Supplementary Material

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy compared with other therapies for the treatment of COPD: a network meta-analysis

Authors
Prof. Afisi S. Ismaila¹,², Dr. Katrin Haeussler³, Dr. Alexandrosz Czira⁴, Dr. Ji-Hee Youn⁵, Mia Malmenäs⁶, Dr. Nancy A. Risebrough⁷, Jatin Agarwal⁸, Maria Nassim³, Dr. Raj Sharma⁴, Dr. Chris Compton⁴, Prof. Claus F. Vogelmeier⁹,¹⁰, Prof. MeiLan K. Han¹¹, Prof. David M. G. Halpin¹²

Affiliations
¹Value Evidence and Outcomes, GlaxoSmithKline, Collegeville, PA, USA
²Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
³ICON Health Economics, ICON plc, Munich, Germany
⁴Value Evidence and Outcomes, R&D Global Medical, GlaxoSmithKline, Brentford, United Kingdom
⁵ICON Health Economics, ICON plc, London, United Kingdom
⁶ICON Health Economics, ICON plc, Stockholm, Sweden
⁷ICON Health Economics, ICON plc, Ontario, Canada
⁸ICON Health Economics, ICON plc, Karnataka, India
⁹Department of Medicine, Pulmonary and Critical Care Medicine, Philipps-Universität Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany
¹⁰German Center for Lung Research (DZL), Marburg, Germany
¹¹Division of Pulmonary and Critical Care, University of Michigan, MI, USA
University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, United Kingdom

**Corresponding author**

Prof. Afisi S. Ismaila

Value Evidence and Outcomes, GlaxoSmithKline

1250 South Collegeville Road, Collegeville

PA 19426-0989

USA

Tel: +1 919 315 8229

afisi.s.ismaila@gsk.com
Search Strategy

To complement the evidence from the bibliographic databases, a secondary systematic search was performed in clinical trial registries including Clinicaltrials.gov (https://clinicaltrials.gov/ct2/search/advanced), the US National Institutes of Health clinical trial register; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://apps.who.int/trialsearch/AdvSearch.aspx); Klinische Prüfungen PharmNet.Bund (http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm); the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/#searchadvanced); Australian New-Zealand Clinical Trials Registry (ANZCTR; https://www.anzctr.org.au/); and EU Clinical Trials Register (EU-CTR; www.clinicaltrialsregister.eu).

Network meta-analysis methodology

Frequentist network meta-analysis (NMA) is based on weighted least squares regression. In an ordinary least squares regression, equal variances are assumed for all observations. In a weighted least squares regression, a study with a large variance contributes less than a study with smaller variance. A frequentist NMA considers the geometry of the corresponding network and P-scores can be calculated to rank the treatments.

The residuals $e_i$ of a study $i$ are weighted by the study weight $w_i$, which is again the inverse of the corresponding within-studies variance $v_i$ in a fixed effects (FE) model or the sum of within-studies variance $v_i$ and the between studies variance $\tau^2$ in a random effects (RE) model. The analyses were based on Rücker [1] and performed with the R package netmeta [2].

The model based on weighted least square regression is given as:

$$\hat{\theta} = X\theta^{trt} + \epsilon, \quad \epsilon \sim N(0, \Sigma),$$

where $\hat{\theta}$ represents a vector of $m$ observed pairwise comparisons with known standard errors $s = (s_1, s_2, ..., s_m)$, $X$ is the $m \times n$ design matrix defining the network structure, $\theta^{trt}$ is a
vector of length \( n \) including the number of treatments, and \( \Sigma \) is a diagonal matrix whose \( i^{th} \) entry is \( s_i^2 \).

In a fictional example network with \( n = 4 \) treatments including \( k = 5 \) studies each providing a single pairwise treatment comparison, we would have \( m = 5 \) pairwise treatment comparisons and the model would be defined as

\[
\begin{pmatrix}
\hat{\theta}_{1}^{\text{AB}} \\
\hat{\theta}_{2}^{\text{BC}} \\
\hat{\theta}_{3}^{\text{CD}} \\
\hat{\theta}_{4}^{\text{AD}} \\
\hat{\theta}_{5}^{\text{BD}}
\end{pmatrix} =
\begin{pmatrix}
1 & -1 & 0 & 0 \\
0 & 1 & -1 & 0 \\
0 & 0 & 1 & -1 \\
1 & 0 & 0 & -1 \\
0 & 1 & 0 & -1
\end{pmatrix}
\begin{pmatrix}
\theta_A \\
\theta_B \\
\theta_C \\
\theta_D
\end{pmatrix} +
\begin{pmatrix}
\epsilon_1 \\
\epsilon_2 \\
\epsilon_3 \\
\epsilon_4 \\
\epsilon_5
\end{pmatrix}
\]

\[ W = \text{diag}\left(\frac{1}{s_1^2}, \ldots, \frac{1}{s_m^2}\right) \]

including the inverse variance weights. The network estimates are given by \( \hat{\theta}^{\text{NMA}} = H\hat{\theta} \), where

\[
H = X(X^T W)^+ X^T W
\]
is the hat matrix in regression. Thus, the network estimates are weighted sums of the observed estimates with weights obtained through the rows of \( H \). The corresponding standard errors are calculated from the variance-covariance matrix

\[
\text{Cov}(\hat{\theta}^{nma}) = X(X^T W X)^+ X^T.
\]

In addition, heterogeneity and inconsistency are measured by the generalized statistic

\[
Q_{\text{total}} = (\hat{\theta} - \hat{\theta}^{nma})^T W (\hat{\theta} - \hat{\theta}^{nma}).
\]

When a RE model is used rather than a FE model, the variance-covariance matrix changes. On the diagonal, \( \tau^2 \) has to be added to the variance terms for the individual arms but also to the off-diagonal elements. The off-diagonal elements correspond to the covariances between different arms of the same trial. Estimation of \( \tau^2 \) is often difficult as it cannot be directly observed. The corresponding degrees of freedom are a function of the number of studies and usually much fewer than those used to estimate the within trial variances [3].

The netmeta package also includes the possibility to run RE models based on a graph theory approach to NMA. The additional between-study variance is estimated as

\[
\tau^2 = \max \left( \frac{Q - df}{\text{tr}((U - H)I W)} \right),
\]

with

\[
df = \sum_k (k - 1)n_k - (n - 1)
\]

representing the degrees of freedom. These are summed over the study arms \( k \) over the number of studies with \( k \) arms \( n_k \). The \( m \times m \) \( U \) matrix includes the number of comparisons \( m \), and the identity matrix \( I \) is derived as \( HH^T / 2 \).

It was decided to use both the FE and RE models to obtain more and less conservative estimates, for all analyses.
Standard error estimation

For continuous outcome (difference in change from baseline [DCFB]), if the standard error (SE) was reported directly, it was used in the analysis. Otherwise, it was calculated from the standard deviation (SD) as

\[
SE(DCFB) = SD \sqrt{\frac{1}{N_T} + \frac{1}{N_C}},
\]

where \(N_T\) and \(N_C\) represent the sample size in active treatment and comparator arms, respectively. If SD was not reported, SE was estimated from a 95% confidence interval (CI) as

\[
SE(DCFB) = \frac{(UCL - LCL)}{3.92},
\]

where \(UCL\) and \(LCL\) represent upper and lower bounds of the 95% CI, and a Normal approximation was conducted.

If neither SD nor a 95% CI were reported, the SE was estimated from the SE of the change from baseline \((SE_{CFB})\) per arm as

\[
SE(DCFB) = \sqrt{SE_{CFB,T}^2 + SE_{CFB,C}^2},
\]

where \(SE_{CFB,T}^2\) and \(SE_{CFB,C}^2\) represent SE of change from baseline in active treatment and comparator arms, respectively.

If none of the above were reported, the SE was imputed from the average SD \(\overline{SD}\) of the CFB per study arm, averaging over all reported and estimated SD in the corresponding networks of evidence as

\[
SE(DCFB) = \overline{SD} \sqrt{\frac{1}{N_T} + \frac{1}{N_C}}.
\]
For multi-arm studies, if not all differences in CFB with corresponding SE for all pairwise comparisons were reported directly, these were estimated through the `pairwise` function of the R package `netmeta`; the function input was the CFB with corresponding SE per arm.

For time-to-event and count outcome, if the hazard ratios (HRs) or rate ratios (RaR) with corresponding 95% CIs were reported directly, the corresponding standard error was estimated from the CI as

\[
SE(\ln(\text{HR})) = (\ln(\text{UCL}) - \ln(\text{LCL}))/3.92,
\]

where UCL and LCL refer to the upper and lower bounds of the corresponding 95% CI. For RaR, the same equation applies.

For count outcome, if no RaR with 95% CI was reported directly, the standard error of the RaR on the log scale was estimated as

\[
SE(\ln(\text{RaR})) = \sqrt{\frac{1}{r_T} + \frac{1}{r_C}},
\]

where \(r_T\) and \(r_C\) refer to the number of events in active treatment and comparator arms, respectively. For multi-arm studies, the same approach was followed as for continuous outcome.

For binary outcome, the number of events \(r_T\) and \(r_C\) as well as sample size \(N_T\) and \(N_C\) in active treatment and comparator arms, respectively, inform the estimation of the SE of an odds ratio on the log scale as

\[
SE(\ln(\text{OR})) = \sqrt{\frac{1}{r_T} + \frac{1}{N_T - r_T} + \frac{1}{r_C} + \frac{1}{N_C - r_C}}.
\]
Data Preparation on Annual Exacerbations

As an input to the NMA, the rate ratio with corresponding SE is required on the log scale. This is usually directly reported and transformed to the log scale. In total, 17 studies reported on moderate/severe exacerbations; 8 reported adjusted rates (the output of generalized linear models adjusting for clinically relevant covariates), 7 reported raw rates (not adjusted for any covariates), and 2 reported the number of events, the sample size and the number of study withdrawals.

If not reported directly, the rate ratio can be estimated as a ratio of the reported rates $\mu_i$ and $\mu_c$ in the intervention and control groups.

If the rate ratios with corresponding 95% CIs are reported directly, the corresponding standard error is estimated from the CI as

$$SE(\ln(RR)) = (\ln(\text{Upper}) - \ln(\text{Lower}))/3.92,$$

where $\text{Upper}$ and $\text{Lower}$ refer to the upper and lower bounds of the corresponding 95% CI [4].

If no rate ratio with 95% CI is reported directly, the standard error of the rate ratio on the log scale is estimated as

$$SE(\ln(RR)) = \sqrt{\frac{1}{a} + \frac{1}{b}},$$

where $a$ and $b$ refer to the number of events in intervention $i$ and control $c$, respectively [5].

The number of events are either reported directly or can estimated through the rates $\mu_i$ and $\mu_c$ in the intervention and control groups, respectively [6], and the total person-years at risk per arm $P_i$ and $P_c$ as

$$a = \mu_i P_i$$

and

$$b = \mu_c P_c.$$
The person-years at risk $P_i$ and $P_c$ are estimated as averages of the sample sizes in the ITT population $N_i$ and the number of patients completing the study (difference in sample size of ITT population and number of withdrawals $W_i$) as

$$P_i = \frac{N_i + (N_i - W_i)}{2};$$

the estimation of the person-years at risk in the control arm $P_c$ is conducted accordingly. This equation considers the definition of person-years at risk as a cohort of people who is followed from study entry until loss to follow-up. Since we do not have individual-level data, we approximate this through an average of ITT population and those completing the study.

If rates are not reported directly, these are estimated from the number of events and person-years at risk as

$$\mu_i = aP_i$$

and

$$\mu_c = bP_c.$$
Supplementary Table S1  Overview of included trials (n = 23)

