Supplementary material

Comparative Efficacy of Umeclidinium/Vilanterol versus Other Bronchodilators for the Treatment of Chronic Obstructive Pulmonary Disease: A Network Meta-analysis

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Running Title: LAMA/LABA dual therapy in COPD: network meta-analysis

Supplementary Methods

Frequentist NMA is based on weighted least squares (LS) regression. In an ordinary LS regression, equal variances are assumed for all observations. In a weighted LS 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.

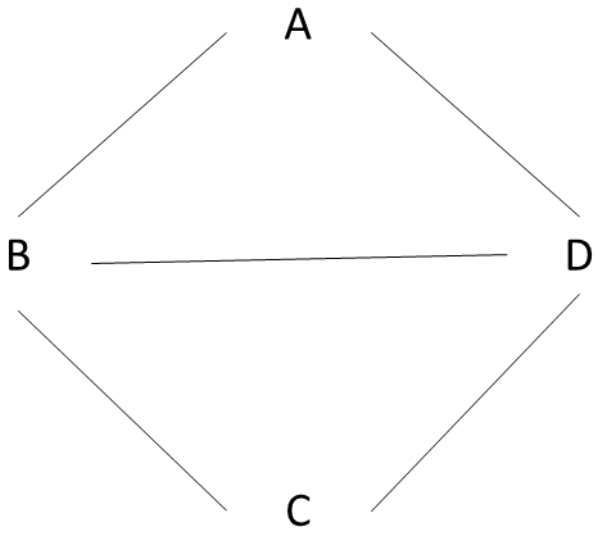
The residuals e_i of a study i are weighted by the study weight w_i, which is again the inverse of the corresponding within-studies variance v_i in a FE model or the sum of within-studies variance v_i and the between studies variance τ^2 in a RE model. The analyses were based on Rücker [1] and performed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

The model based on weighted LS regression is given as:

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

where $\widehat{\boldsymbol{\theta}}$ represents a vector of m observed pairwise comparisons with known standard errors $\boldsymbol{s} = (s_1, s_2, \ldots, s_m)$, $\boldsymbol{X}$ is the $m \times n$ design matrix defining the network structure, $\boldsymbol{\theta}^{\boldsymbol{trt}}$ is a vector of length n including the number of treatments, and $\boldsymbol{\Sigma}$ is a diagonal matrix whose i^{th} entry is $\boldsymbol{s_i^2}$.
In a fictional example network with $n = 4$ treatments including $k = 5$ studies each providing a single pairwise treatment comparison (**Supplementary Methods Figure**), we would have $m = 5$ pairwise treatment comparisons and the model would be defined as

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



Supplementary Methods Figure. 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 $\boldsymbol{W} = diag\left(\frac{1}{s_1^2}, \ldots, \frac{1}{s_m^2}\right)$, including the inverse variance weights. The network estimates are given by $\widehat{\boldsymbol{\theta}}^{nma} = \boldsymbol{H}\widehat{\boldsymbol{\theta}}$, where

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

is the hat matrix in regression. Thus, the network estimates are weighted sums of the observed estimates with weights obtained through the rows of $\boldsymbol{H}$. The corresponding standard errors are calculated from the variance-covariance matrix

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

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

$$Q_{\boldsymbol{total}} = \left(\widehat{\boldsymbol{\theta}} - \widehat{\boldsymbol{\theta}}^{nma}\right)^{T}\boldsymbol{W}\left(\widehat{\boldsymbol{\theta}} - \widehat{\boldsymbol{\theta}}^{nma}\right).$$

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

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

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 $m \times m$ $\boldsymbol{U}$ matrix includes the number of comparisons m, and the identity matrix $\boldsymbol{I}$ is derived as $\boldsymbol{HH^{T/2}}$.

In this study, for all analyses, both the FE and RE models were used in order to obtain more and less conservative estimates.

For continuous outcomes (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 outcomes, if the hazard ratios (HRs) or rate ratios (RaR) with corresponding 95% CIs were reported directly, the corresponding SE 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 equation is the same.

For count outcomes, if no RaR with 95% CI was reported directly, the SE 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 outcomes, 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 (OR) on the log scale as

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

Supplementary Methods References

1. Rucker G. Network meta-analysis, electrical networks and graph theory. Res Synth Methods 2012;3(4):312-24. doi: 10.1002/jrsm.1058.

2. Rucker G, Krahn U, König J, Efthimiou O, Schwarzer G.: Package ‚netmeta'. Network Meta-Analysis using Frequentist Methods. Available from: https://cran.r-project.org/web/packages/netmeta/netmeta.pdf

3. Senn S, Gavini F, Magrez D, Scheen A. Issues in performing a network meta-analysis. Stat Methods Med Res. 2013;22(2):169-89.

Supplementary Table S1. Random effects model of outcomes of interest with UMEC/VI versus dual and monotherapies at 24 weeks

	Trough FEV_1, mean CFB, mL (95% CI)	**SGRQ total score, mean CFB (95% CI)**	**SGRQ responders, OR (95% CI)**	**TDI focal score, mean CFB (95% CI)**	**TDI responders, OR (95% CI)**	**Rescue medication use, mean CFB, puffs/day (95% CI)**	**Annualised moderate/severe exacerbations, incidence rate ratio (95% CI)**	**Time to first exacerbation, HR (95% CI)**
UMEC/VI vs dual therapies								
ACL/FOR 400/6	**101.94 (65.92, 137.96) p≤0.0001**	0.23 (-2.01, 2.46) p=0.8434	1.08 (0.75, 1.55) p=0.6689	-0.19 (-0.57, 0.2) p=0.3414	0.71 (0.48, 1.05) p=0.0825	-0.31 (-0.79, 0.18) p=0.2160	**0.43 (0.18, 0.99) p=0.0486**	NR
ACL/FOR 400/12	**87.57 (56.98, 118.17) p≤0.0001**	-0.37 (-2.25, 1.51) p=0.7008	1.02 (0.75, 1.38) p=0.9096	-0.22 (-0.58, 0.14) p=0.2355	0.78 (0.53, 1.15) p=0.2121	**-0.51 (-0.94, -0.09) p=0.0173**	**0.45 (0.21, 0.94) p=0.0348**	NR
GLY/FOR 18/9.6	**71.79 (47.23, 96.35) p≤0.0001**	-0.45 (-2.17, 1.27) p=0.6087	1.17 (0.88, 1.54) p=0.2804	**0.33 (0.13,0.52) p=0.0013**	0.82 (0.51, 1.31) p=0.4038	-0.14 (-0.55, 0.28) p=0.5246	1.02 (0.72, 1.47) p=0.8944	1.03 (0.68, 1.56) p=0.8857
GLY/FOR (MDI) 18/9.6	NR	NR	1.19 (0.85, 1.68) p=0.3056	NR	NR	NR	NR	NR
IND/GLY 110/50	24.93 (-3.3, 53.16) p=0.0835	1.04 (-0.60, 2.69) p=0.2129	0.93 (0.71, 1.21) p=0.5906	-0.18 (-0.51, 0.15) p=0.2908	0.95 (0.64 ,1.41) p=0.7873	-0.18 (-0.75, 0.39) p=0.5434	0.60 (0.29, 1.23) p=0.1653	0.89 (0.48, 1.63) p=0.6980
TIO 18 + FOR 10	NR	-0.28 (-2.97, 2.42) p=0.8393	NR	NR	NR	NR	NR	NR
TIO 18 + FOR 12	**92.93 (43.81, 142.06) p=0.0002**	NR	NR	0.20 (-0.34, 0.75) p=0.4639	1.27 (0.74, 2.16) p=0.3870	NR	NR	0.72 (0.34, 1.50) p=0.3778
UMEC/VI vs LAMA monotherapies								
UMEC 62.5	**64.38 (36.44, 92.33) p≤0.0001**	0.03 (-1.32, 1.38) p=0.9639	1.19 (0.98, 1.45) p=0.0825	**0.32 (0.08, 0.57) p=0.0090**	**1.31 (1.04, 1.65) p=0.0202**	-0.33 (-0.70, 0.04) p=0.0833	0.82 (0.58, 1.18) p=0.2848	0.80 (0.58, 1.09) p=0.1615
UMEC 125	**47.89 (14.49, 81.28) p=0.0049**	**-1.88 (-3.67, -0.08) p=0.041**	1.26 (0.96, 1.65) p=0.094	**0.55 (0.16, 0.93) p=0.0053**	1.18 (0.87, 1.60) p=0.2934	-0.42 (-0.93, 0.08) p=0.1027	NR	1.05 (0.65, 1.70) p=0.8497

ACL 400	**101.4 (69.01, 133.8) p≤0.0001**	-0.99 (-2.94, 0.97) p=0.3234	1.08 (0.81, 1.45) p=0.5986	0.18 (-0.21, 0.57) p=0.3570	0.99 (0.67, 1.47) p=0.9798	**-0.56 (-1.01, -0.10) p=0.0166**	**0.44 (0.21, 0.92) p=0.0292**	NR
GLY 18	**127.53 (99.31, 155.75) p≤0.0001**	**-2.01 (-3.76, -0.27) p=0.0235**	**1.52 (1.16, 1.99) p=0.0024**	**0.68 (0.32, 1.04) p=0.0003**	1.22 (0.76, 1.98) p=0.4099	**-0.66 (-1.08, -0.24) p=0.0021**	NR	NR
GLY 50	**97.67 (68.4, 126.93) p<0.0001**	-1.26 (-2.95, 0.42) p=0.1413	1.16 (0.89, 1.51) p=0.2717	0.06 (-0.29, 0.41) p=0.7386	1.15 (0.77, 1.71) p=0.4852	**-0.84 (-1.41, -0.27) p=0.0040**	0.53 (0.26, 1.09) p=0.0845	0.70 (0.39, 1.28) p=0.2446
TIO 18	**87.22 (65.35, 109.09) p≤0.0001**	**-1.29 (-2.52, -0.07) p=0.0386**	1.17 (0.97, 1.41) p=0.1097	**0.34 (0.03, 0.64) p=0.0310**	1.23 (0.93, 1.62) p=0.1438	**-0.55 (-0.83, -0.27) p=0.0001**	0.54 (0.28, 1.05) p=0.0687	1.00 (0.65, 1.53) p=0.9917
UMEC/VI vs LABA monotherapies								
VI 25	**95.76 (68.86, 122.66) p≤0.0001**	-0.37 (-1.85, 1.11) p=0.625	1.10 (0.89, 1.36) p=0.3996	**0.42 (0.13, 0.71) p=0.0045**	**1.37 (1.07, 1.75) p=0.0111**	-0.33 (-0.84, 0.17) p=0.1904	NR	0.69 (0.45, 1.05) p=0.0844
FOR 9.6	**134.16 (105.93, 162.38) p≤0.0001**	-0.76 (-2.5, 0.98) p=0.3912	**1.35 (1.03, 1.76) p=0.0294**	**0.48 (0.11, 0.84) p=0.0104**	0.94 (0.58, 1.52) p=0.7961	-0.34 (-0.76, 0.08) p=0.1115	NR	NR
FOR 10	NR	-0.33 (-3.02, 2.37) p=0.811	NR	NR	NR	NR	NR	NR
FOR 12	**138.21 (106.21, 170.22) p≤0.0001**	-1.23 (-3.24, 0.78) p=0.2304	1.11 (0.82, 1.5) p=0.4852	0.22 (-0.17, 0.61) p=0.2605	0.95 (0.64, 1.41) p=0.8131	-0.45 (-0.92, 0.02) p=0.0579	**0.42 (0.20, 0.88) p=0.0217**	NR
SAL 50	**140.19 (105.66, 174.72) p≤0.0001**	**-1.80 (-3.44, -0.15) p=0.0322**	**1.47 (1.15, 1.88) p=0.0024**	**0.43 (0.14, 0.72) p=0.0040**	**1.40 (1.04, 1.87) p=0.0248**	-0.28 (-0.65, 0.09) p=0.1417	**0.68 (0.48, 0.96) p=0.0270**	**0.63 (0.44, 0.92) p=0.0174**
IND 150	**81.69 (41.23, 122.14) p≤0.0001**	-0.92 (-3.68, 1.85) p=0.5155	1.01 (0.73, 1.39) p=0.9492	0.11 (-0.23, 0.45) p=0.5259	1.11 (0.74, 1.65) p=0.6413	-0.49 (-1.06, 0.08) p=0.0943	NR	NR
UMEC/VI vs placebo	**207.78 (184.88, 230.67) p≤0.0001**	**-3.21 (-4.59, -1.84) p≤0.0001**	**1.71 (1.39, 2.11) p≤0.0001**	**1.08 (0.82, 1.35) p≤0.0001**	**1.82 (1.39, 2.37) p≤0.0001**	**-1.20 (-1.57, -0.83) p≤0.0001**	**0.40 (0.18, 0.88) p=0.0219**	**0.46 (0.30, 0.71) p=0.0004**

ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Table S2. Fixed and random effects models of outcomes of interest with UMEC/VI versus dual and monotherapies at 12 weeks

	SGRQ total score, mean CFB (95% CI)		**SGRQ responders, OR (95% CI)**		**TDI focal score, mean CFB (95% CI)**		**TDI responders, OR (95% CI)**		**Rescue medication use, mean CFB, puffs/day (95% CI)[a]**	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
UMEC/VI vs dual therapies										
ACL/FOR 400/6	NR	NR	1.06 (0.74, 1.53) p=0.7505	1.06 (0.74, 1.53) p=0.7505	NR	NR	0.82 (0.55, 1.22) p=0.3351	0.82 (0.55, 1.22) p=0.3351	NR	NR
ACL/FOR 400/12	NR	NR	0.94 (0.65, 1.36) p=0.7484	0.94 (0.65, 1.36) p=0.7484	0.22 (-0.23, 0.66) p=0.3367	0.21 (-0.33, 0.75) p=0.4416	0.85 (0.57, 1.26) p=0.4180	0.85 (0.57, 1.26) p=0.4180	NR	NR
IND/GLY 27.5/15.6	1.04 (-0.87, 2.96) p=0.2862	1.07 (-1.06, 3.20) p=0.3246	0.74 (0.53, 1.02) p=0.0647	0.74 (0.53, 1.02) p=0.0647	**-0.51 (-0.93, -0.08) p=0.0196**	**-0.51 (-1.00, -0.01) p=0.0439**	0.95 (0.67, 1.34) p=0.7621	0.95 (0.67, 1.34) p=0.7621	**0.50 (0.06, 0.93) p=0.0256**	0.49 (-0.25, 1.24) p=0.1942
IND/GLY 110/50	**1.13 (0.02, 2.24) p=0.0458**	1.24 (-0.08, 2.57) p=0.0662	0.88 (0.67, 1.14) p=0.3306	0.88 (0.67, 1.14) p=0.3306	-0.16 (-0.38, 0.06) p=0.1529	-0.18 (-0.46, 0.10) p=0.2182	NR	NR	NR	NR
IND/GLY 150/50	NR	NR	NR	NR	-0.38 (-0.92, 0.16) p=0.1641	-0.39 (-1.04, 0.26) p=0.2403	NR	NR	NR	NR
TIO/OLO 2.5/5	-0.04 (-1.92, 1.84) p=0.9665	-0.03 (-2.13, 2.06) p=0.9744	0.87 (0.61, 1.24) p=0.4456	0.87 (0.61, 1.24) p=0.4456	**-0.50 (-0.94, -0.05) p=0.0278**	-0.50 (-1.01, 0.01) p=0.0562	NR	NR	NR	NR
TIO/OLO 5/5	0.79 (-1.09, 2.67) p=0.4083	0.80 (-1.29, 2.89) p=0.4540	0.71 (0.50, 1.01) p=0.0547	0.71 (0.50, 1.01) p=0.0547	**-0.51 (-0.96, -0.07) p=0.0231**	**0.51 (-1.02, 0) p=0.0487**	NR	NR	**-0.25 (-0.37, -0.13) p≤0.0001**	-0.25 (-0.76, 0.26) p=0.3325
TIO 18 + FOR 12	-0.52 (-3.63, 2.59) p=0.7425	-0.49 (-3.80, 2.81) p=0.7707	NR	NR	0.40 (-0.40, 1.19) p=0.3246	0.39 (-0.46, 1.24) p=0.3713	NR	NR	0.31 (-0.20, 0.83) p=0.2351	0.05 (-0.73, 0.83) p=0.9030
TIO 18 + IND 150	**1.38 (0.04, 2.73) p=0.0440**	1.48 (-0.08, 3.05) p=0.0627	1.08 (0.84, 1.40) p=0.5437	1.08 (0.84, 1.40) p=0.5437	-0.30 (-0.65, 0.05) p=0.0956	-0.30 (-0.74, 0.14) p=0.1837	0.89 (0.69, 1.17) p=0.4089	0.89 (0.69, 1.17) p=0.4089	**0.35 (0.19, 0.50) p≤0.0001**	0.31 (-0.08, 0.69) p=0.1151
UMEC/VI vs LAMA monotherapies										
UMEC 62.5	-0.90 (-1.90, 0.10) p=0.0764	-0.89 (-2.11, 0.34) p=0.1556	**1.31 (1.12, 1.53) p=0.0009**	**1.31 (1.12, 1.53) p=0.0009**	**0.53 (0.30, 0.76) p≤0.0001**	**0.51 (0.22, 0.80) p=0.0006**	**1.43 (1.22, 1.68) p≤0.0001**	**1.43 (1.22, 1.68) p≤0.0001**	**-0.31 (-0.47, -0.15) p=0.0001**	-0.31 (-0.83, 0.21) p=0.2399

UMEC 125	-2.03 (-4.19, 0.12) p=0.0646	-2.02 (-4.36, 0.32) p=0.0909	1.12 (0.88, 1.42) p=0.3704	1.12 (0.88, 1.42) p=0.3704	**0.34 (0.01, 0.68) p=0.0453**	0.34 (-0.05, 0.73) p=0.0878	1.22 (0.95, 1.56) p=0.1129	1.22 (0.95, 1.56) p=0.1129	-0.30 (-0.93, 0.33) p=0.3531	-0.58 (-1.40, 0.25) p=0.1713
ACL 400	NR	NR	**1.47 (1.02, 2.12) p=0.0410**	**1.47 (1.02, 2.12) p=0.0410**	NR	NR	1.15 (0.78, 1.70) p=0.4858	1.15 (0.78, 1.70) p=0.4858	NR	NR
GLY 15.6	-0.52 (-2.90, 1.86) p=0.6676	-0.50 (-3.05, 2.05) p=0.7003	1.09 (0.79, 1.50) p=0.6134	1.09 (0.79, 1.50) p=0.6134	0.22 (-0.12, 0.56) p=0.2137	0.21 (-0.21, 0.64) p=0.3247	**1.56 (1.10, 2.20) p=0.0117**	**1.56 (1.10, 2.20) p=0.0117**	0 (-0.40, 0.39) p=0.9857	0 (-0.73, 0.72) p=0.9900
GLY 50	-1.21 (-2.62, 0.20) p=0.0928	-1.20 (-2.81, 0.41) p=0.1439	1.12 (0.86, 1.45) p=0.4115	1.12 (0.86, 1.45) p=0.4115	0.25 (-0.01, 0.52) p=0.0582	0.25 (-0.11, 0.61) p=0.1811	NR	NR	NR	NR
TIO 5	-1.30 (-3.18, 0.59) p=0.1776	-1.29 (-3.39, 0.80) p=0.2266	1.14 (0.80, 1.62) p=0.4790	1.14 (0.80, 1.62) p=0.4790	0.08 (-0.36, 0.52) p=0.7195	0.08 (-0.43, 0.59) p=0.7534	NR	NR	NR	NR
TIO 18	**-1.53 (-2.38, -0.69) p=0.0004**	**-1.50 (-2.48, -0.52) p=0.0026**	1.16 (0.98, 1.38) p=0.0775	1.16 (0.98, 1.38) p=0.0775	**0.47 (0.25, 0.69) p≤0.0001**	**0.46 (0.19, 0.72) p=0.0007**	**1.58 (1.27, 1.95) p≤0.0001**	**1.58 (1.27, 1.95) p≤0.0001**	**-0.19 (-0.28, -0.10) p=0.0001**	**-0.45 (-0.78, -0.13) p=0.0065**
UMEC/VI vs LABA monotherapies										
VI 25	-1.17 (-2.48, 0.14) p=0.0806	-1.16 (-2.63, 0.32) p=0.1245	1.19 (0.98, 1.43) p=0.0728	1.19 (0.98, 1.43) p=0.0728	**0.45 (0.20, 0.71) p=0.0004**	**0.45 (0.15, 0.74) p=0.0034**	**1.31 (1.08, 1.58) p=0.0069**	**1.31 (1.08, 1.58) p=0.0069**	0.20 (-0.39, 0.80) p=0.5040	-0.13 (-0.92, 0.66) p=0.7492
FOR 12	NR	NR	1.38 (0.95, 1.99) p=0.0893	1.38 (0.95, 1.99) p=0.0893	NR	NR	1.20 (0.81, 1.78) p=0.3590	1.20 (0.81, 1.78) p=0.3590	NR	NR
SAL 50	**-1.26 (-2.44, -0.07) p=0.0376**	-1.25 (-2.76, 0.27) p=0.1062	**1.39 (1.15, 1.68) p=0.0006**	**1.39 (1.15, 1.68) p=0.0006**	**0.56 (0.27, 0.84) p=0.0001**	**0.55 (0.17, 0.92) p=0.0046**	**1.41 (1.17, 1.70) p=0.0003**	**1.41 (1.17, 1.70) p=0.0003**	**-0.31 (-0.47, -0.15) p=0.0001**	-0.31 (-0.83, 0.21) p=0.2395
IND 27.5	-0.68 (-3.06, 1.70) p=0.5775	-0.66 (-3.21, 1.90) p=0.6146	0.94 (0.68, 1.30) p=0.7269	0.94 (0.68, 1.30) p=0.7269	0.27 (-0.08, 0.61) p=0.1280	0.26 (-0.17, 0.68) p=0.2325	1.25 (0.88, 1.76) p=0.2115	1.25 (0.88, 1.76) p=0.2115	0.17 (-0.23, 0.57) p=0.4003	0.17 (-0.55, 0.89) p=0.6439
IND 150	NR	NR	NR	NR	0.11 (-0.15, 0.37) p=0.4049	0.10 (-0.26, 0.47) p=0.5711	NR	NR	NR	NR
UMEC/VI vs placebo	**-3.93 (-5.19, -2.67) p≤0.0001**	**-3.92 (-5.31, -2.54) p≤0.0001**	**1.78 (1.45, 2.18) p≤0.0001**	**1.78 (1.45, 2.18) p≤0.0001**	**1.11 (0.87, 1.35) p≤0.0001**	**1.11 (0.82, 1.40) p≤0.0001**	**2.39 (1.88, 3.04) p≤0.0001**	**2.39 (1.88, 3.04) p≤0.0001**	**-0.70 (-1.05, -0.35) p=0.0001**	**-0.70 (-1.31, -0.09) p=0.0234**

[a]Data on Weeks 1–12 were used throughout.

ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; OLO, olodaterol; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Table S3. Fixed and random effects models of outcomes of interest with dual and mono-therapies versus placebo at 24 weeks

	SGRQ total score, mean CFB (95% CI)		**SGRQ responders, OR (95% CI)**		**TDI focal score, mean CFB (95% CI)**		**TDI responders, OR (95% CI)**		**Rescue medication use, mean CFB, puffs/day (95% CI)**		**Annualised moderate/severe exacerbations, incidence rate ratio (95% CI)**		**Time to first exacerbation, HR (95% CI)**	
Active comparator	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Dual therapies														
UMEC/VI 62.5/25	**-3.30 (-4.50, -2.10) p≤0.0001**	**-3.21 (-4.59, -1.84) p≤0.0001**	**1.73 (1.44, 2.08) p≤0.0001**	**1.71 (1.39, 2.11) p≤0.0001**	**1.08 (0.82, 1.35) p≤0.0001**	**1.08 (0.82, 1.35) p≤0.0001**	**1.83 (1.47, 2.27) p≤0.0001**	**1.82 (1.39, 2.37) p≤0.0001**	**-1.16 (-1.33, -0.98) p≤0.0001**	**-1.2 (-1.57, -0.83) p≤0.0001**	**0.40 (0.20, 0.80) p=0.0091**	**0.40 (0.18, 0.88) p=0.0219**	**0.47 (0.32, 0.67) p<0.0001**	**0.46 (0.3, 0.71) p=0.0004**
ACL/FOR 400/6	**-3.49 (-5.26, -1.73) p=0.0001**	**-3.44 (-5.37, -1.51) p=0.0005**	**1.57 (1.19, 2.08) p=0.0014**	**1.58 (1.15, 2.18) p=0.0050**	**1.27 (0.98, 1.56) p≤0.0001**	**1.27 (0.98, 1.56) p≤0.0001**	**2.58 (2.04, 3.26) p≤0.0001**	**2.57 (1.93, 3.44) p≤0.0001**	**-0.99 (-1.21, -0.76) p≤0.0001**	**-0.89 (-1.23, -0.56) p≤0.0001**	0.94 (0.68, 1.3) p=0.7082	0.94 (0.63, 1.41) p=0.7639	NR	NR
ACL/FOR 400/12	**-2.88 (-4.28, -1.48) p=0.0001**	**-2.85 (-4.41, -1.28) p=0.0004**	**1.67 (1.34, 2.1) p≤0.0001**	**1.68 (1.3, 2.18) p=0.0001**	**1.3 (1.04, 1.56) p≤0.0001**	**1.3 (1.04, 1.56) p≤0.0001**	**2.35 (1.86, 2.96) p≤0.0001**	**2.33 (1.75, 3.11) p≤0.0001**	**-0.7 (-0.86, -0.55) p≤0.0001**	**-0.68 (-0.96, -0.41) p≤0.0001**	0.94 (0.76, 1.16) p=0.5447	0.90 (0.66, 1.22) p=0.4905	NR	NR
GLY/FOR 18/9.6	**-2.75 (-3.83, -1.67) p≤0.0001**	**-2.76 (-4.02, -1.51) p≤0.0001**	**1.47 (1.21, 1.78) p=0.0001**	**1.47 (1.18, 1.83) p=0.0006**	**0.76 (0.48, 1.03) p≤0.0001**	**0.76 (0.48, 1.03) p≤0.0001**	**2.22 (1.63, 3.04) p≤0.0001**	**2.22 (1.5, 3.3) p=0.0001**	**-1.07 (-1.26, -0.88) p≤0.0001**	**-1.06 (-1.34, -0.79) p≤0.0001**	**0.39 (0.19, 0.82) p=0.0125**	**0.39 (0.17, 0.93) p=0.0326**	**0.45 (0.29, 0.72) p=0.0008**	**0.44 (0.24, 0.81) p=0.0082**
GLY/FOR (MDI) 18/9.6	NR	NR	**1.42 (1.12, 1.81) p=0.0041**	**1.43 (1.08, 1.91) p=0.0133**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IND/GLY 110/50	**-4.30 (-5.40, -3.21) p≤0.0001**	**-4.26 (-5.69, -2.82) p≤0.0001**	**1.86 (1.53, 2.28) p≤0.0001**	**1.84 (1.45, 2.33) p≤0.0001**	**1.26 (1.02, 1.5) p≤0.0001**	**1.26 (1.02, 1.5) p≤0.0001**	**1.94 (1.45, 2.58) p≤0.0001**	**1.92 (1.34, 2.76) p=0.0004**	**-0.96 (-1.29, -0.63) p≤0.0001**	**-1.02 (-1.49, -0.55) p≤0.0001**	**0.67 (0.47, 0.95) p=0.0239**	0.67 (0.40, 1.11) p=0.1210	**0.53 (0.29, 0.99) p=0.0455**	0.52 (0.25, 1.08) p=0.0796
TIO 18 + FOR 10	**-2.94 (-5.19, -0.68) p=0.0106**	**-2.93 (-5.41, -0.46) p=0.0201**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
TIO 18 + FOR 12	NR	NR	NR	NR	**0.88 (0.39,**	**0.88 (0.39,**	1.45 (0.98,	1.44 (0.86,	NR	NR	NR	NR	0.66 (0.34,	0.64 (0.27,

					1.38) p=0.0005	**1.38) p=0.0005**	2.14) p=0.0614	2.38) p=0.1619					1.30) p=0.2287	1.49) p=0.2986
LAMA monotherapies														
UMEC 62.5	**-3.34 (-4.81, -1.86) p≤0.0001**	**-3.24 (-4.97, -1.52) p=0.0002**	**1.45 (1.17, 1.8) p=0.0007**	**1.44 (1.12, 1.85) p=0.0051**	**0.76 (0.44, 1.08) p≤0.0001**	**0.76 (0.44, 1.08) p≤0.0001**	**1.37 (1.08, 1.74) p=0.0087**	**1.39 (1.02, 1.88) p=0.0345**	**-0.83 (-1.06, -0.60) p≤0.0001**	**-0.87 (-1.39, -0.34) p≤0.0001**	0.49 (0.23, 1.02) p=0.0551	0.49 (0.21, 1.15) p=0.1013	**0.58 (0.40, 0.85) p=0.0051**	**0.57 (0.36, 0.91) p=0.0187**
UMEC 125	-1.41 (-2.96, 0.15) p=0.0763	-1.34 (-3.09, 0.41) p=0.1336	**1.37 (1.09, 1.74) p=0.0081**	**1.36 (1.04, 1.77) p=0.0227**	**0.54 (0.17, 0.9) p=0.0044**	**0.54 (0.17, 0.9) p=0.0044**	**1.54 (1.21, 1.98) p=0.0006**	**1.54 (1.14, 2.09) p=0.0051**	**-0.80 (-1.15, -0.44) p≤0.0001**	**-0.78 (-1.21, -0.34) p≤0.0001**	NR	NR	**0.43 (0.29, 0.64) p≤0.0001**	**0.44 (0.27, 0.70) p=0.0005**
ACL 400	**-2.26 (-3.74, -0.77) p=0.0029**	**-2.23 (-3.87, -0.59) p=0.0078**	**1.57 (1.27, 1.95) p≤0.0001**	**1.58 (1.23, 2.03) p=0.0003**	**0.90 (0.61, 1.19) p≤0.0001**	**0.90 (0.61, 1.19) p≤0.0001**	**1.83 (1.46, 2.31) p≤0.0001**	**1.83 (1.37, 2.43) p≤0.0001**	**-0.79 (-0.99, -0.60) p≤0.0001**	**-0.64 (-0.96, -0.32) p≤0.0001**	0.91 (0.72, 1.16) p=0.4438	0.92 (0.67, 1.28) p=0.6373	NR	NR
GLY 18	**-1.18 (-2.30, -0.07) p=0.0371**	-1.20 (-2.48, 0.08) p=0.0668	1.13 (0.94, 1.35) p=0.1907	1.13 (0.92, 1.38) p=0.2422	**0.4 (0.04, 0.77) p=0.029**	**0.4 (0.04, 0.77) p=0.029**	**1.48 (1.08, 2.04) p≤0.0156**	1.48 (1, 2.21) p=0.0523	**-0.57 (-0.77, -0.37) p≤0.0001**	**-0.54 (-0.82, -0.26) p≤0.0001**	NR	NR	NR	NR
GLY 50	**-1.87 (-2.99, -0.76) p=0.0010**	**-1.95 (-3.44, -0.45) p=0.0106**	**1.49 (1.22, 1.81) p=0.0001**	**1.48 (1.17, 1.87) p=0.0012**	**1.02 (0.76, 1.29) p≤0.0001**	**1.02 (0.76, 1.29) p≤0.0001**	**1.59 (1.2, 2.11) p=0.0013**	**1.58 (1.10, 2.26) p=0.0128**	-0.30 (-0.63, 0.03) p=0.0792	-0.36 (-0.83, 0.11) p=0.0792	0.75 (0.53, 1.07) p=0.1149	0.76 (0.45, 1.26) p=0.2810	0.68 (0.37, 1.24) p=0.2072	0.65 (0.31, 1.36) p=0.2562
TIO 18	**-1.93 (-2.86, -1.00) p≤0.0001**	**-1.92 (-2.97, -0.87) p=0.0003**	**1.47 (1.27, 1.70) p≤0.0001**	**1.47 (1.24, 1.73) p≤0.0001**	**0.75 (0.51, 0.98) p≤0.0001**	**0.75 (0.51, 0.98) p≤0.0001**	**1.46 (1.16, 1.83) p=0.0011**	**1.48 (1.12, 1.95) p=0.0054**	**-0.66 (-0.83, -0.48) p≤0.0001**	**-0.65 (-0.90, -0.40) p≤0.0001**	0.74 (0.54, 1.01) p=0.0577	0.74 (0.49, 1.13) p=0.1594	**0.47 (0.28, 0.81) p=0.0059**	**0.46 (0.25, 0.83) p=0.0106**
LABA monotherapies														
VI 25	**-2.86 (-4.20, -1.51) p≤0.0001**	**-2.84 (-4.35, -1.34) p=0.0002**	**1.57 (1.29, 1.91) p≤0.0001**	**1.56 (1.25, 1.95) p=0.0001**	**0.66 (0.37, 0.96) p≤0.0001**	**0.66 (0.37, 0.96) p≤0.0001**	**1.33 (1.07, 1.63) p=0.0085**	**1.33 (1.02, 1.71) p=0.0323**	**-0.87 (-1.21, -0.52) p≤0.0001**	**-0.86 (-1.30, -0.43) p≤0.0001**	NR	NR	0.67 (0.43, 1.06) p=0.0849	0.67 (0.40, 1.12) p=0.1268
FOR 9.6	**-2.44 (-3.56, -1.33) p≤0.0001**	**-2.45 (-3.73, -1.17) p=0.0002**	**1.27 (1.06, 1.52) p=0.0080**	**1.27 (1.04, 1.55) p=0.0197**	**0.61 (0.24, 0.97) p=0.0010**	**0.61 (0.24, 0.97) p=0.0010**	**1.94 (1.41, 2.66) p=0.0001**	**1.94 (1.30, 2.88) p=0.0012**	**-0.88 (-1.08, -0.68) p≤0.0001**	**-0.86 (-1.14, -0.58) p≤0.0001**	NR	NR	NR	NR
FOR 10	**-2.89**	**-2.88**	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

