,533	1,534	1,521	1,524	6,112

Tx completion status					
Completed	1,011 (66)	947 (62)	960 (63)	851 (56)	3,769 (62)
Prematurely d/c	522 (34)	587 (38)	561 (37)	673 (44)	~~2,318 (38)~~ **2,343 (38)**
Adverse event	289 (~~19~~ **55**)	360 (~~23~~ **61**)	303 (~~20~~ **54**)	366 (~~24~~ **54**)	~~1,311 (57)~~ **1,318 (56)**
Lack of efficacy	33 (~~2~~ **6**)	45 (~~3~~ **8**)	63 (~~4~~ **11**)	103 (~~7~~ **15**)	244 (10)
Other reasons	200 (~~13~~ **38**)	182 (~~12~~ **31**)	195 (~~13~~ **35**)	204 (~~13~~ **30**)	781 (~~13~~ **33**)
Study completion status					
Completed	**1,011 (66)**	**947 (62)**	**960 (63)**	**851 (56)**	**3,769 (62)**
Prematurely w/d	**522 (34)**	**587 (38)**	**561 (37)**	**673 (44)**	**2,343 (38)**
Vital status data (ITT population with on-and-off treatment data)					
Complete data	**1,532 (>99)**	**1,534 (100)**	**1,521 (100)**	**1,524 (100)**	**6,111 (>99)**

Source: Reviewer, adapted from Applicant's submitted materials for the TORCH trial. Percentages for subheadings of "Prematurely ~~Discontinued~~ **d/c**" and "Prematurely withdrawn" are based upon the total number of subjects who prematurely discontinued and prematurely withdrew, respectively.
All values are expressed as n (%) unless stated otherwise.
Abbreviations: d/c, discontinued; FP/ SAL, fluticasone propionate 500 µg / salmeterol 50 µg; FP, fluticasone propionate 500 µg; f/u, follow-up; ITT, intention to treat; Pbo, placebo; SAL, salmeterol 50 µg; w/d, withdrawn; **Tx, treatment**

42. On page 168, 1st paragraph, 4th sentence should read "Similar to the paradigm of ICS removal discussed for IMPACT subgroup comparison (Section 4.5.4), under this "flipped" interpretation that describes the potential effects of ICS removal, subjects with pre-study ICS randomized to SAL (i.e., ICS removal) demonstrated a hazard ratio for death of ~~1.07~~ **1.08** (95% CI 0.8 to 1.45) compared to those randomized to FP/SAL (i.e., ICS continuation), and subjects with pre-study ICS randomized to placebo (i.e., ICS removal) demonstrated a hazard ratio for death of 1.04 (95% CI 0.8 to 1.35) compared to those randomized to FP (i.e., ICS continuation) at Week 156"

43. On page 169, Table 39. Pre-study ICS = Yes Subgroup: All-cause Mortality Subgroup Results at Week 156 (ITT-E Including Both On- and Off-treatment Data

- In category "Comparator vs FP/Sal"
  i. Row "ACM HR"
    1. Column "SAL N=701" should read "~~1.07~~ **1.08**"
    2. Column "Pbo N=803" should read "~~1.31~~ **1.32**"
  ii. Row "95% CI", Column "Pbo" should read "0.99, ~~1.72~~ **1.74**"

44. On page 172 Table 42. Pre-study ICS = No Subgroup: All-cause Mortality Subgroup Results at Day 90 (ITT-E Including Both On- and Off-treatment Data

- Column heading for "FP/SAL" should read "FP/SAL N=~~740~~ **761**"
- Column heading for "FP" should read "FP N=~~732~~ **768**"
- Column heading for "SAL" should read "SAL N=~~701~~ **776**"
- Column heading for "Pbo" should read "Pbo N=~~803~~ **679**"

45. On page 173, Table 43. TORCH: Study Attrition Among Subjects Who Did Not Start Treatment by Pre-study ICS Subgroup

- In category “Subjects with SAEs**”
    i. Row “COPD as SAE”, Column “Pre-study ICS Use”, subcolumn “Yes”, should read “~~28~~ **29** (5)”