Supplementary Material

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

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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 τ^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:

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

where $\hat{\theta}$ *represents a vector of* m *observed pairwise comparisons with known standard errors* $s = (s_1, s_2, \ldots, s_m)$, X *is the* $m \times n$ *design matrix defining the network structure,* θ^{trt} *is a*

vector of length n *including the number of treatments, and* Σ *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

$$\begin{pmatrix} \hat{\theta}_1^{AB} \\ \hat{\theta}_2^{BC} \\ \hat{\theta}_3^{CD} \\ \hat{\theta}_4^{AD} \\ \hat{\theta}_5^{BD} \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 1 & 0 & 0 & -1 \\ 0 & 1 & 0 & -1 \end{pmatrix} \begin{pmatrix} \theta_A \\ \theta_B \\ \theta_C \\ \theta_D \end{pmatrix} + \begin{pmatrix} \epsilon_1 \\ \epsilon_2 \\ \epsilon_3 \\ \epsilon_4 \\ \epsilon_5 \end{pmatrix}$$

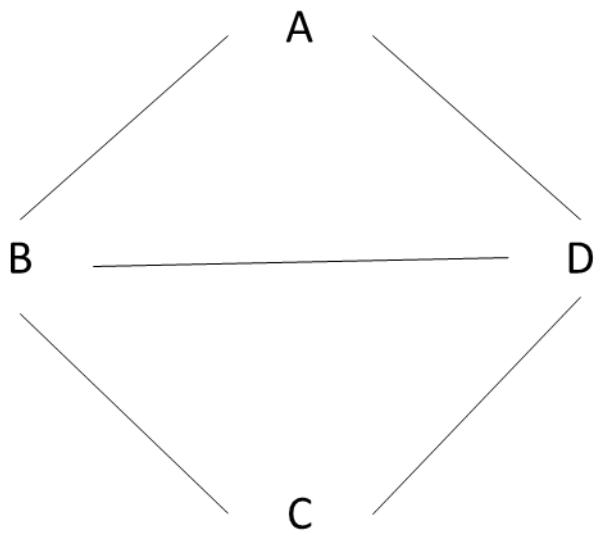


Fig. 1 Fictional example network of four treatments (letters) connected by five studies (lines)

Under the FE model, the diagonal matrix of dimension $m \times m$ is represented by $W = \mathrm{diag}\left(\frac{1}{s_1^2}, \ldots, \frac{1}{s_m^2}\right)$, including the inverse variance weights. The network estimates are given by $\hat{\theta}^{nma} = H\hat{\theta}$, where

$$H = X\left(X^T W X\right)^{+} X^T W$$

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

$$\widehat{\mathrm{Cov}}\left(\hat{\theta}^{\mathrm{nma}}\right) = \mathrm{X}\left(\mathrm{X}^{\mathrm{T}}\mathrm{W}\mathrm{X}\right)^{+}\mathrm{X}^{\mathrm{T}}.$$

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

$$\mathrm{Q}_{\mathrm{total}} = \left(\hat{\theta} - \hat{\theta}^{\mathrm{nma}}\right)^{\mathrm{T}}\mathrm{W}\left(\hat{\theta} - \hat{\theta}^{\mathrm{nma}}\right).$$

When a RE model is used rather than a FE model, the variance-covariance matrix changes. On the diagonal, τ^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 τ^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

$$\tau^2 = \max\left(\frac{\mathrm{Q} - \mathrm{df}}{\mathrm{tr}\left((\mathrm{U} - \mathrm{H})\mathrm{IW}\right)}\right),$$

with

$$\mathrm{df} = \sum_{\mathrm{k}}(\mathrm{k} - 1)\mathrm{n}_{\mathrm{k}} - (\mathrm{n} - 1)$$

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

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

$$SE(DCFB) = \sqrt{SE^2_{CFB\_T} + SE^2_{CFB_C},}$$

where $SE^2_{CFB\_T}$ and $SE^2_{CFB\_C}$ 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

$$\mathrm{SE}(\ln(\mathrm{HR})) = (\ln(\mathrm{UCL}) - \ln(\mathrm{LCL}))/3.92,$$

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

$$\mathrm{SE}(\ln(\mathrm{RaR})) = \sqrt{\frac{1}{r_T} + \frac{1}{r_C}},$$

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

$$SE(\ln(\mathrm{OR})) = \sqrt{\frac{1}{r_T} + \frac{1}{N_T - r_T} + \frac{1}{r_C} + \frac{1}{N_C - r_C}}.$$

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 μ_i and μ_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

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

where Upper and 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

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

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 μ_i and μ_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
UMEC 62.5 + FF/VI 100/25							
Siler 2015 [7] NCT01957163	- 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)
Siler 2015 [7] NCT02119286	- 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 nebules were issued throughout the study for rescue medication use as-needed.
FF/UMEC/VI 100/62.5/25							
FULFIL [8] NCT02345161	- FF/UMEC/VI 100/62.5/25 µg QD - BUD/FOR 400/12 µg BD	RCT, DB, parallel group, 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.

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	Participants were provided with albuterol/salbutamol to be used for spirometry assessments and as needed during the study.

						exacerbation in the 12 months prior to Screening, and a COPD Assessment Test (CAT) score of ≥10 at Screening.	
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.
UMEC 62.5 + ICS/LABA							
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

Siler 2016 [14] NCT01772134	- UMEC 62.5 µg QD + FP/SAL 250/50 µg BD - UMEC 125 µg QD + FP/SAL 250/50 µg BD - FP/SAL 250/50 µg BD	RCT, DB, MC	617	12	Trough FEV1 on treatment Day 85	Male and female subjects, treated as outpatients, age ≥40 years; established clinical history of COPD in 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	Albuterol/salbutamol as rescue medication
Siler 2016 [14] NCT01772147	- UMEC 62.5 µg QD + FP/SAL 250/50 µg BD - UMEC 125 µg QD + FP/SAL 250/50 µg BD - FP/SAL 250/50 µg BD	RCT, DB, MC	608	12	Trough FEV1 on treatment Day 85	Male and female subjects, treated as outpatients, age ≥40 years; established clinical history of COPD in 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	Albuterol/salbutamol as rescue medication
TIO 18 + BDP/FOR 100/6							
TRINITY [15] NCT01911364	- TIO 18 µg QD + BDP/FOR 100/6 µg two actuations BD - BDP/FOR/GLY 100/6/12.5 µg two actuations BD - TIO 18 µg QD	RCT, DB, MC	2,689	52	Exacerbation rate after 52 weeks	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	Salbutamol when needed
TIO 18 + BUD/FOR 320/9							
SECURE 1 [16] NCT01397890	- TIO 18 µg QD + BUD/FOR 320/9 µg BD - TIO 18 µg QD	RCT, OL, MC	578	12	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 packs years; pre-bronchodilator forced expiratory volume in 1s (FEV1) ration <70%	NR

Welte 2009 [17] NCT00496470	- TIO 18 µg QD + BUD/FOR 320/9 µg BD - TIO 18 µg QD	RCT, DB, MC	660	12	CFB pre-dose FEV1 from randomization (Week 0) to the full treatment period (mean FEV1 at 1, 6, and 12 week of treatment)	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
BDP/GLY/FOR 100/12.5/6							
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	CFB in pre-dose (morning) FEV1 CFB in 2-h post-dose FEV1 TDI focal score	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	CFB in SGRQ total score	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 ≥ 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	Rate of moderate/severe COPD exacerbations over 52 weeks of treatment	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.	
BUD/GLY/FOR 320/18/9.6							
KRONOS [21] NCT02497001	- 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	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

					lower bound of 95% CI 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	
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 Extension duration in weeks: 24	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)	Salbutamol allowed as rescue medication
ETHOS [22] NCT02465567	- BUD/GLY/FOR 320/18/9.6 µg BD - BUD/GLY/FOR 160/18/9.6 µg BD - GLY/FOR 18/9.6 µg BD - BUD/FOR MDI 320/9.6 µg BD	RCT, DB	8,588	52	Rate of moderate or severe COPD exacerbations	Male/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)	Albutamol allowed as rescue medication
TIO 18 + FP/SAL 500/50							
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	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	Salbutamol allowed as rescue medication