	(-5.14, -0.63) p=0.012	**(-5.36, -0.41) p=0.0223**												
FOR 12	**-2.03 (-3.58, -0.48) p=0.0102**	**-1.98 (-3.68, -0.29) p=0.0219**	**1.53 (1.22, 1.91) p=0.0002**	**1.54 (1.19, 1.99) p=0.0011**	**0.86 (0.57, 1.15) p≤0.0001**	**0.86 (0.57, 1.15) p≤0.0001**	**1.92 (1.52, 2.42) p≤0.0001**	**1.9 (1.43, 2.54) p≤0.0001**	**-0.89 (-1.1, -0.67) p≤0.0001**	**-0.75 (-1.08, -0.41) p≤0.0001**	0.94 (0.76, 1.16) p=0.553	0.96 (0.71, 1.30) p=0.791	NR	NR
SAL 50	-1.51 (-3.18, 0.17) p=0.0773	-1.42 (-3.48, 0.64) p=0.1777	1.18 (0.91, 1.52) p=0.2043	1.17 (0.85, 1.59) p=0.3333	**0.66 (0.28, 1.03) p=0.0006**	**0.66 (0.28, 1.03) p=0.0006**	1.3 (0.99, 1.71) p=0.0613	1.3 (0.89, 1.89) p=0.1682	**-0.88 (-1.11, -0.65) p≤0.0001**	**-0.92 (-1.44, -0.39) p≤0.0001**	0.59 (0.29, 1.23) p=0.1590	0.59 (0.25, 1.39) p=0.2304	0.73 (0.48, 1.11) p=0.1426	0.72 (0.42, 1.24) p=0.236
IND 150	-2.29 (-4.68, 0.10) p=0.0605	-2.30 (-4.9, 0.30) p=0.0833	**1.72 (1.34, 2.20) p≤0.0001**	**1.69 (1.26, 2.27) p=0.0004**	**0.97 (0.72, 1.23) p≤0.0001**	**0.97 (0.72, 1.23) p≤0.0001**	**1.66 (1.25, 2.20) p=0.0005**	**1.64 (1.15, 2.35) p=0.0069**	**-0.65 (-0.98, -0.32) p=0.0001**	**-0.71 (-1.18, -0.24) p=0.0001**	NR	NR	NR	NR

ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Table S4. Fixed and random effects models on outcomes of interest with dual and mono-therapies versus placebo at 12 weeks

	SGRQ total score, mean CFB (95% CI)		**SGRQ responders, OR (95% CI)**		**TDI focal score, mean CFB (95% CI)**		**TDI responders, OR (95% CI)**		**Rescue medication use, mean CFB, puffs/day (95% CI)[a]**	
Active comparator	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Dual therapies										
UMEC/VI 62.5/25	**-3.93 (-5.19, -2.67) p≤0.0001**	**-3.92 (-5.31, -2.54) p≤0.0001**	**1.78 (1.45, 2.18) p≤0.0001**	**1.78 (1.45, 2.18) p≤0.0001**	**1.11 (0.87, 1.35) p≤0.0001**	**1.11 (0.82, 1.40) p≤0.0001**	**2.39 (1.88, 3.04) p≤0.0001**	**2.39 (1.88, 3.04) p≤0.0001**	**-0.7 (-1.05, -0.35) p=0.0001**	**-0.7 (-1.31, -0.09) p=0.0234**
ACL/FOR 400/12	NR	NR	**1.89 (1.39, 2.57) p=0.0001**	**1.89 (1.39, 2.57) p=0.0001**	**0.89 (0.41, 1.38) p=0.0003**	**0.90 (0.31, 1.49) p=0.0003**	**2.82 (2.06, 3.85) p≤0.0001**	**2.82 (2.06, 3.85) p≤0.0001**	NR	NR
ACL/FOR 400/6	NR	NR	**1.68 (1.23, 2.28) p=0.0010**	**1.68 (1.23, 2.28) p=0.0010**	NR	NR	**2.91 (2.12, 3.98) p≤0.0001**	**2.91 2.12, 3.98) p≤0.0001**	NR	NR
IND/GLY 27.5/15.6	**-4.97 (-6.42, -3.53) p≤0.0001**	**-4.99 (-6.61, -3.38) p≤0.0001**	**2.41 (1.87, 3.10) p≤0.0001**	**2.41 (1.87, 3.1) p≤0.0001**	**1.62 (1.26, 1.97) p≤0.0001**	**1.62 (1.22, 2.02) p≤0.0001**	**2.52 (1.96, 3.25) p≤0.0001**	**2.52 (1.96, 3.25) p≤0.0001**	**-1.20 (-1.45, -0.94) p≤0.0001**	**-1.19 (-1.62, -0.76) p≤0.0001**
IND/GLY 110/50	**-5.06 (-6.50, -3.62) p≤0.0001**	**-5.17 (-6.81, -3.52) p≤0.0001**	**2.03 (1.47, 2.81) p≤0.0001**	**2.03 (1.47, 2.81) p≤0.0001**	**1.27 (1.04, 1.5) p≤0.0001**	**1.29 (0.98, 1.59) p≤0.0001**	NR	NR	NR	NR
IND/GLY 150/50	NR	NR	NR	NR	**1.49 (0.96, 2.02) p≤0.0001**	**1.50 (0.86, 2.14) p≤0.0001**	NR	NR	NR	NR
TIO/OLO 2.5/5	**-3.89 (-5.28, -2.50) p≤0.0001**	**-3.89 (-5.46, -2.33) p≤0.0001**	**2.04 (1.53, 2.73) p≤0.0001**	**2.04 (1.53, 2.73) p≤0.0001**	**1.61 (1.23, 1.98) p≤0.0001**	**1.61 (1.19, 2.03) p≤0.0001**	NR	NR	NR	NR
TIO/OLO 5/5	**-4.72 (-6.12, -3.33 p≤0.0001**	**-4.72 (-6.29, -3.16) p≤0.0001**	**2.51 (1.88, 3.36) p≤0.0001**	**2.51 (1.88, 3.36) p≤0.0001**	**1.62 (1.25, 2.00) p≤0.0001**	**1.62 (1.2, 2.04) p≤0.0001**	NR	NR	**-0.45 (-0.82, -0.08) p=0.0177**	-0.45 (-1.24, 0.34) p=0.2634
TIO 18 + FOR 12	**-3.41 (-6.71, -0.11) p=0.043**	-3.43 (-6.95, 0.08) p=0.0554	NR	NR	0.71 (-0.09, 1.51) p=0.0802	0.72 (-0.14, 1.58) p=0.0802	NR	NR	**-1.01 (-1.64, -0.39) p=0.0015**	-0.75 (-1.74, 0.24) p=0.1371
TIO 18 + IND 150	**-5.31 (-7.15, -3.47) p≤0.0001**	**-5.41 (-7.50, -3.32) p≤0.0001**	**1.64 (1.19, 2.28) p=0.0028**	**1.64 (1.19, 2.28) p=0.0028**	**1.41 (0.98, 1.84) p≤0.0001**	**1.41 (0.88, 1.94) p≤0.0001**	**2.67 (1.87, 3.82) p≤0.0001**	**2.67 (1.87, 3.82) p≤0.0001**	**-1.05 (-1.43, -0.66) p≤0.0001**	**-1.01 (-1.73, -0.29) p=0.0058**
LAMA monotherapies										