| Trial name       | Comparisons                                                                 | Study design | Total N randomized | Duration of study (weeks) | Primary outcome                          | Inclusion criteria                                                                                                                                                                                                                     | Background treatment                                                                                                                                                                                                                         |
|------------------|-----------------------------------------------------------------------------|--------------|--------------------|---------------------------|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Siler 2015 [7]   | UMEC 62.5 μg QD + FF/VI 100/25 μg QD - FF/VI 100/25 μg QD - UMEC 125 μg QD + FF/VI 100/25 μg QD | RCT, DB, MC  | 619                | 12                        | Trough FEV1 on Day 85                    | Male and female subjects, age ≥40 years; history of COPD, smoking history (current or former) of ≥10 pack-years; a pre-and post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a pre- and post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values; dyspnea score of ≥2 on the mMRC Dyspnea Scale at Visit 1; meet corrected QT interval (QTc) Criteria. | Oxygen (1% to 4% across the treatment groups), other treatments (mucolytics; cold, cough, nasal and/or throat medication; inhaled corticosteroids; short-acting anticholinergics, and SABAs) |
| NCT01957163     |                                                                             |              |                    |                           |                                          |                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                           |
| Siler 2015 [7]   | UMEC 62.5 μg QD + FF/VI 100/25 μg QD - FF/VI 100/25 μg QD - UMEC 125 μg QD + FF/VI 100/25 μg QD | RCT, DB, MC  | 620                | 12                        | Trough FEV1 on Day 85                    | Male and female subjects treated as outpatients, age ≥40 years with history of COPD; smoking history (current or former) of ≥10 pack-years; a pre and post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and a pre and post-albuterol/salbutamol FEV1 of ≥70% of predicted normal values; a dyspnea score of ≥2 on the mMRC Dyspnea Scale at Visit 1; corrected QT interval (QTc) Criteria; corrected QT interval using Fridericia’s formula (QTc(F)) <450 msec or QTc(F) <480 msec for patients with QRS duration 120 msec | Albuterol/salbutamol metered-dose-inhaler (MDI) or nebulizers were issued throughout the study for rescue medication use as needed.                                                            |
| NCT02119286     |                                                                             |              |                    |                           |                                          |                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                           |
| FULFIL [8]       | FF/UMEC/VI 100/62.5/25 μg QD - BUD/FOR 400/12 μg BD                          | RCT, DB, MC  | 1,810              | 24                        | CFB in trough FEV1 at Week 24 CFB in SGRQ Total Score at Week 24 | Male or non-pregnant female subjects age ≥40 years; COPD diagnosis (American Thoracic Society /European Respiratory Society); current or former cigarette smokers with a history of >10 pack-years; a post-bronchodilator FEV1 <50% predicted normal OR a post-bronchodilator FEV1 <80% predicted normal and a documented history of ≥2 moderate exacerbations or ≥1 severe exacerbation in the previous 12 months; post albuterol/salbutamol FEV1/FVC ratio of <0.70 at screening. | Short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study.                                                                                                                   |
| Study | NCT Number | Drug Regimen | Study Design | Sample Size | Outcome Measure | Inclusion Criteria | Intervention | Notes |
|-------|-------------|--------------|--------------|-------------|----------------|------------------|-------------|-------|
| Bremner 2018 [9] NCT02729051 | - FF/UMEC/VI 100/62.5/25 μg QD - UMEC 62.5 μg QD + FF/VI 100/25 μg QD | RCT, DB, MC | 1,055 | 24 | CFB in pre-bronchodilator FEV1 at week 24 | Male and non-pregnant, non-lactating female subjects ≥40 years of age; current or former cigarette smokers (with a history of ≥10 pack-years at Screening); diagnosed with COPD as defined by the ATS/ERS with at Screening: 1) A score of ≥10 on the COPD Assessment Test, collected prior to spirometry. 2) A post-bronchodilator FEV1 of <50% predicted normal and a documented history of ≥1 moderate COPD exacerbation or ≥1 severe (hospitalized) exacerbation in the previous 12 months OR a post-bronchodilator FEV1 of ≥50% and <80% predicted normal and a documented history of ≥2 moderate exacerbations or ≥1 severe (hospitalized) exacerbation in the previous 12 months. 3) A post-bronchodilator FEV1/forced vital capacity (FVC) ratio of <0.70. 4) Have been receiving daily maintenance treatment for their COPD for at least three months | Study-supplied rescue salbutamol as needed |
| IMPACT [10] NCT02164513 | - FF/UMEC/VI 100/62.5/25 μg QD - FF/VI 100/25 μg QD - UMEC/VI 62.5/25 μg QD | RCT, DB, MC | 10,355 | 52 | Annual rate of moderate/severe exacerbations | Male and non-pregnant, non-lactating female subjects aged ≥40 years; diagnosis of COPD according to ATS-ERS criteria; cigarette smoking history ≥10 pack-years; a score of ≥10 on the COPD Assessment Test; post-albuterol FEV1/FVC of <0.70; have been receiving daily maintenance treatment for their COPD for at least three months; a post-bronchodilator FEV1 of <50% predicted normal and a documented history of ≥1 moderate COPD exacerbation or ≥1 severe (hospitalized) exacerbation in the previous 12 months OR a post-bronchodilator FEV1 of ≥50% and <80% predicted normal and a documented history of ≥2 moderate exacerbations or ≥1 severe (hospitalized) exacerbation in the previous 12 months | Study-supplied rescue salbutamol as needed, mucolytics, long-term oxygen therapy, maintenance phase of pulmonary rehabilitation treatment |
| Ferguson 2020 [11] NCT03478683 | - FF/UMEC/VI 100/62.5/25 μg QD - TIO 18 μg QD + BUD/FOR 320/9 μg BD | RCT, DB, triple dummy, parallel-group, MC | 729 | 12 | The weighted mean change from baseline in FEV1 over 0-24 hours at Week 12 | Eligible participants were male or female, aged ≥40 years, current or former smokers, with an established clinical history of COPD, receiving COPD maintenance treatment for at least 3 months prior to Screening, with a post-bronchodilator FEV1 of <50% predicted normal or <80% predicted normal and a documented history of ≥2 moderate or 1 severe exacerbations in the previous 12 months | Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study. |
| Study | Author | Study ID | Treatment | Design | N | Week | Summary | Participants | Notes |
|-------|--------|----------|-----------|--------|----|------|---------|--------------|-------|
| Ferguson 2020 [11] NCT03478696 | - FF/UMEC/VI 100/62.5/25 μg QD - TIO 18 μg QD + BUD/FOR 320/9 μg BD | RCT, DB, triple dummy parallel-group, MC | 732 | 12 | The weighted mean change from baseline in FEV1 over 0-24 hours at Week 12 | Eligible participants were male or female, aged ≥40 years, current or former smokers, with an established clinical history of COPD, receiving COPD maintenance treatment for at least 3 months prior to Screening, with a post-bronchodilator FEV1 of <50% predicted normal or <80% predicted normal and a documented history of ≥2 moderate or 1 severe exacerbation in the 12 months prior to Screening, and a COPD Assessment Test (CAT) score of ≥10 at Screening. | Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study. |
| Obeid 2020 [12] NCT03474081 | - FF/UMEC/VI 100/62.5/25 μg QD - TIO 18 μg QD | RCT, PC, DB, double dummy, parallel group, MC | 800 | 12 | Trough FEV1 on treatment Day 85 | Eligible participants were male or female who were non-pregnant, non-lactating, not of childbearing potential or of childbearing potential that followed contraceptive guidance, aged ≥40 years, current or former smokers (≥10 pack-years at screening), with an established clinical history of COPD, receiving COPD daily maintenance treatment with TIO alone for at least 3 months prior to Screening, with a post-bronchodilator forced expiratory volume in 1 second (FEV1) of <50% predicted normal or <80% predicted normal and a documented history of ≥2 moderate exacerbations or 1 severe (hospitalized) exacerbation in the 12 months prior to Screening, and a COPD Assessment Test (CAT) score of ≥10 at Screening. Participant eligibility also included being symptomatic at Screening and at Randomization. | Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study. |
| Sousa 2016 [13] NCT02257372 | - UMEC 62.5 μg QD + ICS/LABA QD - ICS/LABA* QD | RCT, DB, MC | 236 | 12 | Trough FEV1 on Day 85 | Male and female subjects, treated as outpatients, age ≥40 years; established clinical history of COPD; smoking history (current or former) of ≥10 pack-years; a pre-and post-albuterol/salbutamol FEV1/FVC ratio of <0.70; a pre-and post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values; a dyspnea score of ≥2 on the mMRC Dyspnea Scale at Visit 1 | NR |

**UMEC 62.5 + ICS/LABA**

| Study | Author | Study ID | Treatment | Design | N | Week | Summary | Participants | Notes |
|-------|--------|----------|-----------|--------|----|------|---------|--------------|-------|
| Ferguson 2020 [11] NCT03478696 | - FF/UMEC/VI 100/62.5/25 μg QD - TIO 18 μg QD + BUD/FOR 320/9 μg BD | RCT, DB, triple dummy parallel-group, MC | 732 | 12 | The weighted mean change from baseline in FEV1 over 0-24 hours at Week 12 | Eligible participants were male or female, aged ≥40 years, current or former smokers, with an established clinical history of COPD, receiving COPD maintenance treatment for at least 3 months prior to Screening, with a post-bronchodilator FEV1 of <50% predicted normal or <80% predicted normal and a documented history of ≥2 moderate or 1 severe exacerbation in the 12 months prior to Screening, and a COPD Assessment Test (CAT) score of ≥10 at Screening. | Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study. |
| Obeid 2020 [12] NCT03474081 | - FF/UMEC/VI 100/62.5/25 μg QD - TIO 18 μg QD | RCT, PC, DB, double dummy, parallel group, MC | 800 | 12 | Trough FEV1 on treatment Day 85 | Eligible participants were male or female who were non-pregnant, non-lactating, not of childbearing potential or of childbearing potential that followed contraceptive guidance, aged ≥40 years, current or former smokers (≥10 pack-years at screening), with an established clinical history of COPD, receiving COPD daily maintenance treatment with TIO alone for at least 3 months prior to Screening, with a post-bronchodilator forced expiratory volume in 1 second (FEV1) of <50% predicted normal or <80% predicted normal and a documented history of ≥2 moderate exacerbations or 1 severe (hospitalized) exacerbation in the 12 months prior to Screening, and a COPD Assessment Test (CAT) score of ≥10 at Screening. Participant eligibility also included being symptomatic at Screening and at Randomization. | Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study. |
| Sousa 2016 [13] NCT02257372 | - UMEC 62.5 μg QD + ICS/LABA QD - ICS/LABA* QD | RCT, DB, MC | 236 | 12 | Trough FEV1 on Day 85 | Male and female subjects, treated as outpatients, age ≥40 years; established clinical history of COPD; smoking history (current or former) of ≥10 pack-years; a pre-and post-albuterol/salbutamol FEV1/FVC ratio of <0.70; a pre-and post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values; a dyspnea score of ≥2 on the mMRC Dyspnea Scale at Visit 1 | NR |
| Study               | Intervention                                                                 | NCT Number   | Weekly Dose | Primary Endpoint                                 |
|---------------------|-------------------------------------------------------------------------------|--------------|-------------|-------------------------------------------------|
| Siler 2016 [14]     | **RCT, DB, MC** UMEC 62.5 μg QD + FP/SAL 250/50 μg BD **UMEC 125 μg QD +**  | NCT01772134 | 617         | Trough FEV1 on treatment Day 85                  |
|                     | **FP/SAL 250/50 μg BD** **UMEC 125 μg QD + FP/SAL 250/50 μg BD** **FP/SAL**  |              |             | Male and female subjects, age ≥40 years;        |
|                     | **250/50 μg BD** **UMEC 62.5 μg QD + FP/SAL 250/50 μg BD** **FP/SAL 250/50** |              |             | established clinical history of COPD in         |
|                     | **μg BD**                                                                      |              |             | accordance with the definition by the American  |
|                     |                                                                               |              |             | Thoracic Society/European Respiratory Society;  |
|                     |                                                                               |              |             | current or former cigarette smokers with a      |
|                     |                                                                               |              |             | history of smoking of ≥10 pack-years; a pre-     |
|                     |                                                                               |              |             | and post-salbutamol FEV1/FVC ratio of <0.70 and  |
|                     |                                                                               |              |             | a pre- and post-salbutamol FEV1 of ≤70% of      |
|                     |                                                                               |              |             | predicted normal values; a score of ≥2 on the   |
|                     |                                                                               |              |             | mMRC Dyspnea Scale                              |
| Siler 2016 [14]     | **RCT, DB, MC** UMEC 62.5 μg QD + FP/SAL 250/50 μg BD **UMEC 125 μg QD +**  | NCT01772147 | 608         | Trough FEV1 on treatment Day 85                  |
|                     | **FP/SAL 250/50 μg BD** **UMEC 125 μg QD + FP/SAL 250/50 μg BD** **FP/SAL**  |              |             | Male and female subjects, age ≥40 years;        |
|                     | **250/50 μg BD** **UMEC 62.5 μg QD + FP/SAL 250/50 μg BD** **FP/SAL 250/50** |              |             | established clinical history of COPD in         |
|                     | **μg BD**                                                                      |              |             | accordance with the definition by the American  |
|                     |                                                                               |              |             | Thoracic Society/European Respiratory Society;  |
|                     |                                                                               |              |             | current or former cigarette smokers with a      |
|                     |                                                                               |              |             | history of smoking of ≥10 pack-years; a pre-     |
|                     |                                                                               |              |             | and post-salbutamol FEV1/FVC ratio of <0.70 and  |
|                     |                                                                               |              |             | a pre- and post-salbutamol FEV1 of ≤70% of      |
|                     |                                                                               |              |             | predicted normal values; a score of ≥2 on the   |
|                     |                                                                               |              |             | mMRC Dyspnea Scale                              |
| **TIO 18 + BDP/FOR 100/6** | **RCT, DB, MC** TIO 18 μg QD + BDP/FOR 100/6 μg two actuations BD | NCT01397890 | 578         | Exacerbation rate after 52 weeks                |
| **TRINITY [15]**    | **BDP/FOR/GLY 100/6/12.5 μg two actuations BD** **TIO 18 μg QD**              |              |             | Male and female subjects, age ≥40 years;        |
|                     |                                                                               |              |             | current or ex-smokers; had a diagnosis of COPD,  |
|                     |                                                                               |              |             | with post bronchodilator (salbutamol 400 μg)    |
|                     |                                                                               |              |             | FEV1 of less than 50% and a ratio of FEV1/FVC    |
|                     |                                                                               |              |             | of less than 0.7; COPD Assessment Test total     |
|                     |                                                                               |              |             | score of at least 10; ≥1 moderate or severe     |
|                     |                                                                               |              |             | COPD exacerbation in the previous 12 months      |
| **SECURE 1 [16]**   | **RCT, OL, MC** TIO 18 μg QD                                                 | NCT01397890 | 578         | CFB in pre-dose FEV1 week 1.6, and 12            |
|                     |                                                                               |              |             | Male and female subjects, age ≥40 years;        |
|                     |                                                                               |              |             | Diagnosis of COPD with symptoms for > 2 years;  |
|                     |                                                                               |              |             | a history of ≥ 1 COPD exacerbation requiring a   |
|                     |                                                                               |              |             | course of oral steroids and/or antibiotics      |
|                     |                                                                               |              |             | within 1-2 months; a current or prior smoking   |
|                     |                                                                               |              |             | history of ≥ 10 pack years; pre-                 |
|                     |                                                                               |              |             | bronchodilator forced expiratory volume in 1s    |
|                     |                                                                               |              |             | (FEV1) ration <70%                               |
| Study          | Intervention                                                                 | Design | Sample Size | Follow-Up | Criteria                                                                                                                                                                                                 | Medication                                                                 |
|---------------|------------------------------------------------------------------------------|--------|-------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| **Welte 2009** [17] NCT00496470 | - TIO 18 μg QD + BUD/FOR 320/9 μg BD  
- TIO 18 μg QD | RCT, DB, MC | 660         | 12        | Male and female subjects aged ≥ 40 years, eligible for inhaled corticosteroid/long-acting β2-agonist (ICS/LABA) combination therapy; a clinical diagnosis of COPD and symptoms for at least 2 years; at least one COPD exacerbation in the previous 12 months requiring systemic steroids and/or antibiotics; current or previous smokers with a smoking history of ≥ 10 pack-years; FEV1 ≤ 50% of predicted normal value and FEV1/FVC< 70% pre-dose | Terbutaline 0.5mg/ inhalation when needed                                   |
| **TRILOGY [18] NCT01917331** | - BDP/GLY/FOR 100/12.5/6 μg two actuations BD  
- BDP/FOR 100/6 μg two actuations BD | RCT, DB, MC | 1,368       | 52        | Male and female subjects; age ≥40 years; having a diagnosis of COPD; a post-bronchodilator FEV1 of < 50% and a ratio of FEV1/FVC < 0.7; at least one moderate or severe COPD exacerbation in the previous 12 months; CAT total score of 10 or more; a BDI focal score of ≤10 at screening | Salbutamol (100 μg per actuation by pressurized metered dose inhaler) as rescue medication |
| **TRISTAR [19] NCT02467452 2014-001487-35** | - BDP/GLY/FOR 100/12.5/6 μg two actuations BD  
- FF/VI 100/25 μg QD + TIO 18 μg QD | RCT, OL, MC | 1,157       | 26        | Male and female subjects; age ≥40 years; having a diagnosis of COPD for at least 12 month; current or previous smokers with a smoking history of at least 10 pack-years; post-bronchodilator FEV1 of <50% predicted and a ratio of FEV1/FVC <0.7; at least one COPD exacerbation in the previous 12 months; CAT total score of 10 or more; under double therapy for ≥2 months with ICS plus LABA or LAMA, or with LABA/LAMA double combination | NR                                                                       |
| **TRIBUTE [20] NCT02579850** | - BDP/GLY/FOR 87/9/5 μg two actuations BD  
- IND/GLY 85/43 μg QD | RCT, DB, MC | 1,532       | 52        | Male and female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure; Patients with a diagnosis of severe or very severe COPD airflow obstruction (according to GOLD document, updated 2014) at least 12 months before the screening visit; Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack years [pack-years = (number of cigarettes per day x number of years)/20]; A post-bronchodilator FEV1 <50% of the predicted normal value and a post- | NR                                                                       |
bronchodilator FEV1/FVC ratio <0.7. (Post-bronchodilator means at least 10-15 min after 4 puffs (4 x 100 μg) of salbutamol pMDI). If this criterion is not met at screening, the test can be repeated once before randomization visit; A documented history of at least one exacerbation in the 12 months preceding the screening visit; Patients under double therapy for at least 2 months prior to screening. Double therapy was defined by treatment with any of the following: Orally inhaled corticosteroids and long-acting β2-agonist or orally inhaled corticosteroids and long-acting muscarinic antagonist or orally inhaled long-acting β2-agonist and inhaled long-acting muscarinic antagonist or patients under monotherapy with long-acting muscarinic antagonist for at least 2 months prior to screening; Symptomatic patients at screening with a CAT score ≥ 10; A cooperative attitude and ability to use correctly the pMDI inhalers and Breezhaler® inhalers; A cooperative attitude and ability to use correctly the spacer AeroChamber PlusTM Flow-Vu antistatic. The criterion on spacer applies only to patients who are using a spacer for the administration of their COPD medications at screening; A cooperative attitude and ability to use correctly electronic devices with COPD questionnaire.  