Aaron 2007 [24] ISRCTN29870041	- TIO 18 µg QD + FP/SAL 500/50 µg BD - TIO 18 µg QD + SAL 50 µg BD - TIO 18 µg QD	RCT, DB, MC	449	52	Proportion of patients who experienced a COPD exacerbation within 52 weeks of randomization	Male and female subjects; age ≥35 years; at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization; a history of 10 pack-years or more of cigarette smoking; documented chronic airflow obstruction, with an FEV1/FVC ratio less than 0.70, and a post-bronchodilator FEV1 less than 65% of the predicted value.	Albuterol when necessary to relieve symptoms; therapy with other respiratory medications, such as oxygen, antileukotrienes, and methylxanthines, was continued in all patient groups.
TIO 18 + FP/SAL 250/50							
Hanania 2012 [25] ADC111114 NCT00784550	- TIO 18 µg QD + FP/SAL 250/50 µg BD - TIO 18 µg QD	RCT, DB, MC	342	24	AM pre-dose FEV1 at endpoint	Male and female subjects aged ≥40 years; diagnosis of COPD according to ATS-ERS criteria; cigarette smoking history ≥10 pack-years; post-albuterol FEV1 ≥40–≤80% of predicted normal and a post-albuterol FEV1/FVC of ≤0.70 according to NHANES III reference values; ≥2 on the mMRC Dyspnea Scale following 4-week run-in.	Albuterol was supplied as rescue medication during run-in and throughout the rest of the study.
Jung 2012 [26] A102065	- TIO 18 µg QD + FP/SAL 250/50 µg BD - TIO 18 µg QD	RCT, OL, MC	479	24	Mean CFB in pre-bronchodilator FEV1 (L) at week 24	Eligible patients were 40–80 years of age and a smoking history of at least 10 pack-years; patients diagnosed with COPD; post bronchodilator FEV1/FVC ratio of less than 0.70 and FEV1 of <65% of the predicted value in the past 1 year or at screening.	All patients were provided with a salbutamol inhalation aerosol and instructed to use it when necessary to relieve symptoms.

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, *FEV_1* 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 β_2-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 β_2-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)
UMEC 62.5 + FF/VI 100/25										
Siler 2015 [7] NCT01957163	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] NCT02119286	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
FF/UMEC/VI 100/62.5/25										
FULFIL [8] NCT02345161	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] NCT02729051	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] NCT02164513	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] NCT03478683	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] NCT03478696	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] NCT03474081	FF/UMEC/VI 100/62.5/25 µg QD	400	69.0%	66.2	47.0%	53.0%	71.0%	71.0%	<10.%	8.5
	TIO 18 µg QD	400	67.0%	66.1	48.0%	51.0%	73.0%	73.0%	0	8.42
UMEC 62.5 + ICS/LABA										
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] NCT01772134	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] NCT01772147	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
TIO 18 + BDP/FOR 100/6										
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
TIO 18 + BUD/FOR 320/9										
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	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	331	74.0%	62.5	NR	NR	100.0%	NR	60.0%	5.7
BDP/GLY/FOR 100/12.5/6										
TRILOGY [18] NCT01917331	BDP/GLY/FOR 100/12.5/6 µg two actuations BD	687	74.0%	63.3	47.0%	100.0%	100.0%	NR	75.0%	7.7
	BDP/FOR 100/6 µg two actuations BD	680	77.0%	63.8	47.0%	100.0%	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%	100.0%	NR	NR	NR
	FF/VI 100/25 µg QD + TIO 18 µg QD	579	74.1%	64.2	NR	100.0%	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
	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										
KRONOS [21] NCT02497001	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
	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/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/FOR DPI 400/12 µg BD	318	74.2%	65.9	38.4%	49.7%	26.4%	7.9%	70.8%	6.7
KRONOS Extension (Safety population ; US patients) NCT02536508	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
	GLY/FOR 18/9.6 µg BD	88	50.0%	62.4	54.6%	47.7%	23.9%	3.4%	73.0%	7.7
	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
	BUD/FOR DPI 400/12 µg BD	NR	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] NCT02465567	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
TIO 18 + FP/SAL 500/50										
GLISTEN [23] NCT01513460	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
TIO 18 + FP/SAL 250/50										
Hanania 2012 [25] ADC111114 NCT00784550	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, FEV_1 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 β_2-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 β_2-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	2897	70.0%
		FF/VI 100/25	52	4,134	2800	68.0%
		UMEC/VI 62.5/25	52	2,070	1429	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%

		UMEC 125 + FP/SAL 250/50	12	202	73	36.0%
TIO 18 + BDP/FOR 100/6						
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 + BUD/FOR 320/9						
SECURE 1 [16] NCT01397890	Full population	BUD/FOR 320/9 + TIO 18	12	289	75	26.0%
		TIO 18	12	289	76	26.3%
Welte 2009 [17] NCT00496470	ITT	BUD/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%
BUD/GLY/FOR 320/18/9.6						
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%
KRONOS Extension (Safety population; US patients) NCT02536508	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
ETHOS [22] NCT02465567	Safety population	BUD/GLY/FOR 320/18/9.6	52	2,144	1368	63.8%
		BUD/GLY/FOR 160/18/9.6	52	2,124	1356	63.8%
		GLY/FOR 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%
TIO 18 + FP/SAL 250/50						

Hanania 2012 [25] ADC111114 NCT00784550	ITT	FP/SAL 250/50 + TIO 18	24	173	97	56.0%
		TIO 18	24	169	85	50.0%
Jung 2012 [26] A102065	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 β_2-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] NCT01957163	Full population	UMEC 62.5 + FF/VI 100/25	12	206	2	1.0%
		UMEC 125 + FF/VI 100/25	12	207	7	3.4%
		FF/VI 100/25	12	206	6	2.9%
Siler 2015 [7] NCT02119286	Full population	UMEC 62.5 + FF/VI 100/25	12	206	8	4.0%
		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] NCT02345161	ITT	FF/UMEC/VI 100/62.5/25	24	911	49	5.4%
		BUD/FOR 400/12	24	899	51	5.7%
FULFIL [8] NCT02345161	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] NCT02729051	ITT	FF/UMEC/VI 100/62.5/25	24	527	52	10.0%
		UMEC 62.5 + FF/VI 100/25	24	528	57	11.0%
IMPACT [10] NCT02164513	ITT	FF/UMEC/VI 100/62.5/25	52	4,151	895	22.0%
		FF/VI 100/25	52	4,134	850	21.0%
		UMEC/VI 62.5/25	52	2,070	470	23.0%
Ferguson 2020 [11] NCT03478683	ITT	FF/UMEC/VI 100/62.5/25	12	363	25	7.0%
		TIO 18 QD + BUD/FOR 320/9	12	365	14	4.0%
Ferguson 2020 [11] NCT03478696	ITT	FF/UMEC/VI 100/62.5/25	12	366	12	3.0%
		TIO 18 + BUD/FOR 320/9	12	366	17	5.0%
Obeid 2020 [12] NCT03474081	ITT	FF/UMEC/VI 100/62.5/25	12	400	13	3.0%
		TIO 18	12	400	10	3.0%
UMEC 62.5 + ICS/LABA						
Sousa 2016 [13] NCT02257372	Full population	UMEC 62.5 + ICS/LABA	12	119	6	5.0%
		ICS/LABA	12	117	5	4.0%
Siler 2016 [14] NCT01772134	ITT	FP/SAL 250/50	12	205	8	4.0%
		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] NCT01772147	ITT	FP/SAL 250/50	12	201	15	7.0%
		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						