UMEC 62.5	**-3.03 (-4.50, -1.55) p=0.0001**	**-3.04 (-4.72, -1.36) p=0.0004**	**1.36 (1.08, 1.71) p=0.0082**	**1.36 (1.08, 1.71) p=0.0082**	**0.58 (0.28, 0.87) p=0.0001**	**0.6 (0.24, 0.97) p=0.0001**	**1.67 (1.29, 2.15) p=0.0001**	**1.67 (1.29, 2.15) p=0.0001**	**-0.39 (-0.78, 0) p=0.0483**	-0.39 (-1.19, 0.41) p=0.3369
UMEC 125	-1.90 (-4.36, 0.57) p=0.1313	-1.91 (-4.58, 0.77) p=0.1623	**1.59 (1.23, 2.06) p=0.0004**	**1.59 (1.23, 2.06) p=0.0004**	**0.77 (0.44, 1.10) p≤0.0001**	**0.77 (0.39, 1.16) p≤0.0001**	**1.96 (1.5, 2.56) p≤0.0001**	**1.96 (1.5, 2.56) p≤0.0001**	-0.40 (-1.13, 0.33) p=0.2798	-0.12 (-1.15, 0.9) p=0.8107
ACL 400	NR	NR	1.21 (0.89, 1.65) p=0.2161	1.21 (0.89, 1.65) p=0.2161	NR	NR	**2.08 (1.52, 2.84) p≤0.0001**	**2.08 (1.52, 2.84) p≤0.0001**	NR	NR
GLY 15.6	**-3.41 (-5.43, -1.39) p=0.0009**	**-3.42 (-5.57, -1.28) p=0.0017**	**1.64 (1.28, 2.10) p=0.0001**	**1.64 (1.28, 2.10) p=0.0001**	**0.89 (0.65, 1.14) p≤0.0001**	**0.90 (0.59, 1.21) p≤0.0001**	**1.53 (1.2, 1.96) p=0.0007**	**1.53 (1.2, 1.96) p=0.0007**	**-0.70 (-0.88, -0.51) p≤0.0001**	**-0.70 (-1.09, -0.3) p=0.0005**
GLY 50	**-2.72 (-4.43, -1.02) p=0.0018**	**-2.72 (-4.62, -0.83) p=0.0048**	**1.59 (1.15, 2.20) p=0.0047**	**1.59 (1.15, 2.20) p=0.0047**	**0.86 (0.61, 1.10) p≤0.0001**	**0.86 (0.52, 1.21) p≤0.0001**	NR	NR	NR	NR
TIO 5	**-2.63 (-4.03, -1.24) p=0.0002**	**-2.63 (-4.20, -1.06) p=0.001**	**1.56 (1.17, 2.10) p=0.0027**	**1.56 (1.17, 2.10) p=0.0027**	**1.03 (0.65, 1.40) p≤0.0001**	**1.03 (0.61, 1.45) p≤0.0001**	NR	NR	NR	NR
TIO 18	**-2.40 (-3.8, -1.00) p=0.0008**	**-2.42 (-3.96, -0.88) p=0.0021**	**1.53 (1.19, 1.96) p=0.0009**	**1.53 (1.19, 1.96) p=0.0009**	**0.64 (0.42, 0.86) p≤0.0001**	**0.65 (0.36, 0.94) p≤0.0001**	**1.52 (1.13, 2.04) p=0.0062**	**1.52 (1.13, 2.04) p=0.0062**	**-0.51 (-0.88, -0.15) p=0.0057**	-0.25 (-0.94, 0.44) p=0.4785
LABA monotherapies										
VI 25	**-2.76 (-4.38, -1.14) p=0.0009**	**-2.77 (-4.56, -0.98) p=0.0025**	**1.50 (1.21, 1.86) p=0.0002**	**1.50 (1.21, 1.86) p=0.0002**	**0.66 (0.39, 0.92) p≤0.0001**	**0.67 (0.35, 0.98) p≤0.0001**	**1.83 (1.45, 2.3) p≤0.0001**	**1.83 (1.45, 2.3) p≤0.0001**	**-0.90 (-1.59, -0.21) p=0.0105**	-0.57 (-1.57, 0.43) p=0.2623
FOR 12	NR	NR	1.29 (0.95, 1.76) p=0.1007	1.29 (0.95, 1.76) p=0.1007	NR	NR	**1.99 (1.46, 2.71) p≤0.0001**	**1.99 (1.46, 2.71) p≤0.0001**	NR	NR
SAL 50	**-2.67 (-4.35, -1.00) p=0.0017**	**-2.68 (-4.66, -0.70) p=0.0081**	1.28 (0.98, 1.66) p=0.0700	1.28 (0.98, 1.66) p=0.0700	**0.55 (0.19, 0.91) p=0.0025**	**0.56 (0.11, 1.02) p=0.0025**	**1.7 (1.27, 2.27) p=0.0004**	**1.7 (1.27, 2.27) p=0.0004**	**-0.39 (-0.78, 0) p=0.048**	-0.39 (-1.19, 0.41) p=0.3367
IND 27.5	**-3.25 (-5.27, -1.24) p=0.0016**	**-3.27 (-5.41, -1.13) p=0.0028**	**1.88 (1.47, 2.42) p≤0.0001**	**1.88 (1.47, 2.42) p≤0.0001**	**0.84 (0.60, 1.09) p≤0.0001**	**0.85 (0.54, 1.16) p≤0.0001**	**1.92 (1.49, 2.46) p≤0.0001**	**1.92 (1.49, 2.46) p≤0.0001**	**-0.87 (-1.05, -0.69) p≤0.0001**	**-0.87 (-1.26, -0.48) p≤0.0001**
IND 150	NR	NR	NR	NR	**1.00 (0.75, 1.24) p≤0.0001**	**1.01 (0.66, 1.35) p≤0.0001**	NR	NR	NR	NR

[a]Data on Weeks 1–12 were used throughout.

ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; OLO, olodaterol; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire; TDI, Transitional Dyspnoea Index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Table S5. Effects of UMEC/VI versus dual and monotherapy on AEs

Author & Year	Study duration, weeks	Treatment	Patients with ≥1 AE			Patients with ≥1 SAE			Pneumonia			Withdrawals due to AEs			Total withdrawals			On-treatment mortality		
			N	n	%	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Lipworth, 2018[30]	24	GLY/FOR (MDI) 18/9.6	551	306	55.5	551	53	9.6	551	9	16.0	551	27	4.9	555	61	11.0	551	1	0.3
		GLY 18	474	250	52.7	474	34	7.2	474	5	1.1	474	25	5.3	480	63	13.1	474	1	0.3
		FOR 9.6	480	256	53.3	480	40	8.3	480	5	1.0	480	24	5.0	483	66	13.7	480	1	0.3
		PBO	235	131	55.7	235	19	8.1	235	6	2.6	235	10	4.3	238	38	16.0	235	1	0.4
Singh, 2015[31] (OTEMTO 1)	12	TIO+OLO 5/5	203	91	44.8	203	10	4.9	NR	NR	NR	202	3	1.5	203	3	1.5	NR	NR	NR
		TIO+OLO 2.5/5	202	86	42.6	202	4	2.0	NR	NR	NR	202	4	2.0	202	4	2.0	NR	NR	NR
		TIO 5	203	90	44.3	203	6	3.0	NR	NR	NR	203	3	1.5	203	3	1.5	NR	NR	NR
		PBO	204	105	51.5	204	11	5.4	NR	NR	NR	202	11	5.4	204	13	6.4	NR	NR	NR
Singh, 2015[31] (OTEMTO 2)	12	TIO+OLO 5/5	202	87	43.1	202	6	3.0	NR	NR	NR	202	1	0.5	203	2	1.0	NR	NR	NR
		TIO+OLO 2.5/5	202	92	45.5	202	4	2.0	NR	NR	NR	202	4	2.0	202	4	2.0	NR	NR	NR
		TIO 5	203	93	45.8	203	12	5.9	NR	NR	NR	203	7	3.4	203	7	3.4	NR	NR	NR
		PBO	202	93	46	202	4	2.0	NR	NR	NR	202	10	5.0	204	10	5.0	NR	NR	NR
Vogelmeier, 2008[32]	24	FOR 10	210	72	34.3	NR	NR	NR	NR	NR	NR	210	6	2.9	210	25	11.9	210	0	0.0
		TIO 18	221	79	35.7	NR	NR	NR	NR	NR	NR	221	13	5.9	221	29	13.1	221	0	0.0
		TIO 18 + FOR 10	207	70	33.8	NR	NR	NR	NR	NR	NR	207	8	3.9	207	25	12.1	207	0	0.0
		PBO	209	82	39.2	NR	NR	NR	NR	NR	NR	209	8	3.8	209	30	30.0	209	1	0.5
Maleki-Yazdi, 2014[33]	24	UMEC/VI 62.5/25	454	202	44	454	16	4.0	454	1	0.2	454	18	4.0	454	53	12.0	454	2	0.4
		TIO 18	451	190	42	451	17	4.0	451	1	0.2	451	14	3.0	451	63	14.0	451	5	1.1
Calverley, 2018[34]	52	TIO/OLO 5/5	3939	2920	74	3939	810	21.0	NR	NR	NR	3939	219	6.0	3939	219	6.0	3939	110	2.8
		TIO 5	3941	2937	75	3941	862	22.0	NR	NR	NR	3941	302	8.0	3941	302	8.0	3941	123	3.1
Kerwin, 2017[49] (A2349)	12	IND/GLY 27.5/15.6 BID	341	141	41.3	341	13.0	3.8	NR	NR	NR	341.0	10.0	2.9	357	45	12.6	341.0	0.0	0.0
		UMEC/VI 62.5/25	340	150	44.1	340	21	6.2	NR	NR	NR	340	11	3.2	-	-	-	340	0	0.0
	12	IND/GLY 27.5/15.6 BID	337	118	35	337	17	5.0	NR	NR	NR	337	4	1.2	355	37	10.4	341.0	0.0	0.0

Kerwin, 2017[49] (A2350)		UMEC/VI 62.5/25	347	120	34.6	347	10	2.9	NR	NR	NR	347	5	1.4	-	-	-	340	0	0.0
Maltais, 2019[22]	24	UMEC/VI 62.5/25	812	315	39	812	50	7.0	812	7	0.9	812	32	4.0	812	95	11.7	812	4	<1.0
		UMEC 62.5	804	316	39	804	35	4.0	804	10	1.2	804	36	4.0	804	154	19.2	804	4	<1.0
		SAL 50	809	314	39	809	38	5.0	809	8	1.0	809	26	3.0	809	126	15.6	809	0	0.0
Feldman, 2017[25]	8	UMEC/VI 62.5/25	235	59	25	235	3	1.0	235	0	0.0	235	1	NR	235	Treatment Period 1: 6.0 Treatment Period 2: 3.0	Treatment Period 1: 3.0 Treatment Period 2: 1.0	235	0	0.0
		TIO/OLO 5/5	230	71	31	230	2	<1.0	230	0	0.0	230	NR	NR	230	Treatment Period 1: 1.0 Treatment Period 2: 1.0	Treatment Period 1: <1.0 Treatment Period 2: <1.0	230	0	0.0
Kalberg, 2016[36]	12	UMEC/VI 62.5/25	482	202	42	482	17	4.0	482	4	NR	482	12	2.0	482	22	5.0	482	4	<1.0
		TIO 18 + IND 150	479	186	39	479	15	3.0	479	4	NR	479	8	2.0	479	22	5.0	479	1	<1.0
Riley, 2018[37]	12	UMEC/VI 62.5/25	198	41.58	21	198	6	3.0	198	1	<1.0	198	Treatment Period 1: 2 Treatment Period 2: 3	NR	198	Treatment Period 1: 10 Treatment Period 2: 5	Treatment Period 1: 5.0 Treatment Period 2:	198	2	1.0