| KRONOS [21] NCT02497001 | BUD/GLY/FOR 320/18/9.6 μg BD | BUD/GLY/FOR 18/9.6 μg BD | RCT, DB, MC* | 1,902 | 24 | Europe and Canada: FEV1 AUC from 0-4h, CFB of morning pre-dose trough FEV1 over 24 weeks, non-inferiority of BUD/FOR MDI versus BUD/FOR DPI with margin of -50mL from Male and female adults aged 40–80 years; Current or former smokers (with a smoking history of ≥10 packyears; Established clinical history of COPD, as defined by the ATS/ERS, or by locally applicable guidelines and confirmed by the investigator; Mild to very severe COPD (25%≤ post-bronchodilator FEV1<80%, according to predicted normal values using National Health and Nutrition Examination Survey III reference equations; or applicable reference norms for Japan and China (adjustment factor of 0.88)); Symptomatic (CAT ≥10) patients despite receiving ≥2 inhaled maintenance therapies for Salbutamol allowed as rescue medication |
| Study | Treatment | Study Design | N | Duration | Endpoint | Inclusion Criteria |
|-------|-----------|--------------|---|----------|----------|-------------------|
| **KRONOS Extension (Safety population; US patients)** NCT02536508 | - BUD/GLY/FOR 320/18/9.6 μg BD  - GLY/FOR 18/9.6 μg BD  - BUD/FOR MDI 320/9.6 μg BD  - BUD/FOR DPI 400/12 μg BD | RCT, DB, MC*  *One arm OL | 627 | 24 weeks | safety and tolerability at Week 52 (CFB in BMD of lumbar spine + LOCS III (P) Score) | Given their signed written informed consent to participate. Must have agreed to participate in and complete the lead-in study KRONOS (NCT02497001) |
| **ETHOS [22]** NCT02465567 | - BUD/GLY/FOR 320/18/9.6 μg BD  - GLY/FOR 18/9.6 μg BD  - BUD/FOR MDI 320/9.6 μg BD | RCT, DB | 8,588 | 52 weeks | Rate of moderate or severe COPD exacerbations | Male and female; 40–80 years of age; established clinical history of COPD with post-bronchodilator FEV1/FVC ratio <0.70 and FEV1 <65% predicted normal; current or former smokers with a smoking history of ≥10 pack-years; CAT score ≥10; receiving ≥ 2 inhaled maintenance therapies for COPD for ≥6 weeks prior to screening (could include scheduled SABA and/or SAMA); history of moderate or severe COPD exacerbations in the 12 months prior to screening (if post-bronchodilator FEV1 <50% of predicted normal: ≥1 moderate or severe; if post-bronchodilator FEV1 ≥50% of predicted normal: ≥ 2 moderate or ≥ 1 severe) |
| **GLISTEN [23]** NCT01513460 | - TIO 18 μg QD + FP/SAL 500/50 μg BD  - GLY 50 μg QD + FP/SAL 500/50 μg BD  - FP/SAL 500/50 μg BD | RCT, blinded, MC | 773 | 12 weeks | FEV1 following 12 weeks of treatment | Male and female subjects age ≥40 years; a smoking history of ≥10 pack years; a diagnosis of moderate to severe stable COPD (GOLD guidelines 2010–19); a post-bronchodilator FEV1/FVC ratio <0.7 and an FEV1 ≥30% and <80% of predicted values |

**Note:** 95% CI: lower bound of Japan and China: NR (only available in protocol text). ≥6 weeks before screening; Patients had to show that they could use an MDI correctly, with training provided if needed; Not required to have had a COPD exacerbation within the preceding year. Salbutamol allowed as rescue medication.
| Study | Design | Pct | Weeks | Description |
|-------|--------|-----|-------|-------------|
| Aaron 2007 [24] ISRCTN29870041 | RCT, DB, MC | 449 | 52 | Proportion of patients who experienced a COPD exacerbation within 52 weeks of randomization |
| Hanania 2012 [25] ADC111114 NCT00784550 | RCT, DB, MC | 342 | 24 | AM pre-dose FEV1 at endpoint |
| Jung 2012 [26] A102065 | RCT, OL, MC | 479 | 24 | Mean CFB in pre-bronchodilator FEV1 (L) at week 24 |

**KRONOS Extension (Safety population) NCT02536508** is listed for completeness but is not counted as a unique trial

*BDP* beclomethasone dipropionate, *BD* twice daily, *BDI* baseline dyspnea index, *BMI* body mass index, *BUD* budesonide, *CAT score* COPD assessment test score, *CFB* change from baseline, *COPD* chronic obstructive pulmonary disease, *DB* double blind, *FF* fluticasone furoate, *FEV1* forced expiratory volume 1, *FOR* formoterol, *FVC* forced vital capacity, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *IND* indacaterol, *ITT* intention to treat, *LABA* long-acting β2 agonist, *LAMA* long-acting muscarinic receptor antagonist, *LOCS* lens opacities classification system, *mMRC* modified Medical Research Council, *MC* multi-center, *NR* not reported, *OL* open label, *QD* once daily, *SABA* short-acting β2-adrenergic, *SAL* salmeterol, *SGRQ* Saint George’s Respiratory Questionnaire, *TIO* tiotropium, *μg* microgram, *UMEC* umeclidinium bromide, *VI* vilanterol
**Supplementary Table S2** Summary of patient characteristics from included trials ($n = 23$)