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						
SECURE 1 [16] NTC01397890	Full population	BUD/FOR 320/9 + TIO 18	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%
BDP/GLY/FOR 100/12.5/6						
TRILOGY [18] NCT01917331	ITT	GLY/BDP/FOR 12.5/100/6	52	687	106	15.0%
		BDP/FOR 100/6	52	680	123	18.0%
TRISTAR [19] NCT02467452 2014-001487-35	ITT	BDP/GLY/FOR 100/12.5/6	26	578	39	6.7%
		FF/VI 100/25 + TIO 18	26	579	56	9.7%
TRIBUTE [20] NCT02579850	ITT	BDP/GLY/FOR 87/9/5	52	764	117	15.0%
		IND/GLY 85/43	52	768	130	17.0%
BUD/GLY/FOR 320/18/9.6						
KRONOS [21] NCT02497001	mITT	BUD/GLY/FOR 320/18/9.6	24	639	55	9.0%
		GLY/FOR 18/9.6	24	625	68	11.0%
		BUD/FOR 320/9.6	24	314	21	7.0%
		BUD/FOR 400/12	24	318	29	9.0%
KRONOS Extension (Safety population; US patients) NCT02536508	Safety population	BUD/GLY/FOR 320/18/9.6	52	194	33	17.0%
		GLY/FOR 18/9.6	52	174	22	12.6%
		BUD/FOR 320/9.6	52	88	7	8.0%
		BUD/FOR 400/12	52	NR	NR	NR
ETHOS [22] NCT02465567	Safety population	- BUD/GLY/FOR 320/18/9.6	52	2,144	426	19.9%
		BUD/GLY/FOR 160/18/9.6	52	2,124	445	21.0%
		GLY/FOR 18/9.6	52	2,125	433	20.4%
		BUD/FOR MDI 320/9.6	52	2,136	440	20.6%
TIO 18 + FP/SAL 500/50						
GLISTEN [23] NCT01513460	Full population	GLY 50 + FP/SAL 500/50	12	257	15	5.8%
		TIO 18 + FP/SAL 500/50	12	258	22	8.5%
		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 + SAL 50	52	148	9	6.0%
		TIO 18 + FP/SAL 500/50	52	145	9	6.0%
TIO 18 + FP/SAL 250/50						
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] A102065	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 β_2-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							
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	18	9.0%
			FF/VI 100/25	12	206	15	7.0%
Siler 2015 [7] NCT02119286	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							
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	NR	NR	NR
			BUD/FOR 400/12	52	NR	NR	NR
Bremner 2018 [9] NCT02729051	Withdrawal from study	ITT	FF/UMEC/VI 100/62.5/25	24	527	30	6.0%
			UMEC 62.5 + FF/VI 100/25	24	528	32	6.0%
IMPACT [10] NCT02164513	Withdrawal from study, based on study completion status information	ITT	FF/UMEC/VI 100/62.5/25	52	4,151	437	11.0%
			FF/VI 100/25	52	4,134	536	13.0%
			UMEC/VI 62.5/25	52	2,070	295	14.0%
Ferguson 2020 [11] NCT03478683	Prematurely withdrawn	ITT	FF/UMEC/VI 100/62.5/25	12	363	13	4.0%
			TIO 18 QD + BUD/FOR 320/9	12	365	18	5.0%
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							
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%
		ITT	FP/SAL 250/50	12	201	31	15.0%

Siler 2016 [14] NCT01772147	Withdrawal from study		UMEC 62.5 + FP/SAL 250/50	12	203	25	12.0%
			UMEC 125 + FP/SAL 250/50	12	202	18	9.0%
TIO 18 + BDP/FOR 100/6							
TRINITY [15] NCT01911364	Withdrawal from study	ITT	BDP/FOR/GLY 100/6/12.5	52	1,078	92	8.5%
			TIO 18	52	1,075	161	15.0%
			TIO 18 + BDP/FOR 100/6	52	538	42	7.8%
TIO 18 + BUD/FOR 320/9							
SECURE 1 [16] NTC01397890	Discontinued from study	Full population	BUD/FOR 320/9 + TIO 18	12	287	23	8.0%
			TIO 18	12	291	31	10.7%
Welte 2009 [17] NCT00496470	Withdrawal from study	ITT	BUD/FOR 320/9 + TIO 18	12	329	26	7.9%
			TIO 18	12	331	28	8.5%
BDP/GLY/FOR 100/12.5/6							
TRILOGY [18] NCT01917331	Total withdrawal	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	Study not completed	ITT	BDP/GLY/FOR 100/12.5/6	26	578	33	5.7%
			FF/VI 100/25 + TIO 18	26	579	30	5.2%
TRIBUTE [20] NCT02579850	Discontinued study	ITT	BDP/GLY/FOR 87/9/5	52	764	98	12.8%
			IND/GLY 85/43	52	768	120	15.6%
BUD/GLY/FOR 320/18/9.6							
KRONOS [21] NCT02497001	Discontinued study	mITT	BUD/GLY/FOR 320/18/9.6	24	639	73	11.4%
			GLY/FOR 18/9.6	24	627	101	16.1%
			BUD/FOR 320/9.6	24	315	48	15.2%
			BUD/FOR 400/12	24	318	40	12.6%
KRONOS Extension (Safety population; US patients) NCT02536508	Total withdrawal	Safety population	BUD/GLY/FOR 320/18/9.6	52	NR	NR	NR
			GLY/FOR 18/9.6	52	NR	NR	NR
			BUD/FOR 320/9.6	52	NR	NR	NR
			BUD/FOR 400/12	52	NR	NR	NR
ETHOS [22] NCT02465567	Withdrew from trial	Safety population	- BUD/GLY/FOR 320/18/9.6	52	2,144	104	4.9%
			- BUD/GLY/FOR 160/18/9.6	52	2,124	94	4.4%
			- GLY/FOR 18/9.6	52	2,125	123	5.8%
			- BUD/FOR MDI 320/9.6	52	2,136	130	6.1%
TIO 18 + FP/SAL 500/50							
GLISTEN [23] NCT01513460	Withdrawal from study	Full population	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] ISRCTN29870041	Discontinued use of study	Full population	TIO 18	52	156	74	47.0%
			TIO 18 + SAL 50	52	148	64	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 NCT00784550	Withdrawal from study	ITT	FP/SAL 250/50 + TIO 18	24	173	36	21.0%
			TIO 18	24	169	42	25.0%
Jung 2012 [26] A102065	Withdrawal from study	ITT	FP/SAL 250/50 + TIO 18	24	237	8	3.4%
			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 β_2-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	%
UMEC 62.5 + FF/VI 100/25							
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%
FF/UMEC/VI 100/62.5/25							
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%

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	4	1.0%
			TIO 18	12	400	3	<1.0%
UMEC 62.5 + ICS/LABA							
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	12	119	7	6.0%
			ICS/LABA	12	117	3	3.0%
Siler 2016 [14] NCT01772134	Withdrawal from study due to adverse events	ITT	FP/SAL 250/50	12	205	6	3.0%
			UMEC 62.5 + FP/SAL 250/50	12	204	5	2.0%
			UMEC 125 + 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	12	201	13	6.0%
			UMEC 62.5 + FP/SAL 250/50	12	203	10	5.0%
			UMEC 125 + FP/SAL 250/50	12	202	6	3.0%
TIO 18 + BDP/FOR 100/6							
TRINITY [15] NCT01911364	Discontinuation due to adverse events	ITT	BDP/FOR/GLY 100/6/12.5	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%
TIO 18 + BUD/FOR 320/9							
SECURE 1 [16] NTC01397890	At least one AE leading to discontinuation	Full population	BUD/FOR 320/9 + 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	12	329	8	2.4%
			TIO 18	12	331	10	3.0%
BDP/GLY/FOR 100/12.5/6							
TRILOGY [18] NCT01917331	Treatment-emergent adverse events leading to study drug discontinuation	ITT	GLY/BDP/FOR 12.5/100/6	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	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	52	764	37	4.8%
			IND/GLY 85/43	52	768	47	6.1%
BUD/GLY/FOR 320/18/9.6							
KRONOS [21] NCT02497001	Discontinuation due to adverse events	mITT	BUD/GLY/FOR 320/18/9.6	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	52	194	16	8.2%
			GLY/FOR 18/9.6	52	174	12	6.9%

(Safety population; US patients) NCT02536508			BUD/FOR 320/9.6	52	88	6	6.8%
			BUD/FOR 400/12	52	NR	NR	NR
ETHOS [22] NCT02465567	NR	Safety population	- BUD/GLY/FOR 320/18/9.6	52	NR	NR	NR
			- BUD/GLY/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
TIO 18 + FP/SAL 500/50							
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%
TIO 18 + FP/SAL 250/50							
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 β_2-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 [9] NCT02729051	On-treatment deaths	ITT	FF/UMEC/VI 100/62.5/25	24	527	4	0.8%
			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 [11] NCT03478683	Death (on-treatment fatal serious adverse event)	ITT	FF/UMEC/VI 100/62.5/25	12	363	0	0%
			TIO 18 QD + BUD/FOR 320/9	12	365	0	0%
Ferguson 2020 [11] NCT03478696	Death (on-treatment fatal serious adverse event)	ITT	FF/UMEC/VI 100/62.5/25	12	366	0	0%
			TIO 18 + BUD/FOR 320/9	12	366	1	<1.0%
Obeid 2020 [12] NCT03474081	Any on-treatment fatal serious adverse events	ITT	FF/UMEC/VI 100/62.5/25	12	400	2	<1.0%
			TIO 18	12	400	1	<1.0%
UMEC 62.5 + ICS/LABA							
Sousa 2016 [13] NCT02257372	Any on-treatment fatal SAE	Full population	UMEC 62.5 + ICS/LABA	12	119	0	0%
			ICS/LABA	12	117	1	<1.0%
Siler 2016 [14] NCT01772134	Any on-treatment fatal SAE	ITT	FP/SAL 250/50	12	205	0	0%
			UMEC 62.5 + FP/SAL 250/50	12	204	0	0%
			UMEC 125 + FP/SAL 250/50	12	205	1	<1.0%
		ITT	FP/SAL 250/50	12	201	1	<1.0%