																During wash out: 4	3.0 During wash out: 2.0			
		PBO	198	45.54	23	198	4	2.0	198	2	1.0	198	Treatment Period 1: 0 Treatment Period 2: 2	NR	198	Treatment Period 1: 8 Treatment Period 2: 16	Treatment Period 1: 4.0 Treatment Period 2: 8.0	198	1	0.5
Mahler, 2012[38] (INTRUST-1)	12	TIO 18 + IND 150	570	258.78	45.4	570	NR	NR	NR	NR	NR	570	20	3.5	570	39	6.8	570	2	<1.0
		TIO 18	561	230.01	41	564	NR	NR	NR	NR	NR	564	10	1.8	564	35	6.2	564	0	0.0
Mahler, 2012[38] (INTRUST-2)	12	TIO 18 + IND 150	572	245.96	43	572	NR	NR	NR	NR	NR	572	13	2.3	572	29	5.1	572	1	<1.0
		TIO 18	570	229.14	40.2	570	NR	NR	NR	NR	NR	570	14	2.5	570	37	6.5	570	2	<1.0
Vincken, 2014[39]	12	IND 150 + GYL 50	226	85	37.6	226	5	2.2	NR	NR	NR	226	3	1.3	226	14	6.2	226	0	0.0
		IND 150	221	75	33.9	221	5	2.3	NR	NR	NR	221	4	1.8	221	13	5.8	223	0	0.0
Wedzicha, 2013[40]	64	IND/GLY 110/50	729	678	93	729	167	23.0	729	33	5.0	741	59	8.0	741	171	23.1	729	23	3.0
		GLY 50	740	694	94	740	179	24.0	740	36	5.0	741	67	9.0	741	203	27.4	740	22	3.0
		TIO 18	737	686	93	737	165	22.0	737	34	5.0	742	47	6.3	742	183	24.7	737	25	3.0
GSK CSR[a] (DB2113374)	24	UMEC 125	222	131	59	222	15	7.0	222	4	2.0	222	17	8.0	222	57	26.0	222	0	0.0
		UMEC/VI 62.5/25	217	127	59	217	22	10.0	217	3	1.0	217	20	9.0	217	54	25.0	217	1	0.5
		UMEC/VI 125/25	215	133	62	215	15	7.0	215	4	2.0	215	15	7.0	215	49	23.0	215	1	0.5
		TIO 18	215	126	59	215	9	4.0	215	3	1.0	215	11	5.0	215	39	18.0	215	2	0.9
	24	UMEC/VI 125/25	214	94	44	214	5	2.0	214	1	<1.0	214	15	7.0	214	41	19.0	208	0	0.0

GSK CSR[a] (DB2113360)		UMEC/VI 62.5/25	212	108	51	212	7	3.0	212	0	0.0	212	10	5.0	212	31	15.0	207	1	0.5
		VI 25	209	99	47	209	15	7.0	209	1	<1.0	209	10	5.0	209	44	21.0	205	1	0.5
		TIO 18	208	82	39	208	13	6.0	208	2	<1.0	208	9	4.0	208	31	15.0	203	0	0.0
GSK CSR[a] (DB2113373)	24	UMEC 62.5	418	216	52	418	27	6.0	418	6	1.0	418	34	8.0	418	94	22.0	418	1	<1.0
		VI 25	421	212	51	421	24	6.0	421	4	<1.0	421	24	6.0	421	103	24.0	421	3	<1.0
		UMEC/VI 62.5/25	413	204	48	413	21	5.0	413	8	2.0	413	23	6.0	413	81	20.0	413	2	<1.0
		PBO	280	130	46	280	9	3.0	280	2	<1.0	280	90	3.0	280	76	27.0	280	0	0.0
Vogelmeier, 2016[41]	24	ACL/FOR 400/12	467	235	50.3	467	35	7.5	NR	NR	NR	467	26	5.6	467	66	14.1	467	3	0.6
		SAL/FP 50/500	466	265	56.9	466	33	7.1	NR	NR	NR	466	34	7.3	466	79	17.0	466	1	0.2
Wedzicha, 2016[42]	52	IND/GLY 110/50	1678	1459	86.9	1678	308	18.4	1678	53	3.2	1678	126	7.5	1680	278	16.5	1678	24	1.4
		SAL/FF 50/500	1680	1498	89.2	1680	334	19.9	1680	80	4.8	1680	143	8.5	1682	320	19.0	1680	24	1.4
Maltais 2019[24]	24	GLY/FOR 18/9.6	552	226	40.9	552	32	5.8	552	4	0.7	552	22	4.0	552	60	10.9	552	3	0.5
		UMEC/VI 62.5/25	552	248	44.9	552	40	7.2	552	4	0.7	552	20	3.6	552	43	7.8	552	3	0.5
Sethi, 2019[43]	24	ACL/FOR 400/12	314	183	58.3	314	23	7.3	NR	NR	NR	314	17	5.4	314	1	0.3	314	1	0.3
		ACL 400	475	289	60.8	475	41	8.6	NR	NR	NR	475	37	7.8	475	1	0.2	475	1	0.2
		FOR 12	319	210	65.8	319	22	6.9	NR	NR	NR	319	27	8.5	319	4	1.3	319	4	1.3
		TIO 18	475	285	60	475	37	7.8	NR	NR	NR	475	32	6.7	475	2	0.4	475	2	0.4
D'Urzo, 2014[44]	24	ACL/FOR 400/12	335	215	64.2	335	19.095	5.7	335	2	0.6	338	21	6.3	338	66	20.0	335	1	0.3
		ACL/FOR 400/6	333	203	61	333	17.982	5.4	333	1	0.3	338	22	6.6	338	62	18.0	333	0	0.0
		ACL 400	337	210	62.3	337	16.85	5.0	337	1	0.3	340	16	4.7	340	72	21.0	337	3	0.9
		FOR 12	332	189	56.9	332	14.94	4.5	332	3	0.9	339	14	4.2	339	69	20.0	332	1	0.3
		PBO	332	181	54.5	332	11.952	3.6	332	3	0.9	337	21	6.3	337	101	30.0	332	0	0.0
D'Urzo, 2017[45]	28	ACL/FOR 400/12	182	120	65.9	182	14	7.7	182	0	0.0	182	6	3.3	184	29	15.8	182	2	1.1
		ACL/FOR 400/6	204	125	61.3	204	14	6.9	204	3	1.5	204	5	2.5	205	26	12.7	204	1	0.5
		ACL 400	194	131	67.5	194	15	7.7	194	2	1.0	194	6	3.1	194	29	14.9	194	1	0.5

		FOR 12	192	124	64.6	192	14	7.3	192	0	0.0	192	4	2.1	192	32	16.7	192	0	0.0
		PBO	146	83	56.8	146	10	6.8	146	0	0.0	146	7	4.8	146	25	17.1	146	2	1.4
Ferguson, 2016[46]	52	IND/GLY 27.5/15.6 BID	204	139	68.1	204	26	12.7	204	7	3.4	204	5	2.5	204	27	13.2	204	1	0.5
		IND/GLY 27.5/31.2 BID	204	142	69.6	204	25	12.3	204	4	2.0	204	8	3.9	204	17	8.3	204	3	1.5
		IND 75	206	139	67.5	206	24	11.7	206	2	1.0	206	12	5.8	207	24	11.6	206	5	2.4
Mahler, 2015[47] (FLIGHT1 & FLIGHT2, pooled)	12	IND/GLY 27.5/15.6 BID	508	221	43.5	508	16	3.2	NR	NR	NR	508	15	3.0	NR	NR	NR	508	0	0.0
		IND 27.5	511	195	38.2	511	18	3.5	NR	NR	NR	511	10	2.0	NR	NR	NR	511	3	0.6
		GLY 15.6	513	214	41.7	513	20	3.9	NR	NR	NR	513	8	1.6	NR	NR	NR	513	3	0.6
		PBO	508	219	43.1	508	21	4.1	NR	NR	NR	508	21	4.1	NR	NR	NR	508	1	0.2
Mahler, 2015[47] (FLIGHT1)	12	IND/GLY 27.5/15.6 BID	NR	NR	NR	NR	NR	NR	NR	NR	NR	260	9	3.5	260	14	5.4	NR	NR	NR
		IND 27.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	260	5	1.9	260	16	6.2	NR	NR	NR
		GLY 15.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	261	4	1.5	261	18	6.9	NR	NR	NR
		PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	261	13	5.0	261	41	15.7	NR	NR	NR
Mahler, 2015[47] (FLIGHT2)	12	IND/GLY 27.5/15.6 BID	NR	NR	NR	NR	NR	NR	NR	NR	NR	250	5	2.0	250	12	4.8	NR	NR	NR
		IND 27.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	251	5	2.0	251	15	6.0	NR	NR	NR
		GLY 15.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	251	4	1.6	251	15	6.0	NR	NR	NR
		PBO	NR	NR	NR	NR	NR	NR	NR	NR	NR	249	7	2.8	249	24	9.6	NR	NR	NR
Siler, 2016[48]	12	UMEC/VI 62.5/25	248	80	32	248	19	7.7	NR	NR	NR	248	8	3.0	248	18	7.0	248	2	<1.0
		PBO	248	75	30	248	13	5.0	NR	NR	NR	248	6	2.0	248	19	8.0	248	0	0.0
Kerwin, 2017[49]	12	UMEC/VI 62.5/25	247	75	30	247	7	2.8	NR	NR	NR	247	5	2.0	247	17	7.0	247	1	<1.0
		TIO 18	247	77	31	247	6	2.0	NR	NR	NR	247	4	2.0	247	16	6.0	247	0	0.0
Donohue, 2016[50]	52	ACL/FOR 400/12	392	NR	71.4	392	NR	9.7	392	4	1.0	392	26	6.6	392	127	32.4	392	5	1.3
		FOR 12	198	NR	65.7	198	NR	10.6	198	1	0.5	198	13	6.6	198	65	32.8	198	1	0.5
Martinez, 2017[51] (PINNACLE-1)	24	GLY/FOR 18/9.6	526	331	62.9	526	44	8.4	526	12	2.3	526	39	7.4	526	98	18.6	526	3	0.6
		GLY 18	451	265	58.8	451	36	8.0	451	10	2.2	451	33	7.3	451	106	23.5	451	0	0.0
		FOR 9.6	452	269	59.5	452	29	6.4	452	6	1.3	452	22	4.9	452	82	18.1	452	0	0.0
		PBO	220	138	62.7	220	16	7.3	220	4	1.8	220	14	6.4	220	60	27.3	220	0	0.0
		TIO 18	451	283	62.7	451	36	8.0	451	2	0.4	451	22	4.9	451	62	13.7	451	4	0.9