| Trial name          | Comparisons                        | ITT (N) | % Male | Age   | % Current smoker | % Severe or very severe COPD | % of pts with ≥1 exacerbation in the previous yrs | % of pts with ≥2 exacerbations in previous yrs | % ICS at baseline | Mean / Median COPD duration (in yrs) |
|---------------------|------------------------------------|---------|--------|-------|------------------|-------------------------------|------------------------------------------------|-----------------------------------------------|------------------|-----------------------------------|
| Siler 2015 [7]      | UMEC 62.5 µg QD + FF/VI 100/25 µg QD | 206     | 67.0%  | 64.9  | 39.0%            | 61.0%                        | 22.0%                                          | 5.0%                                          | 66.0%            | NR                                |
|                     | FF/VI 100/25 µg QD                 | 206     | 68.0%  | 64.7  | 44.0%            | 60.0%                        | 24.0%                                          | 3.0%                                          | 62.0%            | NR                                |
|                     | UMEC 125 µg QD + FF/VI 100/25 µg QD| 207     | 61.0%  | 63.8  | 42.0%            | 60.0%                        | 21.5%                                          | 5.5%                                          | 61.0%            | NR                                |
| Siler 2015 [7]      | UMEC 62.5 µg QD + FF/VI 100/25 µg QD| 206     | 66.0%  | 62.6  | 58.0%            | 52.0%                        | 17.5%                                          | 2.5%                                          | 45.0%            | NR                                |
|                     | FF/VI 100/25 µg QD                 | 206     | 61.0%  | 62.6  | 58.0%            | 54.0%                        | 20.0%                                          | 5.5%                                          | 48.0%            | NR                                |
|                     | UMEC 125 µg QD + FF/VI 100/25 µg QD| 207     | 63.0%  | 63.4  | 56.0%            | 50.0%                        | 23.5%                                          | 4.5%                                          | 44.0%            | NR                                |
| FULFIL [8]          | FF/UMEC/VI 100/62.5/25 µg QD       | 210     | 74.4%  | 64.2  | 43.9%            | 67.2%                        | 65.6%                                          | 38.0%                                         | 65.5%            | 7.7                               |
|                     | BUD/FOR 400/12 µg BD               | 220     | 73.7%  | 63.7  | 43.8%            | 67.4%                        | 64.7%                                          | 36.6%                                         | 66.7%            | 7.5                               |
| Bremner 2018 [9]    | FF/UMEC/VI 100/62.5/25 µg QD       | 527     | 74.0%  | 66.7  | 40.0%            | 66.0%                        | 100.0%                                         | 55.0%                                         | 73.0%            | NR                                |
|                     | UMEC 62.5 µg QD + FF/VI 100/25 µg QD| 528     | 75.0%  | 65.9  | 36.0%            | 62.0%                        | 100.0%                                         | 57.0%                                         | 71.0%            | NR                                |
| IMPACT [10]         | FF/UMEC/VI 100/62.5/25 µg QD       | 4151    | 67.0%  | 65.3  | 35.0%            | 63.0%                        | >99.0%                                         | 55.0%                                         | 72.0%            | NR                                |
|                     | FF/VI 100/25 µg QD                 | 4134    | 66.0%  | 65.3  | 34.0%            | 64.0%                        | >99.0%                                         | 54.0%                                         | 70.0%            | NR                                |
|                     | UMEC/VI 62.5/25 µg QD              | 2070    | 66.0%  | 65.2  | 35.0%            | 64.0%                        | >99.0%                                         | 55.0%                                         | 72.0%            | NR                                |
| Ferguson 2020 [11]  | FF/UMEC/VI 100/62.5/25 µg QD       | 363     | 50.0%  | 65.4  | 51.0%            | 79.0%                        | 40.0%                                          | 40.0%                                         | 67.0%            | 10.48                             |
|                     | TIO 18 µg QD + BUD/FOR 320/9 µg BD | 365     | 55.0%  | 64.9  | 46.0%            | 77.0%                        | 41.0%                                          | 41.0%                                         | 68.0%            | 9.87                              |
| Ferguson 2020 [11]  | FF/UMEC/VI 100/62.5/25 µg QD       | 366     | 51.0%  | 65.5  | 46.0%            | 80.0%                        | 40.0%                                          | 40.0%                                         | 71.0%            | 10.42                             |
|                     | TIO 18 µg QD + BUD/FOR 320/9 µg BD | 366     | 51.0%  | 65.1  | 52.0%            | 77.0%                        | 42.0%                                          | 42.0%                                         | 65.0%            | 9.69                              |
| Trial name                     | Comparisons                              | ITT (N) | % Male | Age | % Current smoker | % Severe or very severe COPD | % of pts with ≥1 exacerbation in the previous yrs | % of pts with ≥2 exacerbations in previous yrs | % ICS at baseline | Mean / Median COPD duration (in yrs) |
|-------------------------------|------------------------------------------|---------|--------|-----|------------------|-------------------------------|------------------------------------------------|-----------------------------------------------|------------------|--------------------------------------|
| Obeid 2020 [12]               | FF/UMEC/VI 100/62.5/25 μg QD             | 400     | 69.0%  | 66.2| 47.0%            | 53.0%                         | 71.0%                                          | 71.0%                                         | <10.0%           | 8.5                                  |
|                              | TIO 18 μg QD                             | 400     | 67.0%  | 66.1| 48.0%            | 51.0%                         | 73.0%                                          | 73.0%                                         | 0                | 8.42                                 |
| Sousa 2016 [13]               | UMEC 62.5 + ICS/LABA                     | 119     | 70%    | 65.2| 49.0%            | 52.0%                         | 23.5%                                          | 4.5%                                          | >99.0%           | NR                                   |
|                              | ICS/LABA                                 | 117     | 64%    | 63.1| 61.0%            | 56.0%                         | 35.0%                                          | 5.0%                                          | 100.0%           | NR                                   |
| Siler 2016 [14]               | UMEC 62.5 μg QD + FP/SAL 250/50 μg BD    | 204     | 65.0%  | 62.7| 50.0%            | 56.0%                         | 18.6%                                          | 5.9%                                          | 55.0%            | NR                                   |
|                              | UMEC 125 μg QD + FP/SAL 250/50 μg BD     | 205     | 69.0%  | 63.2| 56.0%            | 55.0%                         | 24.4%                                          | 4.9%                                          | 52.0%            | NR                                   |
|                              | FP/SAL 250/50 μg BD                      | 205     | 64.0%  | 63.4| 57.0%            | 51.0%                         | 18.5%                                          | 2.9%                                          | 48.0%            | NR                                   |
| Siler 2016 [14]               | UMEC 62.5 μg QD + FP/SAL 250/50 μg BD    | 203     | 69.0%  | 64.5| 36.0%            | 65.0%                         | 32.5%                                          | 10.3%                                         | 59.0%            | NR                                   |
|                              | UMEC 125 μg QD + FP/SAL 250/50 μg BD     | 202     | 59.0%  | 65.5| 39.0%            | 53.0%                         | 29.7%                                          | 7.9%                                          | 60.0%            | NR                                   |
|                              | FP/SAL 250/50 μg BD                      | 201     | 61.0%  | 65.7| 38.0%            | 61.0%                         | 30.8%                                          | 6.0%                                          | 60.0%            | NR                                   |
| TRINITY [15] NCT01911364      | TIO 18 μg QD + BDP/FOR 100/6 μg two actuations BD | 537     | 74.0%  | 62.6| 50.0%            | 100%                          | 100.0%                                         | NR                                            | 73.0%            | 7.8                                  |
|                              | BDP/FOR/GLY 100/6/12.5 μg two actuations BD | 1077    | 77.0%  | 63.4| 48.0%            | 100%                          | 100.0%                                         | NR                                            | 77.0%            | 7.9                                  |
|                              | TIO 18 μg QD                             | 1076    | 77.0%  | 63.3| 47.0%            | 100%                          | 100.0%                                         | NR                                            | 78.0%            | 8.2                                  |
| SECURE 1 [16] NTC01397890     | TIO 18 μg QD + BUD/FOR 320/9 μg BD       | 287     | 97.2%  | 66.6| NR               | 91.6%                         | 100.0%                                         | NR                                            | NR               | 4.6                                  |
| Trial name | Comparisons | ITT (N) | % Male | Age | % Current smoker | % Severe or very severe COPD | % of pts with ≥1 exacerbation in the previous yrs | % of pts with ≥2 exacerbations in previous yrs | % ICS at baseline | Mean / Median COPD duration (in yrs) |
|------------|-------------|---------|--------|-----|-----------------|-----------------------------|-------------------------------------------------|---------------------------------|-----------------|----------------------------------|
| TIO 18 μg QD | TIO 18 μg QD | 290 | 94.1% | 66.9 | NR | 93.5% | 100.0% | NR | NR | 4.7 |
| Welte 2009 [17] NCT00496470 | TIO 18 μg QD + BUD/FOR 320/9 μg BD | 329 | 76.0% | 62.4 | NR | NR | 100.0% | NR | 67.0% | 5.7 |
| TIO 18 μg QD | TIO 18 μg QD | 331 | 74.0% | 62.5 | NR | NR | 100.0% | NR | 60.0% | 5.7 |
| TRILOGY [18] NCT01917331 | BDP/GLY/FOR 100/12.5/6 μg two actuations BD | 687 | 74.0% | 63.3 | 47.0% | 100.0% | NR | 75.0% | 7.7 |
| TRILOGY [18] NCT01917331 | BDP/GLY/FOR 100/12.5/6 μg two actuations BD | 680 | 77.0% | 63.8 | 47.0% | 100.0% | NR | 73.0% | 7.7 |
| TRISTAR [19] NCT02467452 2014-001487-35 | BDP/GLY/FOR 100/12.5/6 μg two actuations BD | 578 | 77.0% | 63.6 | NR | 100.0% | NR | NR | NR |
| TRISTAR [19] NCT02467452 2014-001487-35 | FF/VI 100/25 μg QD + TIO 18 μg QD | 579 | 74.1% | 64.2 | NR | 100.0% | NR | NR | NR |
| TRIBUTE [20] NCT02579850 | BDP/GLY/FOR 87/9/5 μg two actuations BD | 764 | 72.0% | 64.4 | 46.0% | 100.0% | 100.0% | 20.0% | 66.0% | 8.16 |
| TRIBUTE [20] NCT02579850 | IND/GLY 85/43 μg QD | 768 | 72.0% | 64.5 | 43.0% | 100.0% | 100.0% | 18.0% | 64.0% | 7.99 |
| BUD/GLY/FOR 320/18/9.6 | BUD/GLY/FOR 320/18/9.6 μg BD | 639 | 72.0% | 64.9 | 40.1% | 51.2% | 26.6% | 7.0% | 72.6% | 7.1 |
| BUD/GLY/FOR 320/18/9.6 | GLY/FOR 18/9.6 μg BD | 625 | 68.8% | 65.1 | 41.1% | 51.0% | 24.3% | 7.0% | 71.5% | 6.5 |
| BUD/GLY/FOR 320/18/9.6 | BUD/FOR MDI 320/9.6 μg BD | 314 | 71.3% | 65.2 | 36.6% | 50.6% | 25.2% | 5.7% | 71.7% | 7.3 |
| BUD/GLY/FOR 320/18/9.6 | BUD/FOR DPI 400/12 μg BD | 318 | 74.2% | 65.9 | 38.4% | 49.7% | 26.4% | 7.9% | 70.8% | 6.7 |
| KRONOS [21] NCT02497001 | BUD/GLY/FOR 320/18/9.6 μg BD | 194 | 52.6% | 62.6 | 52.1% | 51.0% | 21.6% | 4.6% | 78.4% | 8.6 |
| KRONOS Extension (Safety population ; US patients) NCT02536508 | GLY/FOR 18/9.6 μg BD | 88 | 50.0% | 62.4 | 54.6% | 47.7% | 23.9% | 3.4% | 73.0% | 7.7 |
| KRONOS Extension (Safety population ; US patients) NCT02536508 | BUD/FOR MDI 320/9.6 μg BD | 174 | 60.2% | 64.0 | 47.7% | 48.8% | 25.8% | 6.3% | 83.0% | 9.6 |
| KRONOS Extension (Safety population ; US patients) NCT02536508 | BUD/FOR DPI 400/12 μg BD | NR | NR | NR | NR | NR | NR | NR | NR |
| Trial name                        | Comparisons                                      | ITT (N) | % Male | Age  | % Current smoker | % Severe or very severe COPD | % of pts with ≥1 exacerbation in the previous yrs | % of pts with ≥2 exacerbations in previous yrs | % ICS at baseline | Mean / Median COPD duration (in yrs) |
|----------------------------------|--------------------------------------------------|---------|--------|------|-----------------|-----------------------------|------------------------------------------------|------------------------------------------------|------------------|-------------------------------|
| ETHOS [22]                       | BUD/GLY/FOR 320/18/9.6 μg BD                     | 2137    | 59.0%  | 64.6 | 42.6%           | 100.0%                      | 77.0%                                          | 55.9%                                          | 79.8%            | 8.4                           |
|                                  | BUD/GLY/FOR 160/18/9.6 μg BD                      | 2121    | 61.2%  | 64.6 | 40.8%           | 100.0%                      | 77.8%                                          | 56.0%                                          | 81.5%            | 8.2                           |
|                                  | GLY/FOR 18/9.6 μg BD                              | 2120    | 58.7%  | 64.8 | 40.4%           | 100.0%                      | 77.3%                                          | 57.1%                                          | 80.5%            | 8.2                           |
|                                  | BUD/FOR MDI 320/9.6 μg BD                         | 2131    | 60.0%  | 64.6 | 40.5%           | 100.0%                      | 78.6%                                          | 57.1%                                          | 80.0%            | 8.4                           |
| GLISTEN [23]                     | TIO 18 μg QD + FP/SAL 500/50 μg BD                | 258     | 62.0%  | 68.0 | 35.7%           | 32.2%                       | 35.7%                                          | NR                                            | 66.3%            | 6.5                           |
|                                  | GLY 50 μg QD + FP/SAL 500/50 μg BD                | 258     | 63.4%  | 68.2 | 35.4%           | 33.1%                       | 35.0%                                          | NR                                            | 62.6%            | 7.0                           |
|                                  | FP/SAL 500/50 μg BD                               | 257     | 67.7%  | 67.8 | 36.2%           | 31.5%                       | 33.9%                                          | NR                                            | 68.1%            | 7.2                           |
| Aaron 2007 [24] ISRCTN29870041  | TIO 18 μg QD + FP/SAL 500/50 μg BD                | 145     | 58.0%  | 67.5 | 32.4            | NR                          | 100.0%                                         | NR                                            | 72.8%            | 10.3                          |
|                                  | TIO 18 μg QD + SAL 50 μg BD                       | 148     | 58.0%  | 67.6 | 24.3            | NR                          | 100.0%                                         | NR                                            | 78.8%            | 10.7                          |
|                                  | TIO 18 μg QD                                      | 156     | 54.0%  | 68.1 | 26.9            | NR                          | 100.0%                                         | NR                                            | 77.2%            | 11.3                          |
| Hanania 2012 [25] ADC111114      | TIO 18 μg QD + FP/SAL 250/50 μg BD                | 173     | 50.0%  | 61.3 | 59.0%           | NR                          | 35.3%                                          | 6.4%                                          | NR               | 6.9                           |
|                                  | TIO 18 μg QD                                      | 169     | 43.0%  | 61.0 | 57.0%           | NR                          | 30.2%                                          | 5.9%                                          | NR               | 6.4                           |
| Jung 2012 [26] A102065          | TIO 18 μg QD + FP/SAL 250/50 μg BD                | 223     | 97.3%  | 67.0 | NR              | 43.5%                       | NR                                             | NR                                            | NR               | NR                            |
|                                  | TIO 18 μg QD                                      | 232     | 98.7%  | 67.8 | NR              | 38.8%                       | NR                                             | NR                                            | NR               | NR                            |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.
BDP beclomethasone dipropionate, BD twice daily, BDI baseline dyspnea index, BMI body mass index, BUD budesonide, CAT score COPD assessment test score, CFB change from baseline, COPD chronic obstructive pulmonary disease, DB double blind, FF fluticasone furoate, FEV₁ forced expiratory volume 1, FOR formoterol, FVC forced vital capacity, FP fluticasone propionate, GLY glycopyrronium bromide, GOLD global Initiative for Chronic Obstructive Lung Disease, ICS inhaled corticosteroid, IND indacatero, ITT intention to treat, LABA long-acting β₂-agonist, LAMA long-acting muscarinic receptor antagonist, LOCS lens opacities classification system, mMRC modified Medical Research Council, MC multi-center, NR not reported, OL open label, QD once daily, SABA short-acting β₂-adrenergic, SAL salmeterol, SGRQ Saint George’s Respiratory Questionnaire, TIO tiotropium, μg microgram, UMEC umeclidinium bromide, VI vilanterol
### Supplementary Table S3 Patients with at least one adverse event in included trials (n = 23)