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	Full population	BDP/FOR/GLY 100/6/12.5	52	1,077	20	2.0%
			TIO 18	52	1,076	29	3.0%
			TIO 18 + BDP/FOR 100/6	52	537	8	1.0%
TIO 18 + BUD/FOR 320/9							
SECURE 1 [16] NTC01397890	Adverse events related death	Full population	BUD/FOR 320/9 + TIO 18	12	289	1	0.3%
			TIO 18	12	289	5	1.7%
Welte 2009 [17] NCT00496470	Death not causally related	ITT	BUD/FOR 320/9 + TIO 18	12	329	1	0.3%
			TIO 18	12	331	0	0.0%
BDP/GLY/FOR 100/12.5/6							
TRILOGY [18] NCT01917331	Treatment-emergent adverse events leading to death	ITT	GLY/BDP/FOR 12.5/100/6	52	687	15	2.0%
			BDP/FOR 100/6	52	681	16	2.0%
TRISTAR [19] NCT02467452 2014-001487-35	Number of deaths (all causes)	ITT	BDP/GLY/FOR 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	ITT	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	ITT	BDP/GLY/FOR 87/9/5	52	764	16	2.1%
			IND/GLY 85/43	52	768	21	2.7%
TRIBUTE [20] NCT02579850	Died	ITT	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)	mITT	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	1.0%
			BUD/FOR 400/12	24	318	1	<1.0%
KRONOS Extension (Safety population; US patients) NCT02536508	All-cause deaths	Safety population	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] NCT02465567	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							

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 β_2-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%

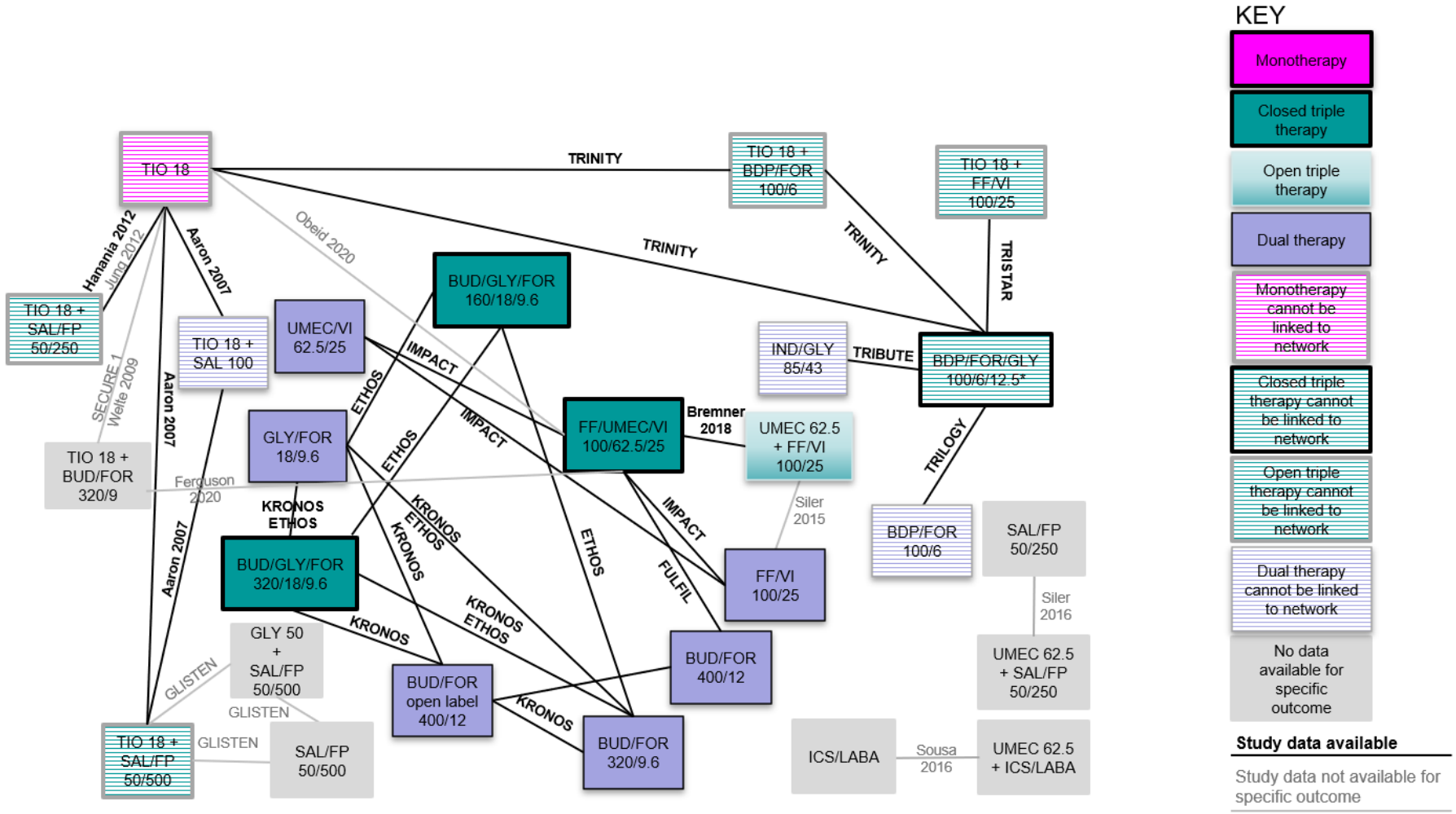
TIO 18 + BDP/FOR 100/6						
TRINITY [15] NCT01911364	Full population	BDP/FOR/GLY 100/6/12.5	52	1,077	28	3.0%
		TIO 18	52	1,076	19	1.0%
		TIO 18 + BDP/FOR 100/6	52	537	9	2.0%
TIO 18 + BUD/FOR 320/9						
SECURE 1 [16] NTC01397890	Full population	BUD/FOR 320/9 + TIO 18	12	289	2	0.7%
		TIO 18	12	289	4	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						
TRILOGY [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%
		BUD/GLY/FOR 160/18/9.6	52	2,124	75	3.5%
		GLY/FOR 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

TIO 18 + FP/SAL 250/50						
Hanania 2012 [25] ADC111114 NCT00784550	ITT	FP/SAL 250/50 + TIO 18	24	173	2	1.2%
		TIO 18	24	169	NR	NR
Jung 2012 [26] A102065	ITT	FP/SAL 250/50 + TIO 18	24	237	2	NR
		TIO 18	24	242	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 β_2-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 FEV_1 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