Martinez, 2017[51] (PINNACLE-2)	24	GLY/FOR 18/9.6	510	286	56.1	510	36	7.1	510	7	1.4	510	25	4.9	510	80	15.7	510	1	0.2
		GLY 18	439	235	53.5	439	37	8.4	439	9	2.1	439	21	4.8	439	75	17.1	439	0	0.0
		FOR 9.6	438	237	54.1	438	37	8.4	438	6	1.4	438	25	5.7	438	93	21.2	438	1	0.2
		PBO	223	117	52.5	223	15	6.7	223	6	2.7	223	19	8.5	223	59	26.5	223	1	0.4
Bateman, 2013[18]	26	IND/GLY 110/50	474	261	55.1	474	22	4.6	NR	NR	NR	474	6	1.3	474	38	8.0	474	1	0.2
		IND 150	476	291	61.1	476	26	5.5	NR	NR	NR	476	24	5.0	476	56	11.7	476	2	0.4
		GLY 50	473	290	61.3	473	29	6.1	NR	NR	NR	473	14	3.0	473	53	11.2	473	1	0.2
		TIO 18	480	275	57.3	480	19	4.0	NR	NR	NR	480	10	2.1	480	42	8.7	480	3	0.6
		PBO	232	134	57.8	232	13	5.6	NR	NR	NR	232	10	4.3	232	45	19.2	232	0	0.0
Buhl, 2015[52]	26	IND/GLY 110/50	476	208	43.7	476	30	6.3	NR	NR	NR	476	36	7.6	476	61	12.8	476	3	0.6
		TIO 18 + FOR 12	458	195	42.6	458	24	5.2	NR	NR	NR	458	27	5.9	458	52	11.4	458	3	0.7
Tashkin, 2009[53]	12	TIO 18 + FOR 12	NR	NR	NR	NR	NR	NR	NR	NR	NR	124	6	5.0	124	18	15.0	NR	NR	NR
		TIO 18	NR	NR	NR	NR	NR	NR	NR	NR	NR	124	1	1.0	124	8	6.0	NR	NR	NR
Frith, 2018[54]	12	IND/GLY 110/50	248	62	25	248	9	NR	NR	NR	NR	248	2	0.8	248	16	6.5	248	1	<1.0
		SAL/FF 50/500	250	72	28.8	250	9	NR	NR	NR	NR	250	3	1.2	250	13	5.2	250	1	<1.0
Celli, 2014[55]	24	PBO	275	134	49	275	17	6.0	275	6	2.0	275	17	6.0	275	92	33.0	275	2	<1.0
		UMEC 125	407	217	53	407	22	5.0	407	12	3.0	407	24	6.0	407	95	23.0	407	2	<1.0
		VI 25	404	215	53	404	20	5.0	404	7	2.0	404	25	6.0	404	106	26.0	404	1	<1.0
		UMEC/VI 125/25	403	211	52	403	23	6.0	403	8	2.0	403	19	5.0	403	78	19.0	403	0	0.0
Singh, 2015[56]	12	UMEC/VI 62.5/25	358	99	28	358	7	2.0	NR	NR	NR	358	6	2.0	358	24	6.7	358	7	2.0
		SAL/FP 50/500	358	105	29	358	2	0.6	NR	NR	NR	358	5	1.0	358	18	5.0	358	2	0.6
Donohue, 2015[57] (DB2114930)	12	UMEC/VI 62.5/25	353	93	26	353	6	2.0	353	1	0.3	353	7	2.0	353	34	9.6	353	0	0.0
		SAL/FP 50/250	353	96	27	353	10	3.0	353	4	1.0	353	10	2.8	353	38	10.8	353	1	0.3
Donohue, 2015[57] (DB2114951)	12	UMEC/VI 62.5/25	349	104	30	349	11	3.0	349	2	0.6	349	9	2.6	349	23	6.6	349	2	0.6
		SAL/FP 50/250	348	108	31	348	13	4.0	348	4	1.1	348	14	4.0	348	36	10.3	348	3	0.9

Vogelmeier, 2013[58]	26	IND/GLY 110/50	258	143	55.4	258	13	5.0	258	0	0.0	258	22	8.5	258	44	17.1	258	0	0.0
		SAL/FF 50/500	264	159	60.2	264	14	5.3	264	4	1.5	264	27	10.2	264	47	17.8	264	1	0.4
Zhong, 2015[59]	26	IND/GLY 110/50	372	149	40.1	372	20	5.4	372	3	0.8	372	12	3.2	372	29	7.8	372	2	0.5
		SAL/FF 50/500	369	175	47.4	369	35	9.5	369	10	2.7	369	17	4.6	372	39	10.5	369	0	0.0
Hoshino, 2015 [60]	NR	TIO 18 + IND 150	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
		SAL/FF 50/250	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Singh, 2014[61]	24	ACL/FOR 400/12	385	194	50.4	385	23	6.0	385	3	0.8	385	16	4.2	385	34	8.8	385	1	0.3
		ACL/FOR 400/6	381	193	50.7	381	18	4.7	381	4	1.0	381	12	3.1	381	40	10.5	381	2	0.5
		ACL 400	385	190	49.4	385	16	4.2	385	0	0.0	385	17	4.4	385	50	13.0	385	0	0.0
		PBO	194	103	53.1	194	12	6.2	194	1	0.5	194	8	4.1	194	34	17.5	194	0	0.0
		FOR 12	384	217	56.5	384	14	3.6	384	0	0.0	384	14	3.6	384	45	11.7	384	1	0.3
ZuWallack, 2014[62] (ANHELTO 1)	12	TIO 18	565	242	42.8	565	26	4.6	NR	NR	NR	565	16	2.8	569	40	7.1	565	1	0.2
		TIO 18 + OLO 5	567	257	45.3	567	40	7.1	NR	NR	NR	567	18	3.2	566	40	7.1	567	7	1.2
ZuWallack, 2014[62] (ANHELTO 2)	12	TIO 18	569	246	43.2	569	27	4.7	NR	NR	NR	569	11	1.9	569	31	5.5	569	2	0.4
		TIO 18 + OLO 5	566	227	40.1	566	24	4.2	NR	NR	NR	566	21	3.7	566	43	7.6	566	3	0.6
Dahl, 2013[63]	52	IND/GLY 110/50	225	130	57.8	225	37	16.4	225	8	3.6	225	13	5.8	226	32	14.2	225	4	1.8
		PBO	113	64	56.6	113	12	10.6	113	0	0.0	113	7	6.2	113	24	21.2	113	1	0.9
Buhl, 2015b[19] (TONADO 1)	52	OLO 5	528	390	73.9	528	75	14.2	528	22	4.2	528	49	9.3	528	97	18.4	NR	NR	NR
		TIO 2.5	525	374	71.2	525	66	12.6	525	11	2.1	525	37	7.0	525	77	14.7	NR	NR	NR
		TIO 5	527	381	72.3	527	79	15.0	527	19	3.6	527	42	8.0	527	72	13.7	NR	NR	NR
		TIO/OLO 2.5/5	522	395	75.7	522	81	15.5	522	20	3.8	522	29	5.6	522	60	11.5	NR	NR	NR
		TIO/OLO 5/5	522	387	74.1	522	87	16.6	522	19	3.6	522	37	7.1	522	56	10.7	NR	NR	NR
Buhl, 2015b[19]	52	OLO 5	510	405	79.4	510	106	20.8	510	14	2.7	510	54	10.6	510	98	19.2	NR	NR	NR
		TIO 2.5	507	384	75.7	507	90	17.8	507	13	2.6	507	53	10.5	507	98	19.3	NR	NR	NR

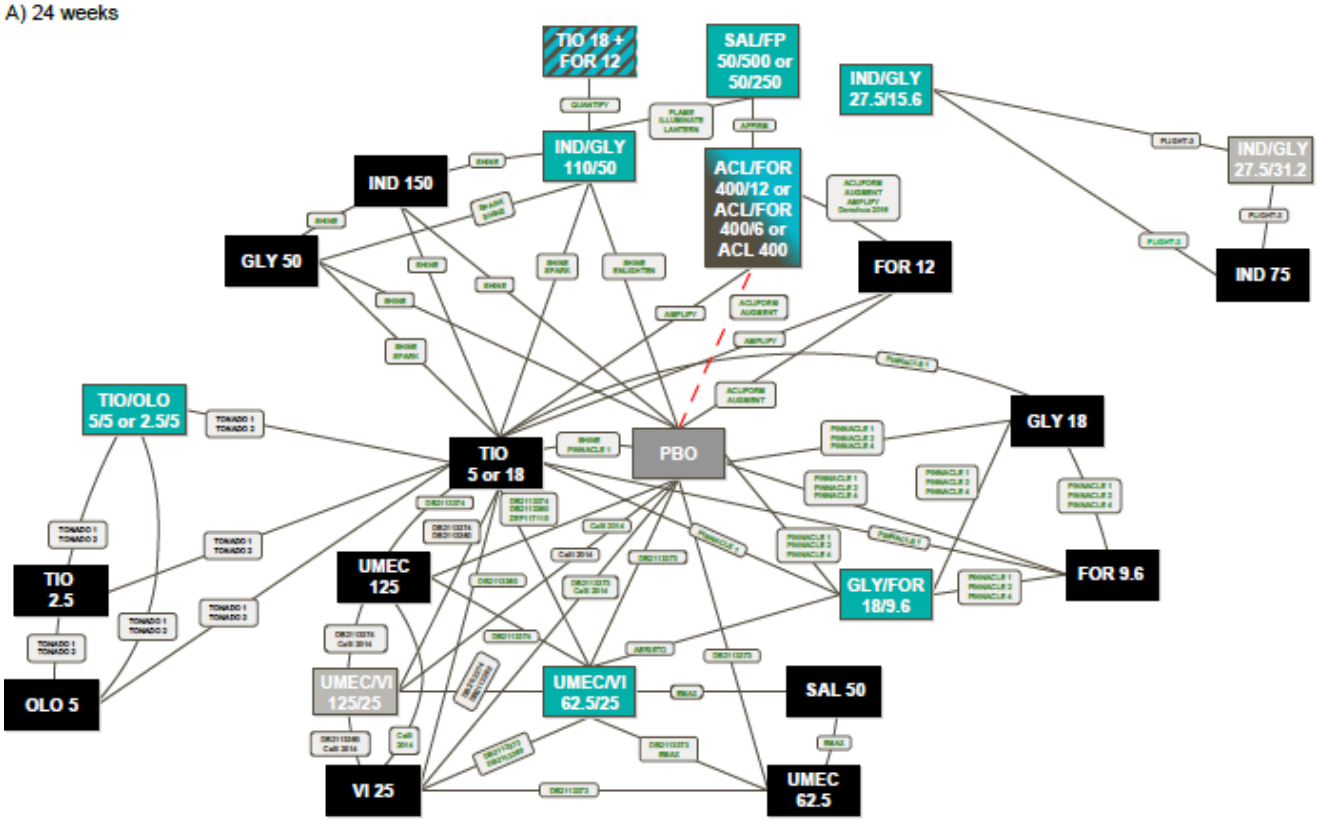
(TONADO 2)		TIO 5	506	376	74.3	506	93	18.4	506	7	1.4	506	51	10.1	506	96	19.0	NR	NR	NR
		TIO/OLO 2.5/5	508	374	73.6	508	87	17.1	508	11	2.2	508	28	5.5	508	63	12.4	NR	NR	NR
		TIO/OLO 5/5	507	374	73.8	507	82	16.2	507	15	3.0	507	39	7.7	507	77	15.2	NR	NR	NR

[a]Available from clinicalstudydatarequest.com.