| Study | Subgroup | Treatment (μg) | Time point in weeks | N  | n  | %  |
|-------|----------|----------------|---------------------|----|----|----|
| **UMEC 62.5 + FF/VI 100/25** | | | | | | |
| Siler 2015 [7] NCT01957163 | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 75 | 36.0% |
| | | UMEC 125 + FF/VI 100/25 | 12 | 207 | 80 | 39.0% |
| | | FF/VI 100/25 | 12 | 206 | 72 | 35.0% |
| Siler 2015 [7] NCT02119286 | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 67 | 33.0% |
| | | UMEC 125 + FF/VI 100/25 | 12 | 207 | 62 | 30.0% |
| | | FF/VI 100/25 | 12 | 206 | 81 | 39.0% |
| **FF/UMEC/VI 100/62.5/25** | | | | | | |
| FULFIL [8] NCT02345161 | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 911 | 354 | 38.9% |
| | | BUD/FOR 400/12 | 24 | 899 | 339 | 37.7% |
| FULFIL [8] NCT02345161 | EXT | FF/UMEC/VI 100/62.5/25 | 52 | 210 | 100 | 47.6% |
| | | BUD/FOR 400/12 | 52 | 220 | 122 | 55.5% |
| Bremner 2018 [9] NCT02729051 | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 527 | 255 | 48.0% |
| | | UMEC 62.5 + FF/VI 100/25 | 24 | 528 | 253 | 48.0% |
| IMPACT [10] NCT02164513 | ITT | FF/UMEC/VI 100/62.5/25 | 52 | 4,151 | 2,897 | 70.0% |
| | | FF/VI 100/25 | 52 | 4,134 | 2,800 | 68.0% |
| | | UMEC/VI 62.5/25 | 52 | 2,070 | 1,429 | 69.0% |
| Ferguson 2020 [11] NCT03478683 | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 363 | 131 | 36.0% |
| | | TIO 18 QD + BUD/FOR 320/9 | 12 | 365 | 121 | 33.0% |
| Ferguson 2020 [11] NCT03478696 | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 366 | 92 | 25.0% |
| | | TIO 18 + BUD/FOR 320/9 | 12 | 366 | 109 | 30.0% |
| Obeid 2020 [12] NCT03474081 | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 400 | 127 | 32.0% |
| | | TIO 18 | 12 | 400 | 115 | 29.0% |
| **UMEC 62.5 + ICS/LABA** | | | | | | |
| Sousa 2016 [13] NCT02257372 | Full population | UMEC 62.5 + ICS/LABA | 12 | 119 | 45 | 38.0% |
| | | ICS/LABA | 12 | 117 | 49 | 42.0% |
| Siler 2016 [14] NCT01772134 | ITT | FP/SAL 250/50 | 12 | 205 | 85 | 41.0% |
| | | UMEC 62.5 + FP/SAL 250/50 | 12 | 204 | 78 | 38.0% |
| | | UMEC 125 + FP/SAL 250/50 | 12 | 205 | 76 | 37.0% |
| Siler 2016 [14] NCT01772147 | ITT | FP/SAL 250/50 | 12 | 201 | 74 | 37.0% |
| | | UMEC 62.5 + FP/SAL 250/50 | 12 | 203 | 78 | 38.0% |
| Study | Comparator | Treatment | N | Efficacy | Relapse Rate |
|-------|------------|-----------|---|----------|--------------|
| TIO 18 + BDP/FOR 100/6 | UMEC 125 + FP/SAL 250/50 | 12 | 202 | 73 | 36.0% |
| TRINITY [15] NCT01911364 | ITT BDP/FOR/GLY 100/6/12.5 | 52 | 1,077 | 594 | 55.0% |
| | TIO 18 | 52 | 1,076 | 622 | 58.0% |
| | TIO 18 + BDP/FOR 100/6 | 52 | 537 | 309 | 58.0% |
| TIO 18 + BDP/FOR 100/6 | TRINITY [15] NCT01911364 | Full population | BDP/FOR 320/9 + TIO 18 | 12 | 289 | 75 | 26.0% |
| | TIO 18 | 12 | 289 | 76 | 26.3% |
| Welte 2009 [17] NCT00496470 | ITT BDP/FOR 320/9 + TIO 18 | 12 | 329 | 81 | 25.0% |
| | TIO 18 | 12 | 331 | 82 | 25.0% |
| BDP/GLY/FOR 100/12.5/6 | TRILOGY [18] NCT01917331 | ITT GLY/BDP/FOR 12.5/100/6 | 52 | 687 | 368 | 54.0% |
| | BDP/FOR 100/6 | 52 | 680 | 379 | 56.0% |
| TRISTAR [19] NCT02467452 2014-001487-35 | ITT BDP/GLY/FOR 100/12.5/6 | 26 | NR | NR | NR |
| | FF/VI 100/25 + TIO 18 | 26 | NR | NR | NR |
| TRIBUTE [20] NCT02579850 | ITT BDP/GLY/FOR 87/9/5 | 52 | 764 | 490 | 64.0% |
| | IND/GLY 85/43 | 52 | 768 | 516 | 67.0% |
| BDP/GLY/FOR 120/18/9.6 | KRONOS [21] NCT02497001 | mITT BUD/GLY/FOR 320/18/9.6 | 24 | 639 | 388 | 61.0% |
| | GLY/FOR 18/9.6 | 24 | 625 | 384 | 61.0% |
| | BUD/FOR 320/9.6 | 24 | 314 | 175 | 56.0% |
| | BUD/FOR 400/12 | 24 | 318 | 183 | 58.0% |
| ETHOS [22] NCT02465567 | Safety population BUD/GLY/FOR 320/18/9.6 | 52 | 194 | 144 | 74.2% |
| | GLY/FOR 18/9.6 | 52 | 174 | 133 | 76.4% |
| | BUD/FOR 320/9.6 | 52 | 88 | 64 | 72.7% |
| | BUD/FOR 400/12 | 52 | NR | NR | NR |
| | Safety population BUD/GLY/FOR 320/18/9.6 | 52 | 2,144 | 1368 | 63.8% |
| | GLY/FOR 18/9.6 | 52 | 2,124 | 1356 | 63.8% |
| | BUD/GLY/FOR 160/18/9.6 | 52 | 2,125 | 1312 | 61.7% |
| | BUD/FOR MDI 320/9.6 | 52 | 2,136 | 1377 | 64.5% |
| TIO 18 + FP/SAL 500/50 | GLISTEN [23] NCT01513460 | Full population GLY 50 + FP/SAL 500/50 | 12 | 257 | 150 | 58.4% |
| | TIO 18 + FP/SAL 500/50 | 12 | 258 | 165 | 64.0% |
| | FP/SAL 500/50 | 12 | 257 | 148 | 57.6% |
| Aaron 2007 [24] ISRCTN29870041 | Full population TIO 18 | 52 | 156 | 37 | 24.0% |
| | TIO 18 + SAL 50 | 52 | 148 | 32 | 22.0% |
| | TIO 18 + FP/SAL 500/50 | 52 | 145 | 44 | 30.0% |
| Study          | ITT               | Comparator                      | N | E | P |
|---------------|------------------|---------------------------------|---|---|---|
| Hanania 2012  | ITT              | FP/SAL 250/50 + TIO 18          | 24 | 173 | 97 | 56.0% |
| [25] ADC111114 | TIO 18           | 24 | 169 | 85 | 50.0% |
| NCT00784550   |                  |                                 |   |     |    |       |
| Jung 2012 [26]| ITT              | FP/SAL 250/50 + TIO 18          | 24 | NR  | NR | NR    |
| A102065       | TIO 18           | 24 | NR  | NR | NR |       |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.

BDP beclomethasone dipropionate, BUD budesonide, EXT extension population, FF fluticasone furoate, FOR formoterol, FP fluticasone propionate, GLY glycopyrronium bromide, ICS inhaled corticosteroid, ITT intention to treat, LABA long-acting β₂-agonist, mITT modified intention to treat, NR not reported, SAL salmeterol, TIO tiotropium, UMEC umeclidinium bromide, VI vilanterol
### Supplementary Table S4  Patients with at least one serious adverse event in included trials (n = 23)

| Study                        | Subgroup         | Treatment (μg)               | Time point in weeks | N   | n   | %  |
|------------------------------|------------------|------------------------------|---------------------|-----|-----|----|
| **UMEC 62.5 + FF/VI 100/25** |                  |                              |                     |     |     |    |
| Siler 2015 [7]               | Full population  | UMEC 62.5 + FF/VI 100/25     | 12                  | 206 | 2   | 1.0% |
| NCT01957163                  |                  | UMEC 125 + FF/VI 100/25      | 12                  | 207 | 7   | 3.4% |
|                             |                  | FF/VI 100/25                 | 12                  | 206 | 6   | 2.9% |
| Siler 2015 [7]               | Full population  | UMEC 62.5 + FF/VI 100/25     | 12                  | 206 | 8   | 4.0% |
| NCT02119286                  |                  | UMEC 125 + FF/VI 100/25      | 12                  | 207 | 3   | 1.0% |
|                             |                  | FF/VI 100/25                 | 12                  | 206 | 11  | 5.0% |
| **FF/UMEC/VI 100/62.5/25**   |                  |                              |                     |     |     |    |
| FULFIL [8]                   | ITT              | FF/UMEC/VI 100/62.5/25       | 24                  | 911 | 49  | 5.4% |
| NCT02345161                  |                  | BUD/FOR 400/12               | 24                  | 899 | 51  | 5.7% |
|                                | EXT              | FF/UMEC/VI 100/62.5/25       | 52                  | 210 | 21  | 10.0% |
|                                |                  | BUD/FOR 400/12               | 52                  | 220 | 28  | 12.7% |
| Bremner 2018 [9]             | ITT              | FF/UMEC/VI 100/62.5/25       | 24                  | 528 | 57  | 11.0% |
| NCT02729051                  |                  | UMEC 62.5 + FF/VI 100/25     | 24                  | 528 | 52  | 10.0% |
| IMPACT [10]                  | ITT              | FF/UMEC/VI 100/62.5/25       | 52                  | 4,151 | 895 | 22.0% |
| NCT02164513                  |                  | FF/VI 100/25                 | 52                  | 4,134 | 850 | 21.0% |
|                             |                  | UMEC/VI 62.5/25              | 52                  | 2,070 | 470 | 23.0% |
| Ferguson 2020 [11]           | ITT              | FF/UMEC/VI 100/62.5/25       | 12                  | 363 | 25  | 7.0% |
| NCT03478683                  |                  | TIO 18 QD + BUD/FOR 320/9    | 12                  | 365 | 14  | 4.0% |
| Ferguson 2020 [11]           | ITT              | FF/UMEC/VI 100/62.5/25       | 12                  | 366 | 12  | 3.0% |
| NCT03478696                  |                  | TIO 18 + BUD/FOR 320/9       | 12                  | 366 | 17  | 5.0% |
| Obeid 2020 [12]              | ITT              | FF/UMEC/VI 100/62.5/25       | 12                  | 400 | 13  | 3.0% |
| NCT03474081                  |                  | TIO 18                       | 12                  | 400 | 10  | 3.0% |
| **UMEC 62.5 + ICS/LABA**     |                  |                              |                     |     |     |    |
| Sousa 2016 [13]              | Full population  | UMEC 62.5 + ICS/LABA         | 12                  | 119 | 6   | 5.0% |
| NCT02257372                  |                  | ICS/LABA                     | 12                  | 119 | 5   | 4.0% |
| Siler 2016 [14]              | ITT              | FP/SAL 250/50                | 12                  | 205 | 8   | 4.0% |
| NCT01772134                  |                  | UMEC 62.5 + FP/SAL 250/50    | 12                  | 204 | 4   | 2.0% |
|                             |                  | UMEC 125 + FP/SAL 250/50     | 12                  | 205 | 6   | 3.0% |
| Siler 2016 [14]              | ITT              | FP/SAL 250/50                | 12                  | 201 | 15  | 7.0% |
| NCT01772147                  |                  | UMEC 62.5 + FP/SAL 250/50    | 12                  | 203 | 6   | 3.0% |
|                             |                  | UMEC 125 + FP/SAL 250/50     | 12                  | 202 | 6   | 3.0% |
| **TIO 18 + BDP/FOR 100/6**   |                  |                              |                     |     |     |    |
| Study | Design | ITT | Treatment | N | Disease Free | Adverse Event | Adverse Event Rate |
|-------|--------|-----|-----------|---|--------------|---------------|-------------------|
| TRINITY [15] NCT01911364 | ITT | BDP/FOR/GLY 100/6/12.5 | 52 | 1,077 | 140 | 13.0% |
| TIO 18 | 52 | 1,076 | 164 | 15.0% |
| TIO 18 + BDP/FOR 100/6 | 52 | 537 | 68 | 13.0% |
| TIO 18 + BUD/FOR 320/9 | 12 | 289 | 14 | 4.8% |
| TIO 18 | 12 | 289 | 24 | 8.3% |
| Welte 2009 [17] NCT00496470 | ITT | BUD/FOR 320/9 + TIO 18 | 12 | 329 | 10 | 3.0% |
| TIO 18 | 12 | 331 | 14 | 4.0% |
| TRISTAR [19] NCT02467452 | mITT | BUD/GLY/FOR 320/18/9.6 | 24 | 639 | 55 | 9.0% |
| TIO 18 | 24 | 625 | 68 | 11.0% |
| TIO 18 + BDP/FOR 100/6 | 24 | 314 | 21 | 7.0% |
| TIO 18 | 24 | 318 | 29 | 9.0% |
| ETHOS [22] NCT02465567 | Safety population | BUD/GLY/FOR 320/18/9.6 | 52 | 194 | 33 | 17.0% |
| TIO 18 | 52 | 174 | 22 | 12.6% |
| TIO 18 | 52 | 88 | 7 | 8.0% |
| TIO 18 + BUD/FOR 400/12 | 52 | NR | NR | NR |
| TIO 18 + FP/SAL 500/50 | Full population | GLY 50 + FP/SAL 500/50 | 12 | 257 | 15 | 5.8% |
| TIO 18 + FP/SAL 500/50 | 12 | 258 | 22 | 8.5% |
| GLYSTEN [23] NCT01513460 | Full population | FP/SAL 500/50 | 12 | 257 | 15 | 5.8% |
| TIO 18 + FP/SAL 500/50 | 12 | 30 | 0 | 0% |
| Aaron 2007 [24] ISRCTN29870041 | Full population | TIO 18 | 52 | 156 | 10 | 6.0% |
| TIO 18 + FP/SAL 500/50 | 52 | 148 | 9 | 6.0% |
| TIO 18 + FP/SAL 250/50 | 52 | 145 | 9 | 6.0% |
| Hanania 2012 [25] ADC111114 NCT00784550 | ITT | FP/SAL 250/50 + TIO 18 | 24 | 173 | 7 | 4.0% |
| TIO 18 | 24 | 169 | 13 | 8.0% |
| Jung 2012 [26] | ITT | FP/SAL 250/50 + TIO 18 | 24 | 237 | 20 | 8.7% |
|---------------|-----|------------------------|----|-----|----|------|
|               | TIO 18 |                       | 24 | 242 | 16 | 6.7% |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial

BDP beclomethasone dipropionate, BUD budesonide, EXT extension population, FF fluticasone furoate, FOR formoterol, FP fluticasone propionate, GLY glycopyrronium bromide, ICS inhaled corticosteroid, ITT intention to treat, LABA long-acting β2-agonist, mITT modified intention to treat, NR not reported, SAL salmeterol, TIO tiotropium, UMEC umeclidinium bromide, VI vilanterol, μg microgram
## Supplementary Table S5
Total withdrawals from included trials ($n = 23$)

| Study | Description | Subgroup | Treatment (µg) | Time point in weeks | N | n | % |
|-------|-------------|----------|----------------|-------------------|---|---|---|
|       |             |          | UMEC 62.5 + FF/VI 100/25 |                  |   |   |   |
|       |             |          | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 11 | 5.0% |
|       |             |          | UMEC 125 + FF/VI 100/25 | 12 | 207 | 18 | 9.0% |
|       |             |          | FF/VI 100/25          | 12 | 206 | 15 | 7.0% |
| Siler 2015 [7] NCT01957163 | Withdrawal from study | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 11 | 5.0% |
|       |             |          | UMEC 125 + FF/VI 100/25 | 12 | 207 | 7  | 3.0% |
|       |             |          | FF/VI 100/25          | 12 | 206 | 26 | 13.0% |
|       |             |          | FF/UMEC/VI 100/62.5/25 | 24 | 527 | 13 | 4.0% |
|       |             |          | TIO 18 QD + BUD/FOR 320/9 | 12 | 365 | 18 | 5.0% |
| Ferguson 2020 [11] NCT03478683 | Prematurely withdrawn | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 366 | 17 | 5.0% |
|       |             |          | TIO 18 + BUD/FOR 320/9 | 12 | 366 | 12 | 3.0% |
|       |             |          | FF/UMEC/VI 100/62.5/25 | 12 | 400 | 17 | 4.0% |
|       |             |          | TIO 18                | 12 | 400 | 13 | 3.0% |
| Bremner 2018 [9] NCT02729051 | Withdrawal from study | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 26 | 13.0% |
|       |             |          | UMEC 125 + FF/VI 100/25 | 12 | 207 | 7  | 3.0% |
|       |             |          | FF/VI 100/25          | 12 | 206 | 26 | 13.0% |
| FULFIL [8] NCT02345161 | Withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 911 | 45 | 4.9% |
|       |             |          | BUD/FOR 400/12        | 24 | 899 | 57 | 6.3% |
| FULFIL [8] NCT02345161 | NR | EXT | FF/UMEC/VI 100/62.5/25 | 52 | 528 | 32 | 6.0% |
|       |             |          | BUD/FOR 400/12        | 52 | NR  | NR | NR |
| IMPACT [10] NCT02164513 | Withdrawal from study, based on study completion status information | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 528 | 32 | 6.0% |
|       |             |          | FF/VI 100/25          | 52 | 4,134 | 536 | 13.0% |
|       |             |          | UMEC/VI 62.5/25       | 52 | 2,070 | 295 | 14.0% |
| Ferguson 2020 [11] NCT03478696 | Prematurely withdrawn | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 366 | 17 | 5.0% |
|       |             |          | TIO 18 + BUD/FOR 320/9 | 12 | 366 | 12 | 3.0% |
| Obeid 2020 [12] NCT03474081 | Withdrawal from study, based on study completion status information | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 400 | 17 | 4.0% |
|       |             |          | TIO 18                | 12 | 400 | 13 | 3.0% |
| UMEC 62.5 + ICS/LABA |          |          | UMEC 62.5 + ICS/LABA | 12 | 119 | 10 | 8.0% |
|       |          |          | ICS/LABA             | 12 | 117 | 7  | 6.0% |
| Sousa 2016 [13] NCT02257372 | Withdrawal from study | Full population | UMEC 62.5 + ICS/LABA | 12 | 119 | 10 | 8.0% |
|       |          |          | ICS/LABA             | 12 | 117 | 7  | 6.0% |
| Siler 2016 [14] NCT01772134 | Withdrawal from study | ITT | FP/SAL 250/50         | 12 | 205 | 27 | 13.0% |
|       |          |          | UMEC 62.5 + FP/SAL 250/50 | 12 | 204 | 14 | 7.0% |
|       |          |          | UMEC 125 + FP/SAL 250/50 | 12 | 205 | 21 | 10.0% |
|       |          |          | FF/SA 250/50          | 12 | 201 | 31 | 15.0% |
| Study ID          | Intervention                          | Withdrawal From Study | Full Population | Patients | Withdrawal Rate |
|------------------|---------------------------------------|-----------------------|-----------------|----------|-----------------|
| Siler 2016 [14]  | Withdrawal from study                 | UMEC 62.5 + FP/SAL 250/50 | 12              | 203      | 12.0%           |
|                  |                                       | UMEC 125 + FP/SAL 250/50 | 12              | 202      | 9.0%            |
| TIO 18 + BDP/FOR 100/6 | Withdrawal from study     | ITT BDP/FOR/GLY 100/6/12.5 | 52              | 1,078    | 8.5%            |
|                  |                                       | TIO 18                | 52              | 1,075    | 15.0%           |
|                  |                                       | TIO 18 + BDP/FOR 100/6 | 52              | 538      | 7.8%            |
| TRINITY [15]     | Withdrawal from study                | ITT                   | 12              | 287      | 8.0%            |
| NCT01911364     |                                       | BDP/FOR/GLY 100/6/12.5 | 12              | 291      | 10.7%           |
| TIO 18 + BDP/FOR 100/6 | Discontinued from study     | Full population       | 12              | 329      | 7.9%            |
| BDP/GLY/FOR 100/12.5/6 | Study not completed        | ITT                   | 12              | 331      | 8.5%            |
| SECURE 1 [16]    | Discontinued study                  | ITT                   | 12              | 287      | 8.0%            |
| NCT01397890     |                                       | BDP/FOR/GLY 100/6/12.5 | 12              | 291      | 10.7%           |
| Welte 2009 [17]  | Withdrawal from study               | ITT                   | 12              | 329      | 7.9%            |
| NCT00496470     |                                       | BDP/FOR/GLY 100/6/12.5 | 12              | 331      | 8.5%            |
| TIO 18 + BDP/FOR 100/6 | Discontinued study          | ITT                   | 12              | 287      | 8.0%            |
| TRIOLOGY [18]    | Total withdrawal                    | ITT                   | 52              | NR       | NR              |
| NCT01917331     |                                       | BDP/FOR 100/6         | 52              | NR       | NR              |
| TRISTAR [19]     | Study not completed                 | ITT                   | 26              | 578      | 5.7%            |
| NCT02467452 2014-001487-35 | Discontinued study      | BDP/GLY/FOR 100/12.5/6 | 26              | 579      | 5.2%            |
| TRIBUTE [20]     | Discontinued study                  | ITT                   | 52              | 764      | 12.8%           |
| NCT02579850     |                                       | BDP/GLY/FOR 87/9/5    | 52              | 768      | 15.6%           |
| BUD/GLY/FOR 320/18/9.6 | Discontinued study          | mITT                  | 24              | 639      | 11.4%           |
| KRONOS [21]      | Discontinued study                  | BUD/GLY/FOR 320/18/9.6 | 24              | 627      | 16.1%           |
| NCT02497001     |                                       | GLY/FOR 18/9.6        | 24              | 315      | 15.2%           |
| KRONOS Extension (Safety population; US patients) NCT02536508 | Total withdrawal | Safety population | 24              | 318      | 12.6%           |
| ETHOS [22]       | Withdrawn from trial                | Safety population     | 52              | 2,144    | 4.9%            |
| NCT02465567     |                                       | BUD/GLY/FOR 320/18/9.6 | 52              | 2,124    | 4.4%            |
|                  |                                       | GLY/FOR 18/9.6        | 52              | 2,125    | 5.8%            |
|                  |                                       | - BUD/GLY/FOR 320/18/9.6 | 52              | 2,136    | 6.1%            |
| GLISTEN [23]     | Discontinued use of study           | Full population       | 52              | 156      | 47.0%           |
| NCT01513460     | Withdrawal from study               | GLY 50 + FP/SAL 500/50 | 12              | 257      | 11.2%           |
|                  |                                       | TIO 18 + FP/SAL 500/50 | 12              | 258      | 12.4%           |
|                  |                                       | FP/SAL 500/50         | 12              | 257      | 21.8%           |
| Aaron 2007 [24]  | Discontinued use of study           | Full population       | TIO 18          | 52       | 43.0%           |
| ISRCTN29870041   |                                       | TIO 18 + SAL 50       | 52              | 148      | 43.0%           |
| Medications before completing 1 year of therapy | TIO 18 + FP/SAL 500/50 |  52 | 145 | 37 | 26.0% |
|-----------------------------------------------|------------------------|-----|-----|----|-------|
| **TIO 18 + FP/SAL 250/50**                    |                        |     |     |    |       |
| Hanania 2012 [25]                             |                        |     |     |    |       |
| ADC111114                                     | Withdrawal from study  | ITT | FP/SAL 250/50 + TIO 18 | 24 | 173 | 36 | 21.0% |
| NCT00784550                                   |                        |     | TIO 18 | 24 | 169 | 42 | 25.0% |
| Jung 2012 [26]                                |                        |     | FP/SAL 250/50 + TIO 18 | 24 | 237 | 8  | 3.4%  |
| A102065                                       | Withdrawal from study  | ITT | TIO 18 | 24 | 242 | 12 | 5.0%  |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.

BDP beclomethasone dipropionate, BUD budesonide, EXT extension population, FF fluticasone furoate, FOR formoterol, FP fluticasone propionate, GLY glycopyrronium bromide, ICS inhaled corticosteroid, ITT intention to treat, LABA long-acting β2-agonist, mITT modified intention to treat, NR not reported, SAL salmeterol, TIO tiotropium, UMEC umeclidinium bromide, VI vilanterol, μg microgram
### Supplementary Table S6 Total withdrawals due to adverse events from included trials (n = 23)

| Study | Description | Subgroup | Treatment (μg) | Time point in weeks | N   | n | %   |
|-------|-------------|----------|----------------|---------------------|-----|---|-----|
| Siler 2015 [7] NCT01957163 | Withdrawal from study due to adverse events | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 2 | 1.0% |
|       |             |          | UMEC 125 + FF/VI 100/25 | 12 | 207 | 4 | 2.0% |
|       |             |          | FF/VI 100/25 | 12 | 206 | 5 | 2.0% |
| Siler 2015 [7] NCT02119286 | Withdrawal from study due to adverse events | Full population | UMEC 62.5 + FF/VI 100/25 | 12 | 206 | 7 | 3.0% |
|       |             |          | UMEC 125 + FF/VI 100/25 | 12 | 207 | 2 | 1.0% |
|       |             |          | FF/VI 100/25 | 12 | 206 | 9 | 4.0% |
| FULFIL [8] NCT02345161 | Any AE leading to discontinuation of treatment or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 911 | 28 | 3.0% |
|       |             |          | BUD/FOR 400/12 | 24 | 899 | 25 | 3.0% |
| FULFIL [8] NCT02345161 | Any AE leading to discontinuation of treatment or withdrawal from study | EXT | FF/UMEC/VI 100/62.5/25 | 52 | 210 | 10 | 5.0% |
|       |             |          | BUD/FOR 400/12 | 52 | 220 | 9  | 4.0% |
| Bremner 2018 [9] NCT02729051 | Withdrawal from study due to adverse events | ITT | FF/UMEC/VI 100/62.5/25 | 24 | 527 | 21 | 4.0% |
|       |             |          | UMEC 62.5 + FF/VI 100/25 | 24 | 528 | 11 | 2.0% |
| IMPACT [10] NCT02164513 | On-treatment adverse events leading to permanent discontinuation of study drug or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 52 | 4,151 | 252 | 6.0% |
|       |             |          | FF/VI 100/25 | 52 | 4,134 | 327 | 8.0% |
|       |             |          | UMEC/VI 62.5/25 | 52 | 2,070 | 187 | 9.0% |
| Ferguson 2020 [11] NCT03478683 | Withdrawal due to adverse event | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 363 | 5  | 1.0% |
|       |             |          | TIO 18 QD + BUD/FOR 320/9 | 12 | 365 | 3  | <1.0% |
| Ferguson 2020 [11] NCT03478683 | On-treatment adverse events leading to permanent discontinuation of study drug or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 363 | 7  | 2.0% |
|       |             |          | TIO 18 QD + BUD/FOR 320/9 | 12 | 365 | 7  | 2.0% |
| Ferguson 2020 [11] NCT03478696 | Withdrawal due to adverse event | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 366 | 1  | <1.0% |
|       |             |          | TIO 18 + BUD/FOR 320/9 | 12 | 366 | 5  | 1.0% |
| Ferguson 2020 [11] NCT03478696 | On-treatment adverse events leading to permanent discontinuation of study drug or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 366 | 2  | <1.0% |
|       |             |          | TIO 18 + BUD/FOR 320/9 | 12 | 366 | 5  | 1.0% |
| Obeid 2020 [12] NCT03474081 | Any on-treatment adverse events that led to permanent discontinuation of study treatment or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | 12 | 400 | 7  | 2.0% |
|       |             |          | TIO 18 | 12 | 400 | 3  | <1.0% |
| Study | Design | Outcome Measure | Treatment Group | Study Code | N | Withdrawal | Events | eDAE Rate |
|-------|--------|----------------|-----------------|------------|---|----------|--------|----------|
| Obeid 2020 [12] NCT03474081 | Any on-treatment adverse events that led to permanent discontinuation of study treatment or withdrawal from study | ITT | FF/UMEC/VI 100/62.5/25 | TIO 18 | 12 | 400 | 4 | 1.0% |
| Sousa 2016 [13] NCT02257372 | On-Treatment adverse events leading to discontinuation of study treatment or withdrawal from the Study | Full population | UMEC 62.5 + ICS/LABA | ICS/LABA | 12 | 119 | 7 | 6.0% |
| | | | | | | | | 12 | 117 | 3 | 3.0% |
| Siler 2016 [14] NCT01772134 | Withdrawal from study due to adverse events | ITT | FP/SAL 250/50 | UMEC 125 + FP/SAL 250/50 | 12 | 204 | 5 | 2.0% |
| | | | | | | | | UMEC 62.5 + FP/SAL 250/50 | 12 | 205 | 10 | 5.0% |
| | | | | | | | | | | | |
| Siler 2016 [14] NCT01772147 | Withdrawal from study due to adverse events | ITT | FP/SAL 250/50 | UMEC 125 + FP/SAL 250/50 | 12 | 203 | 10 | 5.0% |
| | | | | | | | | UMEC 62.5 + FP/SAL 250/50 | 12 | 202 | 6 | 3.0% |
| TRINITY [15] NCT01911364 | Discontinuation due to adverse events | ITT | BDP/FOR/GLY 100/6/12.5 | TIO 18 | 52 | 1,078 | 13 | 1.2% |
| | | | | | | | | TIO 18 | 52 | 1,075 | 26 | 2.4% |
| | | | | | | | | TIO 18 + BDP/FOR 100/6 | 52 | 538 | 5 | 0.9% |
| SECURE 1 [16] NCT01397890 | At least one AE leading to discontinuation | Full population | BUD/FOR 320/9 + TIO 18 | TIO 18 | 12 | 289 | 3 | 1.0% |
| | | | | | | | | TIO 18 | 12 | 289 | 9 | 3.1% |
| Welte 2009 [17] NCT00496470 | Discontinuation due to adverse events | ITT | BUD/FOR 320/9 + TIO 18 | TIO 18 | 12 | 329 | 8 | 2.4% |
| | | | | | | | | TIO 18 | 12 | 331 | 10 | 3.0% |
| TRILogy [18] NCT01917331 | Treatment-emergent adverse events leading to study drug discontinuation | ITT | GLY/BDP/FOR 12.5/100/6 | BDP/FOR 100/6 | 52 | 687 | 35 | 5.0% |
| | | | | | | | | BDP/FOR 100/6 | 52 | 680 | 33 | 5.0% |
| TRISTAR [19] NCT02467452 2014-001487-35 | Not completed due to serious fatal and non-fatal adverse events | ITT | BDP/GLY/FOR 100/12.5/6 | FF/VI 100/25 + TIO 18 | 26 | 578 | 9 | 1.6% |
| | | | | | | | | FF/VI 100/25 + TIO 18 | 26 | 579 | 14 | 2.4% |
| TRIBUTE [20] NCT02579850 | Discontinuation due to adverse events | ITT | BDP/GLY/FOR 87/9/5 | IND/GLY 85/43 | 52 | 764 | 37 | 4.8% |
| | | | | | | | | IND/GLY 85/43 | 52 | 768 | 47 | 6.1% |
| KRONOS [21] NCT02497001 | Discontinuation due to adverse events | mITT | BUD/GLY/FOR 320/18/9.6 | GLY/FOR 18/9.6 | 24 | 639 | 28 | 4.4% |
| | | | | | | | | GLY/FOR 18/9.6 | 24 | 627 | 30 | 4.8% |
| | | | | | | | | BUD/ FOR 320/9.6 | 24 | 315 | 11 | 3.5% |
| | | | | | | | | BUD/ FOR 400/12 | 24 | 318 | 11 | 3.5% |
| KRONOS Extension | Treatment emergent adverse events that led to early discontinuation | Safety population | BUD/GLY/FOR 320/18/9.6 | GLY/FOR 18/9.6 | 52 | 194 | 16 | 8.2% |
| | | | | | | | | GLY/ FOR 18/9.6 | 52 | 174 | 12 | 6.9% |
| Trial Details | Treatment | N | AE | Disposition | Event Rate |
|--------------|-----------|---|----|-------------|------------|
| (Safety population; US patients) NCT02536508 | BUD/FOR 320/9.6 | 52 | 88 | 6 | 6.8% |
| | BUD/FOR 400/12 | 52 | NR | NR | NR |
| | - BUD/GLY/FOR 320/18/9.6 | 52 | NR | NR | NR |
| | - BUD/FOR 160/18/9.6 | 52 | NR | NR | NR |
| | - GLY/FOR 18/9.6 | 52 | NR | NR | NR |
| | - BUD/FOR MDI 320/9.6 | 52 | NR | NR | NR |
| ETHOS [22] NCT02465567 | NR | Safety population | - BUD/GLY/FOR 320/18/9.6 | 52 | NR | NR | NR |
| | TIO 18 + FP/SAL 500/50 | 12 | 257 | 14 | 5.4% |
| GLISTEN [23] NCT01513460 | Discontinuation due to adverse events | Full population | GLY 50 + FP/SAL 500/50 | 12 | 257 | 14 | 5.4% |
| | | | TIO 18 + FP/SAL 500/50 | 12 | 258 | 17 | 6.6% |
| | | | FP/SAL 500/50 | 12 | 257 | 17 | 6.6% |
| Aaron 2007 [24] ISRCTN29870041 | Patient stopped drug therapy and did not complete the study due to adverse events | Full population | TIO 18 | 52 | 156 | 8 | 5.0% |
| | | | TIO 18 + SAL 50 | 52 | 148 | 6 | 4.0% |
| | | | TIO 18 + FP/SAL 500/50 | 52 | 145 | 8 | 6.0% |
| Hanania 2012 [25] ADC111114 NCT00784550 | Withdrawal from study due to adverse events | ITT | FP/SAL 250/50 + TIO 18 | 24 | 173 | 12 | 7.0% |
| | | | TIO 18 | 24 | 169 | 10 | 6.0% |
| Jung 2012 [26] A102065 | Drop-outs due to adverse events | ITT | FP/SAL 250/50 + TIO 18 | 24 | 237 | 2 | 0.8% |
| | | | TIO 18 | 24 | 242 | 4 | 1.7% |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.