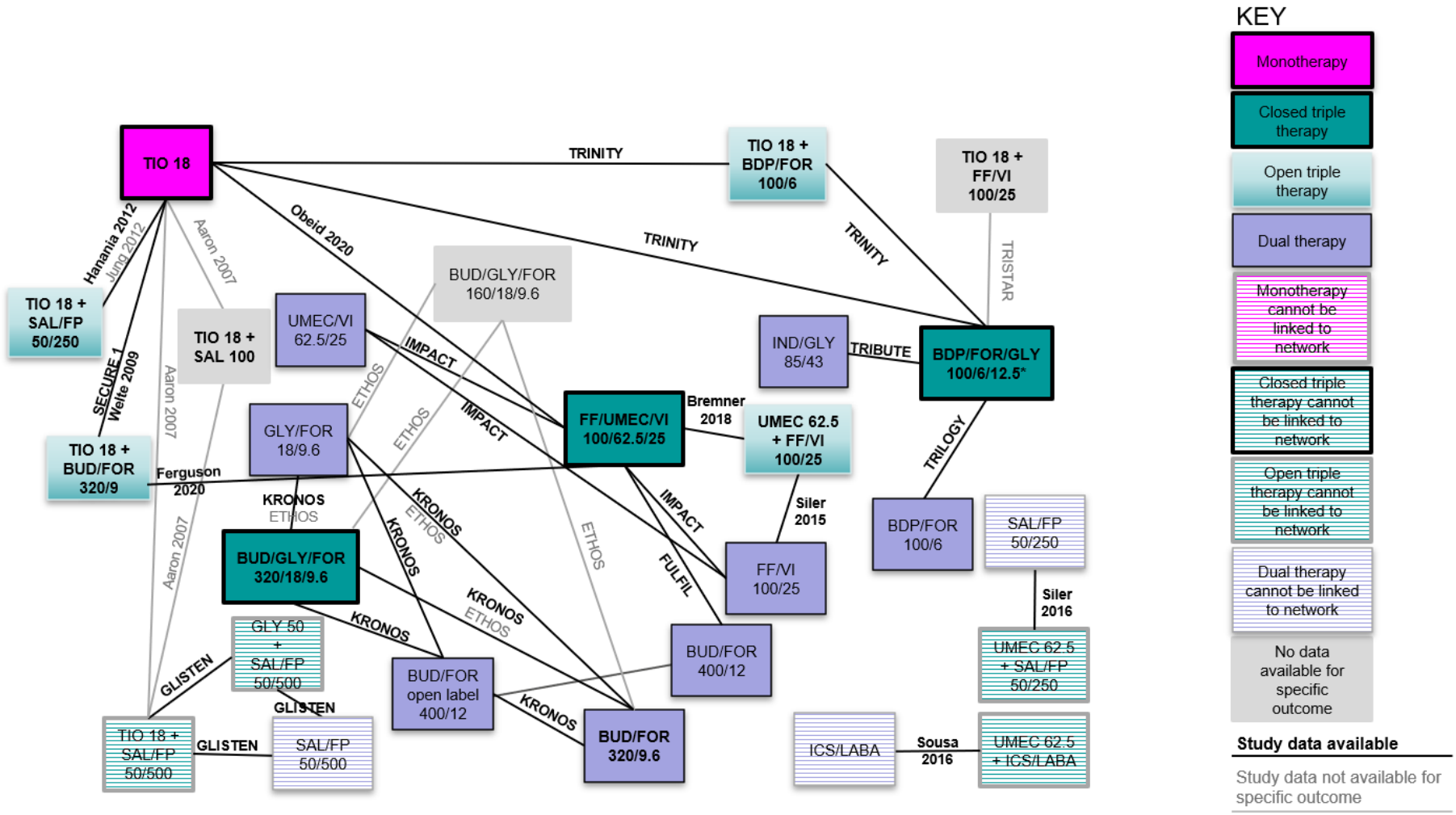
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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

BDP beclomethasone dipropionate, BUD budesonide, *CFB* change from baseline, *CI* confidence interval, *FEV_1* 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 FEV_1 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

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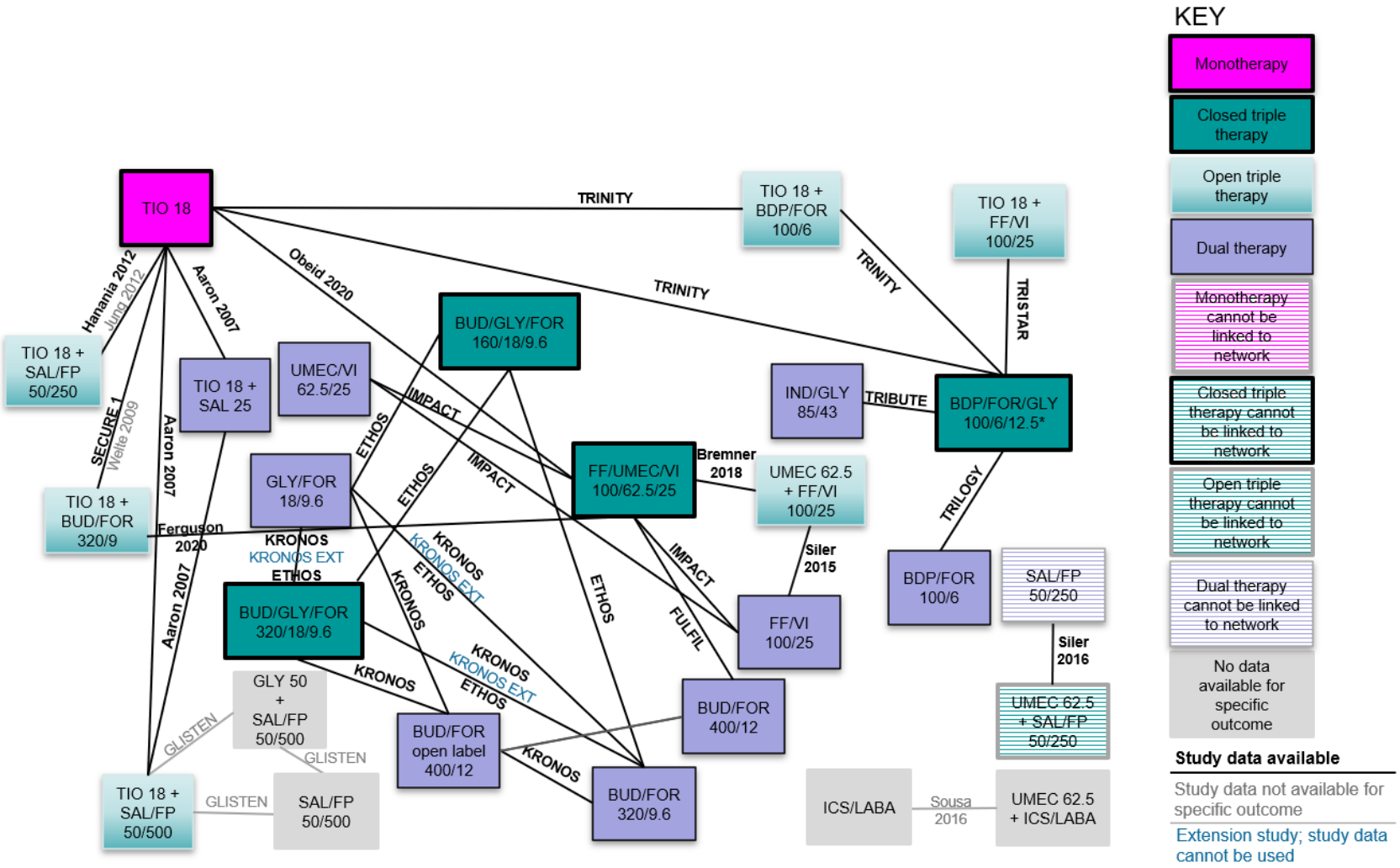
BDP beclomethasone dipropionate, *BUD* budesonide, *CFB* change from baseline, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 second, *FOR* formoterol, *FP* fluticasone propionate, *FF* fluticasone furoate, *GLY* glycopyrronium bromide, *IND* indacaterol, *SAL* salmeterol, *TIO* tiotropium, *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

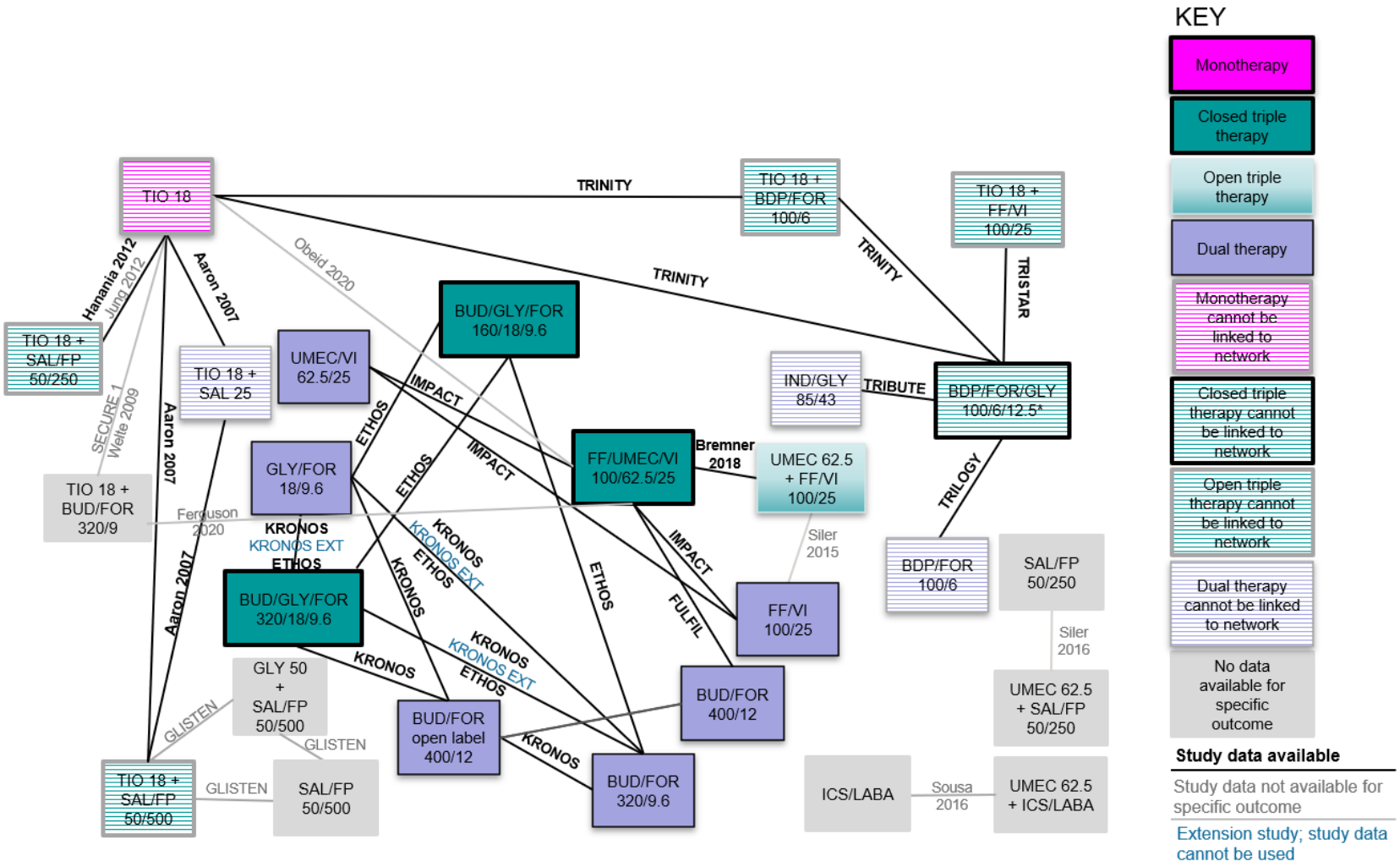
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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, *FEV_1* 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

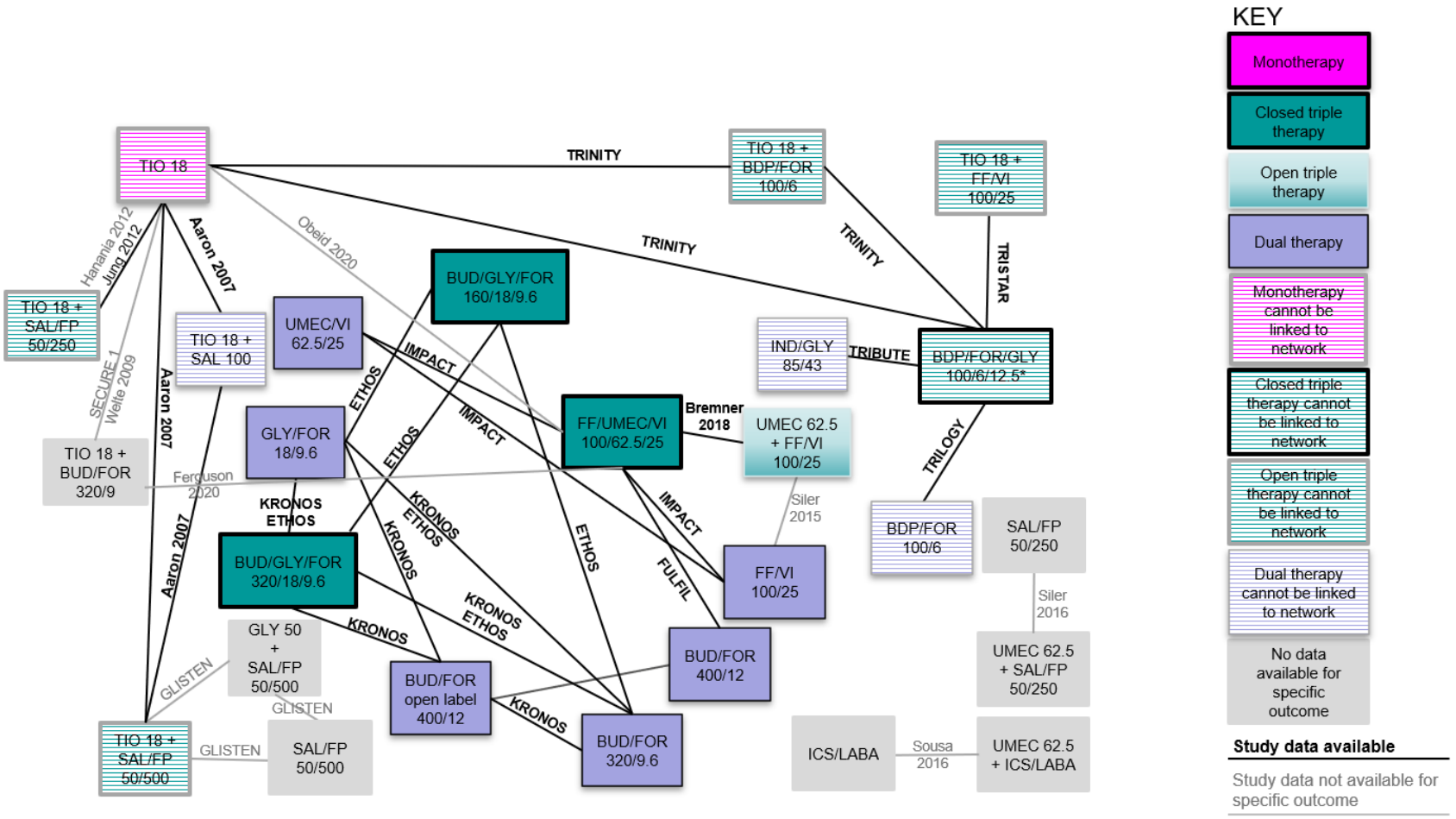
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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, *FEV_1* 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

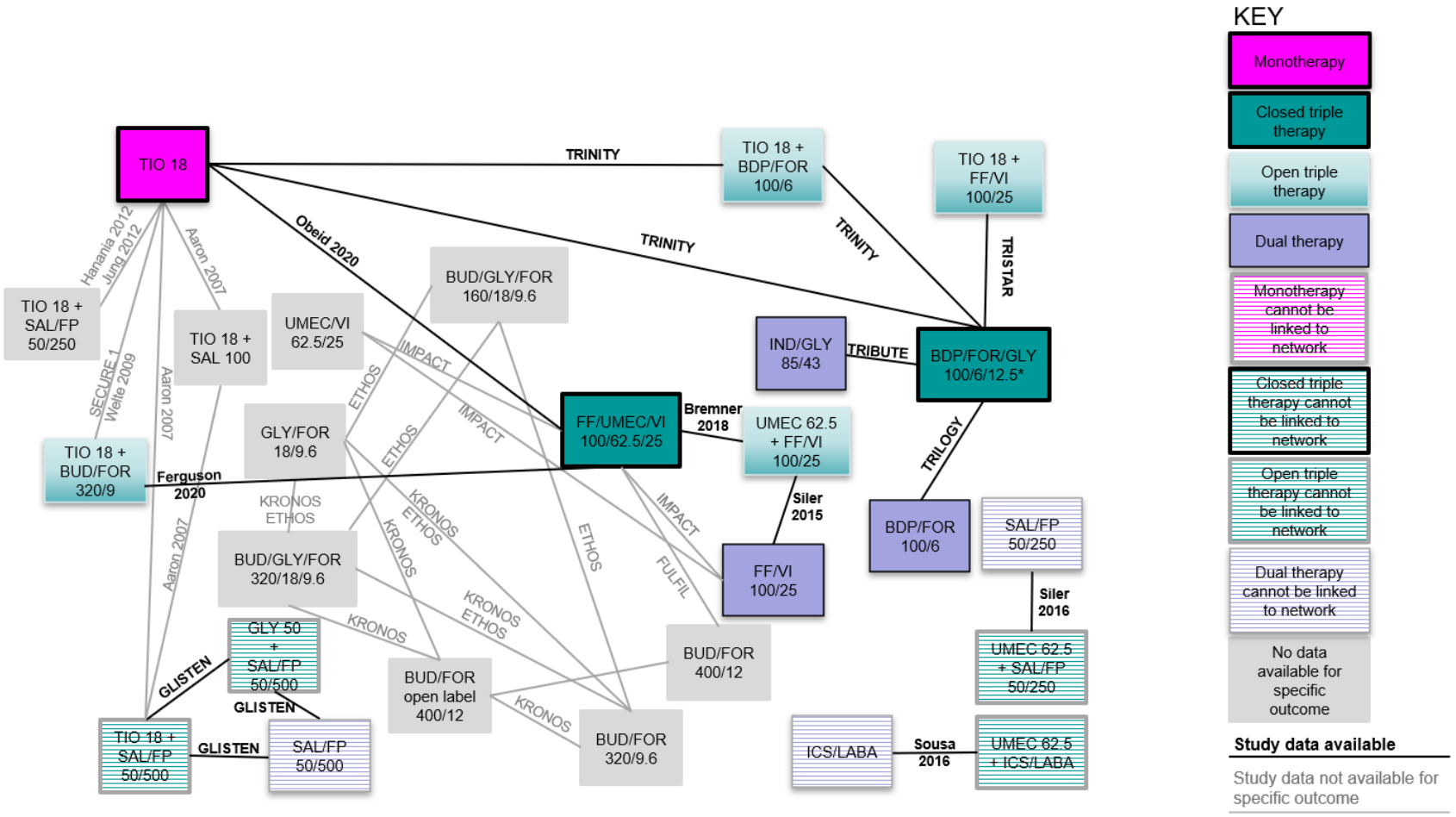
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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, *FEV_1* 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