AE adverse event, BDP beclomethasone dipropionate, BUD budesonide, EXT extension population, FF fluticasone furoate, FOR formoterol, FP fluticasone propionate, GLY glycopyrronium bromide, ICS inhaled corticosteroid, ITT intention to treat, LABA long-acting β₂-agonist, mITT modified intention to treat, NR not reported, SAL salmeterol, TIO tiotropium, UMEC umeclidinium bromide, VI vilanterol, µg microgram
## Supplementary Table S7  Mortality in included trials (n = 23)

| Study          | Description                                      | Subgroup         | Treatment (μg)                  | Time point in weeks | N  | n | %  |
|----------------|--------------------------------------------------|------------------|--------------------------------|---------------------|----|---|----|
|                |                                                  |                  |                                |                     |    |   |    |
| **UMEC 62.5 + FF/VI 100/25** |                                                  |                  |                                |                     |    |   |    |
| Siler 2015 [7] | NCT01957163 Any on-treatment fatal SAE           | Full population  | UMEC 62.5 + FF/VI 100/25       | 12                  | 206| 0 | 0% |
|                |                                                  |                  | UMEC 125 + FF/VI 100/25        | 12                  | 207| 0 | 0% |
|                |                                                  |                  | FF/VI 100/25                   | 12                  | 206| 1 | 0.5% |
| Siler 2015 [7] | NCT02119286 Any on-treatment fatal SAE           | Full population  | UMEC 62.5 + FF/VI 100/25       | 12                  | 206| 1 | 0.5% |
|                |                                                  |                  | UMEC 125 + FF/VI 100/25        | 12                  | 207| 0 | 0% |
|                |                                                  |                  | FF/VI 100/25                   | 12                  | 206| 4 | 2.0% |
| **FF/UMEC/VI 100/62.5/25** |                                                  |                  |                                |                     |    |   |    |
| FULFIL [8]     | NCT02345161 On-treatment fatal serious adverse events up to week 24 | ITT               | FF/UMEC/VI 100/62.5/25         | 24                  | 911| 4 | 0.4% |
|                |                                                  |                  | BUD/FOR 400/12                 | 24                  | 899| 6 | 0.7% |
| FULFIL [8]     | NCT02345161 On-treatment fatal serious adverse events up to week 52 | EXT               | FF/UMEC/VI 100/62.5/25         | 52                  | 210| 2 | 1.0% |
|                |                                                  |                  | BUD/FOR 400/12                 | 52                  | 220| 1 | 0.5% |
| Bremner 2018   | NCT02729051 On-treatment deaths                  | ITT               | FF/UMEC/VI 100/62.5/25         | 24                  | 527| 4 | 0.8% |
| [9]            |                                                  |                  | UMEC 62.5 + FF/VI 100/25       | 24                  | 528| 4 | 1.0% |
| IMPACT [10]    | NCT02164513 On-treatment fatal SAEs              | ITT               | FF/UMEC/VI 100/62.5/25         | 52                  | 4,151| 68 | 2.0% |
|                |                                                  |                  | FF/VI 100/25                   | 52                  | 4,134| 76 | 2.0% |
|                |                                                  |                  | UMEC/VI 62.5/25                | 52                  | 2,070| 49 | 2.0% |
| Ferguson 2020  | NCT03478683 Death (on-treatment fatal serious adverse event) | ITT               | FF/UMEC/VI 100/62.5/25         | 12                  | 363| 0 | 0% |
| [11]           |                                                  |                  | TIO 18 QD + BUD/FOR 320/9      | 12                  | 365| 0 | 0% |
| Ferguson 2020  | NCT03478696 Death (on-treatment fatal serious adverse event) | ITT               | FF/UMEC/VI 100/62.5/25         | 12                  | 366| 0 | 0% |
| [11]           |                                                  |                  | TIO 18 + BUD/FOR 320/9         | 12                  | 366| 1 | <1.0% |
| Obeid 2020     | NCT03474081 Any on-treatment fatal serious adverse events | ITT               | FF/UMEC/VI 100/62.5/25         | 12                  | 400| 2 | <1.0% |
| [12]           |                                                  |                  | TIO 18                        | 12                  | 400| 1 | <1.0% |
| **UMEC 62.5 + ICS/LABA** |                                                  |                  |                                |                     |    |   |    |
| Sousa 2016     | NCT02257372 Any on-treatment fatal SAE           | Full population  | UMEC 62.5 + ICS/LABA           | 12                  | 119| 0 | 0% |
| [13]           |                                                  |                  | ICS/LABA                       | 12                  | 117| 1 | <1.0% |
| Siler 2016     | NCT01772134 Any on-treatment fatal SAE           | ITT               | FP/SAL 250/50                  | 12                  | 205| 0 | 0% |
| [14]           |                                                  |                  | UMEC 62.5 + FP/SAL 250/50      | 12                  | 204| 0 | 0% |
|                |                                                  |                  | UMEC 125 + FP/SAL 250/50       | 12                  | 205| 1 | <1.0% |
|                |                                                  |                  | FP/SAL 250/50                  | 12                  | 201| 1 | <1.0% |
| Study / NCT Number | Treatment | Full Population | Adverse events | Number of Deaths | Event Rate |
|--------------------|-----------|----------------|----------------|------------------|------------|
| Siler 2016 [14] NCT01772147 | Any on-treatment fatal SAE | UMEC 62.5 + FP/SAL 250/50 | 12 | 203 | 1 | <1.0% |
|                      |           | UMEC 125 + FP/SAL 250/50 | 12 | 202 | 0 | 0% |
| **TIO 18 + BDP/FOR 100/6** | TRINITY [15] NCT01911364 | Adverse events leading to death | BDP/FOR/GLY 100/6/12.5 | 52 | 1,077 | 20 | 0.3% |
|                      |         | TIO 18 | 52 | 1,076 | 29 | 1.0% |
|                      |         | TIO 18 + BDP/FOR 100/6 | 52 | 537 | 8 | 0.6% |
| **TIO 18 + BUD/FOR 320/9** | SECURE 1 [16] NCT01397890 | Adverse events related death | BUD/FOR/320/9 + TIO 18 | 12 | 289 | 1 | 0.3% |
|                      |         | TIO 18 | 12 | 289 | 5 | 1.7% |
| **BDP/GLY/FOR 100/12.5/6** | TRILOGY [18] NCT01917331 | Treatment-emergent adverse events leading to death | GLY/BDFOR 12.5/100/6 | 52 | 687 | 15 | 0.3% |
|                      |         | BDP/FOR 100/6 | 52 | 681 | 16 | 0.3% |
|                      | TRISTAR [19] NCT02467452 2014-001487-35 | Number of deaths (all causes) | BDP/GLY/100/12.5/6 | 26 | 578 | 3 | 0.5% |
|                      |         | FF/VI 100/25 + TIO 18 | 26 | 579 | 5 | 0.9% |
|                      | TRIBUTE [20] NCT02579850 | Serious adverse event death | BDP/GLY/FOR 87/9/5 | 52 | 764 | 3 | 0.4% |
|                      |         | IND/GLY/85/43 | 52 | 768 | 8 | 1.0% |
|                      | TRIBUTE [20] NCT02579850 | Adverse events leading to death | BDP/GLY/FOR 87/9/5 | 52 | 764 | 16 | 2.1% |
|                      |         | IND/GLY/85/43 | 52 | 768 | 21 | 2.7% |
|                      | TRIBUTE [20] NCT02579850 | Died | BDP/GLY/FOR 87/9/5 | 52 | 764 | 15 | 2.0% |
|                      |         | IND/GLY/85/43 | 52 | 768 | 20 | 2.6% |
| **BUD/GLY/FOR 320/18/9.6** | KRONOS [21] NCT02497001 | Deaths (all causes) | BUD/GLY/FOR 320/18/9.6 | 24 | 639 | 6 | 1.0% |
|                      |         | GLY/FOR 18/9.6 | 24 | 625 | 3 | <1.0% |
|                      |         | BUD/FOR 320/9.6 | 24 | 314 | 2 | 0.2% |
|                      |         | BUD/FOR 400/12 | 24 | 318 | 1 | <1.0% |
|                      | KRONOS Extension (Safety population; US patients) NCT02536508 | All-cause deaths | BUD/GLY/FOR 320/18/9.6 | 52 | 194 | 3 | 1.5% |
|                      |         | GLY/FOR 18/9.6 | 52 | 174 | 1 | 0.6% |
|                      |         | BUD/FOR 320/9.6 | 52 | 88 | 0 | 0% |
|                      |         | BUD/FOR 400/12 | 52 | NR | NR | NR |
|                      | ETHOS [22] NCT02465557 | Deaths from any cause during treatment period | BUD/GLY/FOR 320/18/9.6 | 52 | 2,144 | 19 | 0.9% |
|                      |         | - BUD/GLY/FOR 160/18/9.6 | 52 | 2,124 | 28 | 1.3% |
|                      |         | - GLY/FOR 18/9.6 | 52 | 2,125 | 35 | 1.6% |
|                      |         | - BUD/FOR MDI 320/9.6 | 52 | 2,136 | 29 | 1.4% |
| **TIO 18 + FP/SAL 500/50** | TIO 18 + FP/SAL 500/50 | Any on-treatment fatal SAE | UMEC 62.5 + FP/SAL 250/50 | 12 | 203 | 1 | <1.0% |
|                      |         | UMEC 125 + FP/SAL 250/50 | 12 | 202 | 0 | 0% |
| GLISTEN [23] NCT01513460 | Deaths | Full population | GLY 50 + FP/SAL 500/50 | 12 | 257 | 0 | 0% |
|--------------------------|--------|----------------|------------------------|----|-----|---|----|
|                          |        | TIO 18 + FP/SAL 500/50 | 12 | 258 | 0 | 0% |
|                          |        | FP/SAL 500/50 | 12 | 257 | 1 | 0.4% |
| Aaron 2007 [24] ISRCTN29870041 | Deaths during study | Full population | TIO 18 | 52 | 156 | 4 | 3.0% |
|                          |        | TIO 18 + SAL 50 | 52 | 148 | 6 | 4.0% |
|                          |        | TIO 18 + FP/SAL 500/50 | 52 | 145 | 6 | 4.0% |

| TIO 18 + FP/SAL 250/50 |
|-----------------------|
| Hanania 2012 [25] ADC111114 NCT00784550 | Mortality | ITT | FP/SAL 250/50 + TIO 18 | 24 | NR | NR | NR |
|                        |            | TIO 18 | 24 | NR | NR | NR |
| Jung 2012 [26] A102065 | Mortality | ITT | FP/SAL 250/50 + TIO 18 | 24 | NR | NR | NR |
|                        |            | TIO 18 | 24 | NR | NR | NR |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.