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

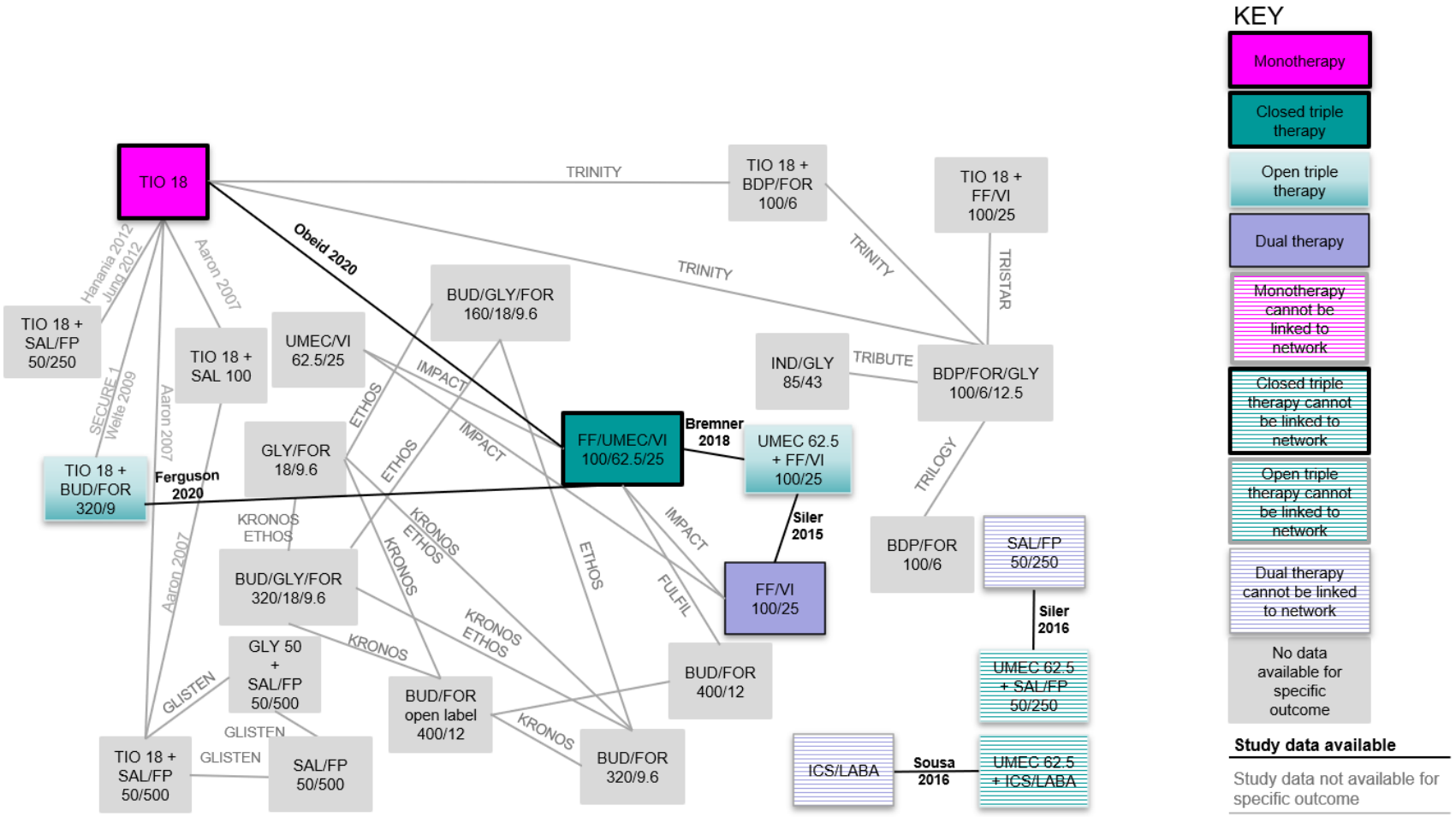
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

Inclusion criteria included patients aged ≥35 years in Aaron 2007, and patients aged 40–80 in ETHOS, 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_1* 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

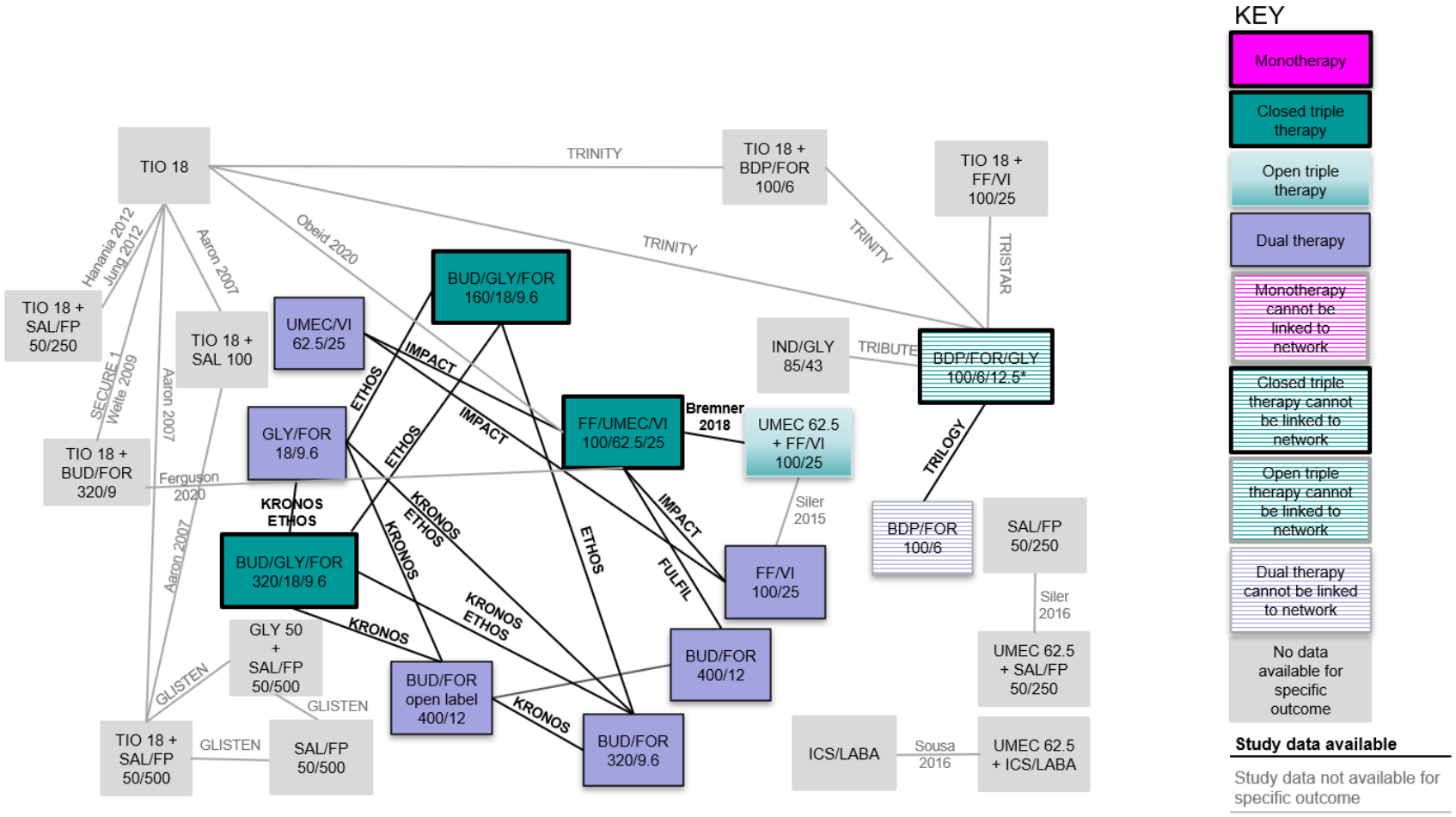
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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, *FEV_1* 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