*BDP* beclomethasone dipropionate, *BUD* budesonide, *EXT* extension population, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *ICS* inhaled corticosteroid, *ITT* intention to treat, *LABA* long-acting β₂-agonist, *mITT* modified intention to treat, *NR* not reported, *SAE* serious adverse event, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium bromide, *VI* vilanterol, *μg* microgram
### Supplementary Table S8 Incidence of pneumonia in included trials (n = 23)

| Study                  | Subgroup                          | Treatment (μg)                               | Time point in weeks | N    | n   | %   |
|------------------------|-----------------------------------|---------------------------------------------|---------------------|------|-----|-----|
|                        |                                   | UMEC 62.5 + FF/VI 100/25                    |                     |      |     |     |
| Siler 2015 [7] NCT01957163 | Full population                   | UMEC 62.5 + FF/VI 100/25                    | 12                  | 206  | 0   | 0%  |
|                        |                                   | UMEC 125 + FF/VI 100/25                    | 12                  | 207  | 3   | 1.0%|
|                        |                                   | FF/VI 100/25                                | 12                  | 206  | 3   | 1.0%|
| Siler 2015 [7] NCT02119286 | Full population                   | UMEC 62.5 + FF/VI 100/25                    | 12                  | 206  | 2   | 1.0%|
|                        |                                   | UMEC 125 + FF/VI 100/25                    | 12                  | 207  | 1   | 0.5%|
|                        |                                   | FF/VI 100/25                                | 12                  | 206  | 1   | 0.5%|
|                        |                                   | FF/UMEC/VI 100/62.5/25                     |                     |      |     |     |
| FULFIL [8] NCT02345161  | ITT                               | FF/UMEC/VI 100/62.5/25                      | 24                  | 911  | 20  | 2.2%|
|                        |                                   | BUD/FOR 400/12                              | 24                  | 899  | 7   | 0.8%|
| FULFIL [8] NCT02345161  | EXT                               | FF/UMEC/VI 100/62.5/25                      | 52                  | 210  | 4   | 1.9%|
|                        |                                   | BUD/FOR 400/12                              | 52                  | 220  | 4   | 1.8%|
| Bremner 2018 [9] NCT02729051 | ITT                               | FF/UMEC/VI 100/62.5/25                      | 24                  | 527  | 14  | 3.0%|
|                        |                                   | UMEC 62.5 + FF/VI 100/25                    | 24                  | 528  | 18  | 3.0%|
| IMPACT [10] NCT02164513 | ITT                               | FF/UMEC/VI 100/62.5/25                      | 52                  | 4,151| 312 | 8.0%|
|                        |                                   | FF/VI 100/25                                | 52                  | 4,134| 282 | 7.0%|
|                        |                                   | UMEC/VI 62.5/25                             | 52                  | 2,070| 95  | 5.0%|
| Ferguson 2020 [11] NCT03478683 | ITT                               | FF/UMEC/VI 100/62.5/25                      | 12                  | 363  | 5   | 1.0%|
|                        |                                   | TIO 18 QD + BUD/FOR 320/9                   | 12                  | 365  | 6   | 2.0%|
| Ferguson 2020 [11] NCT03478696 | ITT                               | FF/UMEC/VI 100/62.5/25                      | 12                  | 366  | 2   | <1.0%|
|                        |                                   | TIO 18 + BUD/FOR 320/9                      | 12                  | 366  | 2   | <1.0%|
| Obeid 2020 [12] NCT03474081 | ITT                               | FF/UMEC/VI 100/62.5/25                      | 12                  | 400  | 3   | <1.0%|
|                        |                                   | TIO 18                                      | 12                  | 400  | 2   | <1.0%|
|                        |                                   | UMEC 62.5 + ICS/LABA                        |                     |      |     |     |
| Sousa 2016 [13] NCT02257372 | Full population                   | UMEC 62.5 + ICS/LABA                        | 12                  | 119  | 3   | 3.0%|
|                        |                                   | ICS/LABA                                    | 12                  | 117  | 2   | 2.0%|
| Siler 2016 [14] NCT01772134 | ITT                               | FP/SAL 250/50                               | 12                  | 205  | 0   | 0%  |
|                        |                                   | UMEC 62.5 + FP/SAL 250/50                   | 12                  | 204  | 1   | <1.0%|
|                        |                                   | UMEC 125 + FP/SAL 250/50                    | 12                  | 205  | 2   | <1.0%|
| Siler 2016 [14] NCT01772147 | ITT                               | FP/SAL 250/50                               | 12                  | 201  | 6   | 3.0%|
|                        |                                   | UMEC 62.5 + FP/SAL 250/50                   | 12                  | 203  | 3   | 1.0%|
|                        |                                   | UMEC 125 + FP/SAL 250/50                    | 12                  | 202  | 5   | 2.0%|
| Study | Type | Treatment | N  | Days | Efficacy | Safety |
|-------|------|-----------|----|------|----------|--------|
| **TIO 18 + BDP/FOR 100/6** |   |           |    |      |          |        |
| TRINITY [15] NCT01911364 | Full population | BDP/FOR/GLY 100/6/12.5 | 52 | 1,077 | 28 | 3.0% |
|  |  | TIO 18 | 52 | 1,076 | 19 | 1.0% |
|  |  | TIO 18 + BDP/FOR 100/6 | 52 | 537 | 9 | 2.0% |
| **TIO 18 + BUD/FOR 320/9** |   |           |    |      |          |        |
| SECURE 1 [16] NCT01397890 | Full population | BUD/FOR 320/9 + TIO 18 | 12 | 289 | 2 | 0.7% |
|  |  | TIO 18 | 12 | 289 | 4 | 1.4% |
| Welte 2009 [17] NCT00496470 | ITT | BUD/FOR 320/9 + TIO 18 | 12 | 329 | 3 | NR |
|  |  | TIO 18 | 12 | 331 | 3 | NR |
| **BDP/GLY/FOR 100/12.5/6** |   |           |    |      |          |        |
| TRILEGACY [18] NCT01917331 | ITT | GLY/BDP/FOR 12.5/100/6 | 52 | NR | NR | NR |
|  |  | BDP/FOR 100/6 | 52 | NR | NR | NR |
| TRISTAR [19] NCT02467452 2014-001487-35 | ITT | BDP/GLY/FOR 100/12.5/6 | 26 | 578 | 9 | 1.6% |
|  |  | FF/VI 100/25 + TIO 18 | 26 | 579 | 11 | 1.9% |
| TRIBUTE [20] NCT02579850 | ITT | BDP/GLY/FOR 87/9/5 | 52 | 764 | 28 | 3.7% |
|  |  | IND/GLY 85/43 | 52 | 768 | 27 | 3.5% |
| **BUD/GLY/FOR 320/18/9.6** |   |           |    |      |          |        |
| KRONOS [21] NCT02497001 | mITT | BUD/GLY/FOR 320/18/9.6 | 24 | 639 | 12 | 2.0% |
|  |  | GLY/FOR 18/9.6 | 24 | 625 | 10 | 2.0% |
|  |  | BUD/FOR 320/9.6 | 24 | 314 | 6 | 2.0% |
|  |  | BUD/FOR 400/12 | 24 | 318 | 4 | 1.0% |
| KRONOS Extension (Safety population; US patients) NCT02536508 | Safety population | BUD/GLY/FOR 320/18/9.6 | 52 | 194 | 4 | 2.1% |
|  |  | GLY/FOR 18/9.6 | 52 | 174 | 6 | 3.4% |
|  |  | BUD/FOR 320/9.6 | 52 | 88 | 1 | 1.1% |
|  |  | BUD/FOR 400/12 | 52 | NR | NR | NR |
| ETHOS [22] NCT02465567 | Safety population | BUD/GLY/FOR 320/18/9.6 | 52 | 2,144 | 90 | 4.2% |
|  |  | GLY/FOR 18/9.6 | 52 | 2,124 | 75 | 3.5% |
|  |  | BUD/GLY/FOR 160/18/9.6 | 52 | 2,125 | 48 | 2.3% |
|  |  | BUD/FOR MDI 320/9.6 | 52 | 2,136 | 96 | 4.5% |
| **TIO 18 + FP/SAL 500/50** |   |           |    |      |          |        |
| GLISTEN [23] NCT01513460 | Full population | GLY 50 + FP/SAL 500/50 | 12 | 257 | 0 | 0.0% |
|  |  | TIO 18 + FP/SAL 500/50 | 12 | 258 | 2 | 0.8% |
|  |  | FP/SAL 500/50 | 12 | 257 | 2 | 0.8% |
| Aaron 2007 [24] ISRCTN29870041 | Full population | TIO 18 | NR | NR | NR | NR |
|  |  | TIO 18 + SAL 50 | NR | NR | NR | NR |
|  |  | TIO 18 + FP/SAL 500/50 | NR | NR | NR | NR |
|                 | ITT                  | FP/SAL 250/50 + TIO 18 | TIO 18 | 24 | 173 | 2 | 1.2% |
|----------------|----------------------|------------------------|--------|----|-----|---|------|
| **Hanania 2012**<br>[25]<br>ADC111114<br>NCT00784550 | ITT                  | FP/SAL 250/50 + TIO 18 | TIO 18 | 24 | 169 | NR| NR   |
| **Jung 2012 [26]**<br>A102065 | ITT                  | FP/SAL 250/50 + TIO 18 | TIO 18 | 24 | 237 | 2 | NR   |

KRONOS Extension (Safety population) NCT02536508 is listed for completeness but is not counted as a unique trial.

*BDP* beclomethasone dipropionate, *BUD* budesonide, *EXT* extension population, *FF* fluticasone furoate, *FOR* formoterol, *FP* fluticasone propionate, *GLY* glycopyrronium bromide, *ICS* inhaled corticosteroid, *ITT* intention to treat, *LABA* long-acting β₂-agonist, *mITT* modified intention to treat, *NR* not reported, *SAE* serious adverse event, *SAL* salmeterol, *TIO* tiotropium, *UMEC* umeclidinium bromide, *VI* vilanterol, *μg* microgram
Supplementary Fig. S1 Network of evidence informing FEV₁ analysis at 24 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator.
TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV, forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S2 Network of evidence informing FEV₁ analysis at 12 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator
*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV₁ forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S3 Network of evidence informing annualized moderate and severe exacerbation analyses

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator
*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS, KRONOS, and KRONOS EXT

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

*BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV₁ forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol*
Supplementary Fig. S4 Network of evidence informing annualized moderate and severe exacerbation analyses at 24 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR
Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator

*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS, KRONOS, and KRONOS EXT

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

*BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV₁ forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol*
Supplementary Fig. S5 Network of evidence informing SGRQ total score at 24 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers.

Open label trials: Jung 2012; SECURE 1; TRISTAR

SECURE1 and Welte 2009 studies reported SGRQ-C scores; these data were not included in the analysis.
Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator.

*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS.

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis.

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV₁ forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol.
Supplementary Fig. S6 Network of evidence informing SGRQ total score at 12 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers.

Open label trials: Jung 2012; SECURE 1; TRISTAR

SECURE 1 and Welte 2009 studies reported SGRQ-C scores; these data were not included in the analysis.

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator.
*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS, KRONOS, and KRONOS EXT

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV, forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S7 Network of evidence informing SGRQ responders at 12 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR

SECURE1 and Welte 2009 studies reported SGRQ-C scores; these data were not included in the analysis

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator
TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV1 forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S8  Network of evidence informing TDI score at 24 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Open label trials: Jung 2012; SECURE 1; TRISTAR

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator
*TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis

BDP beclomethasone dipropionate, BUD budesonide, CFB change from baseline, CI confidence interval, FEV₁ forced expiratory volume in 1 second, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S9 Network of evidence informing rescue medication use at 24 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers.

Open label trials: Jung 2012; SECURE 1; TRISTAR

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS and KRONOS.
Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis.

BDP beclomethasone dipropionate, BUD budesonide, FOR formoterol, FP fluticasone propionate, FF fluticasone furoate, GLY glycopyrronium bromide, IND indacaterol, SAL salmeterol, TIO tiotropium, UMEC umeclidinium, VI vilanterol
Supplementary Fig. S10  Network of evidence informing rescue medication use at 12 weeks

Refer to Supplementary Table S1 for an overview of the included trials and ClinicalTrials.gov identifiers

Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator
Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS, KRONOS, and KRONOS EXT.

Grey lines indicate instances where data were not available at the time point of interest and were not included in the analysis.

*BDP* beclomethasone dipropionate, *BUD* budesonide, *FOR* formoterol, *FP* fluticasone propionate, *FF* fluticasone furoate, *GLY* glycopyrronium bromide, *IND* indacaterol, *SAL* salmeterol, *TIO* tiotropium, *UME*umeclidinium, *VI* vilanterol
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