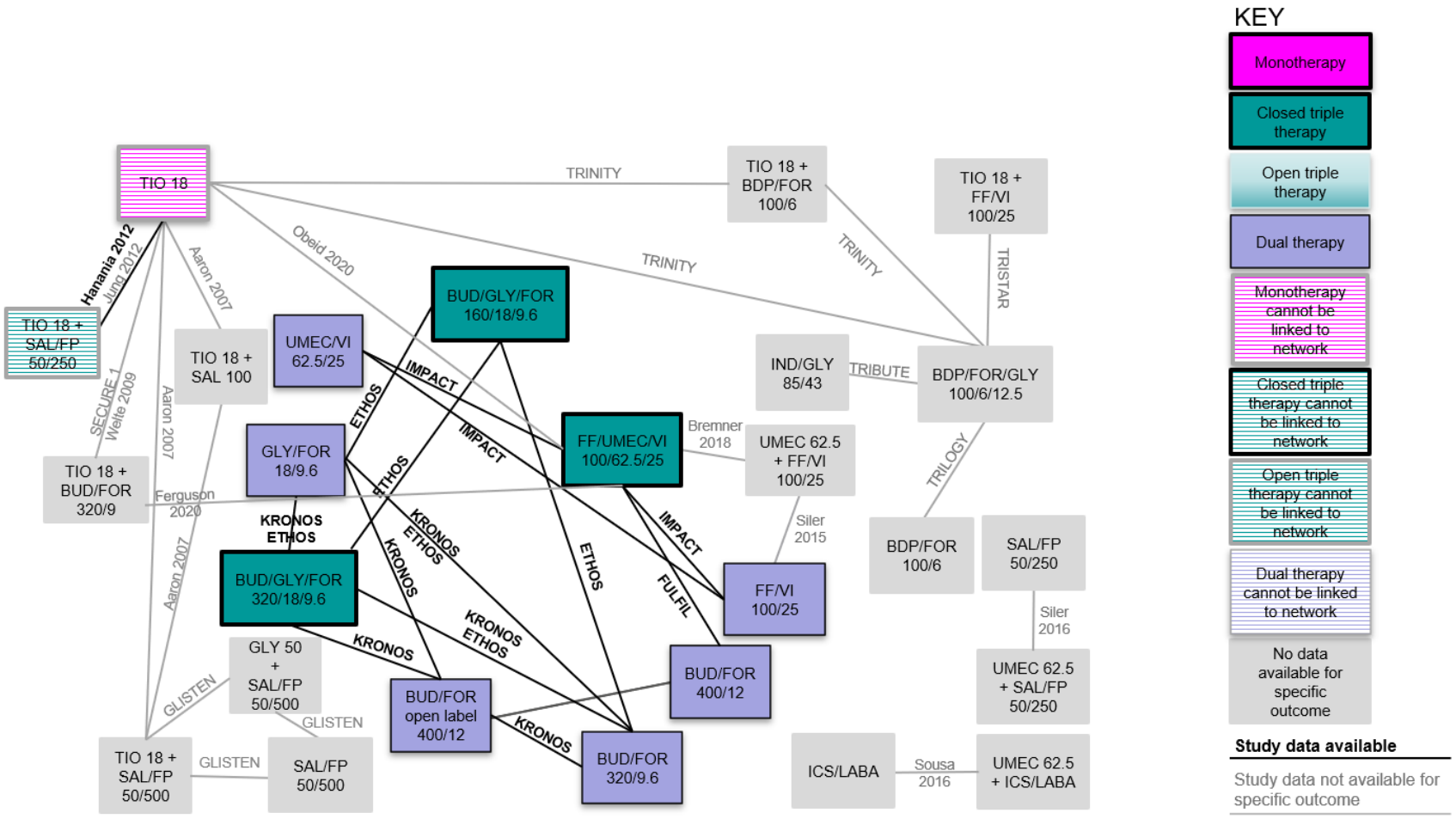
*****TRIBUTE dosage was BDP/FOR/GLY 100/6/10 µg

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, *FEV_1* 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

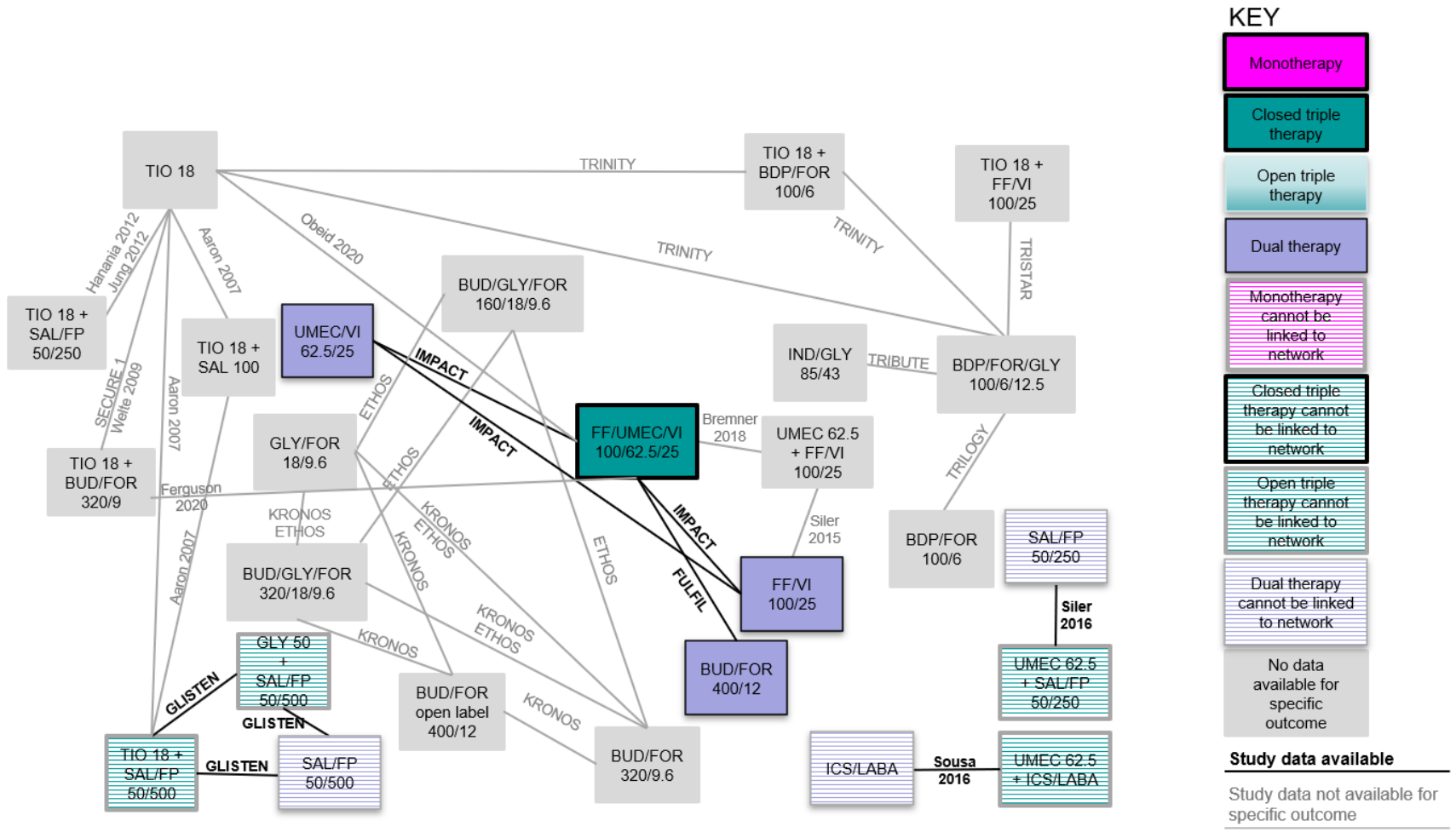
Sousa 2016 and Siler 2016 studies could not be connected to the main network due to non-availability of a common comparator

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, *UMEC* umeclidinium, *VI* vilanterol

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