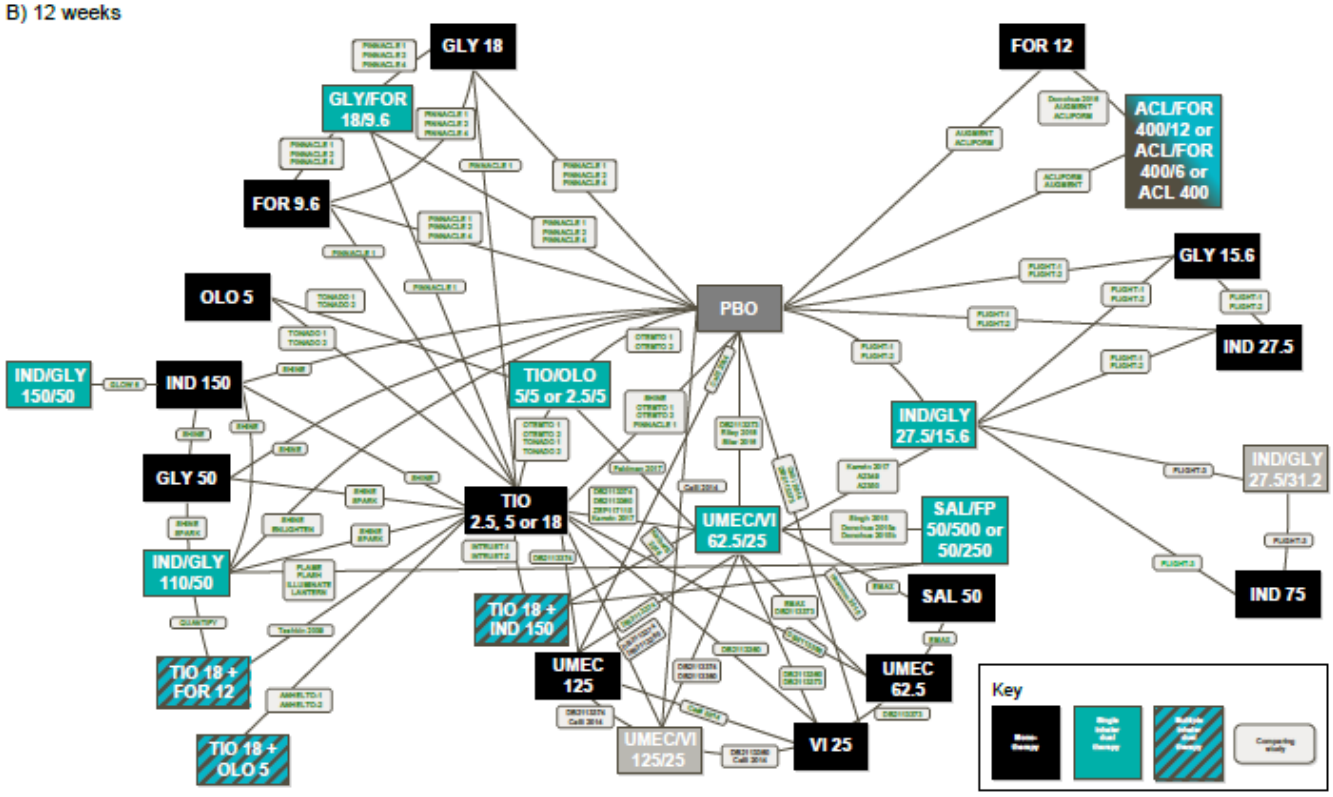
ACL, aclidinium; AE, adverse event; BID, twice daily; FF, fluticasone furoate; FOR, formoterol; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; MDI, metered dose inhaler; NR, not reported; OLO, olodaterol; PBO, placebo; SAE, serious AE; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S1. Network of evidence informing trough FEV_1 analysis at (A) 24 and (B) 12 weeks

A) 24 weeks

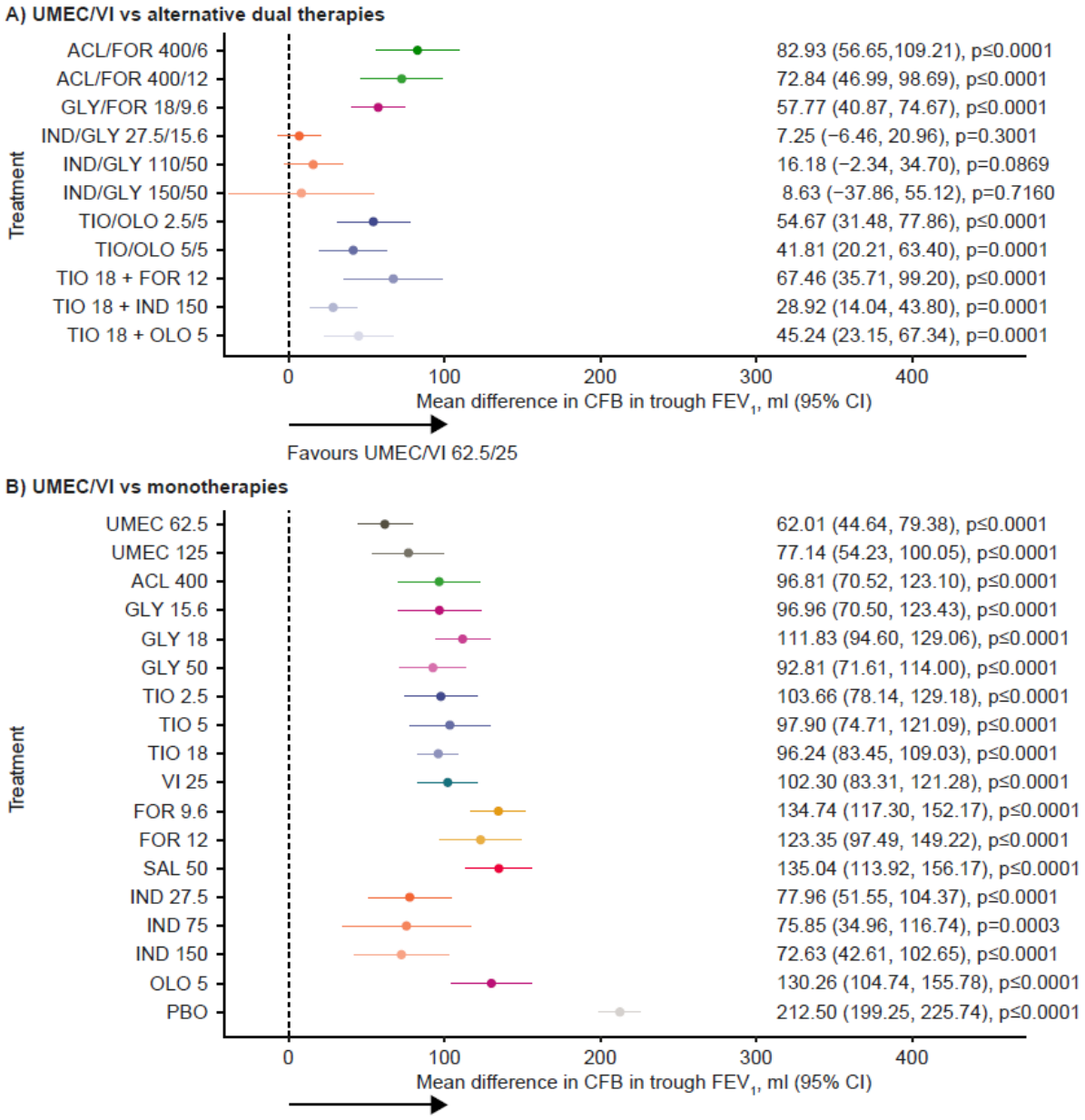


B) 12 weeks



ACL, aclidinium; FEV_1, forced expiratory volume in 1 second; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

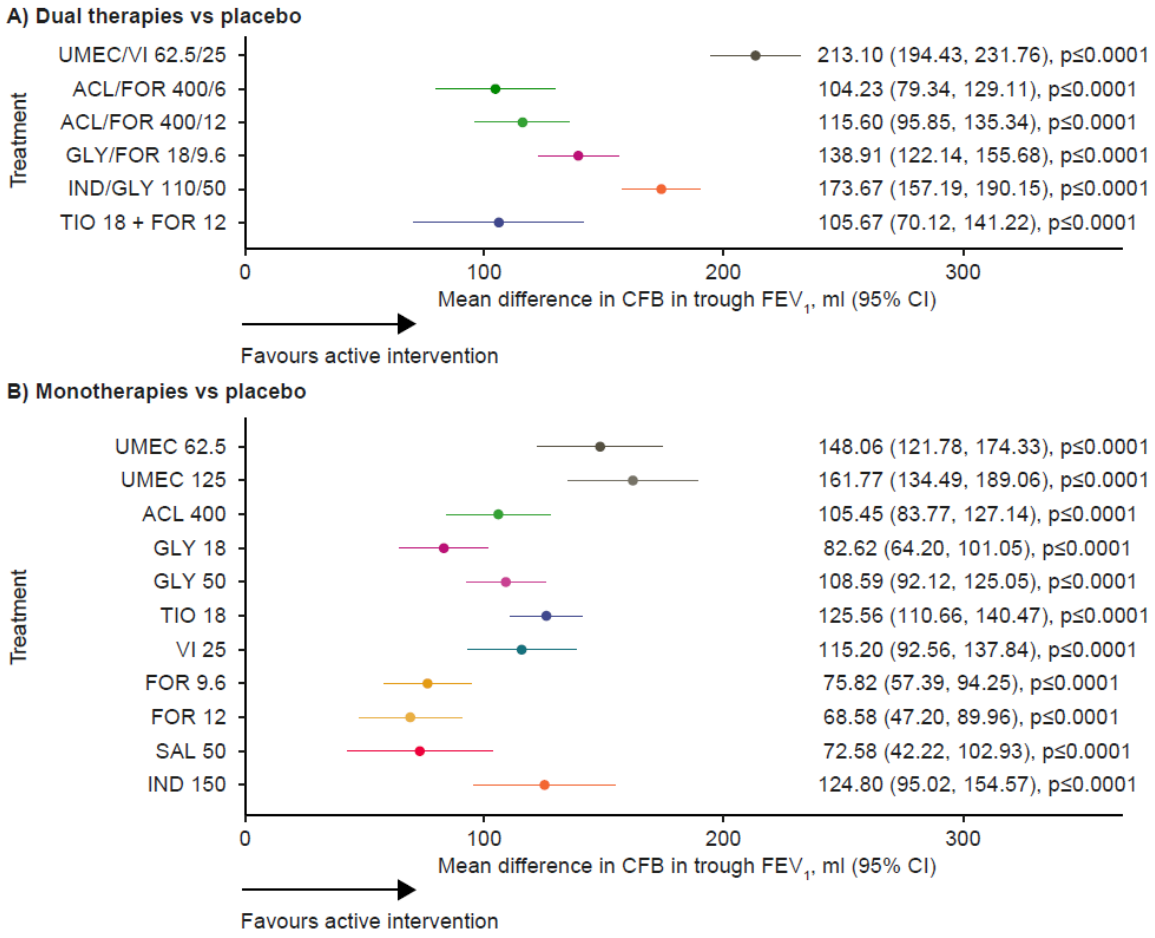
Supplementary Figure S2. Fixed effects model of mean difference in change from baseline in trough FEV_1 with UMEC/VI versus (A) dual therapy and (B) monotherapy at 12 weeks



Assessment of heterogeneity/inconsistency: I^2=38.64%; Q=81.48; p=0.0033.

ACL, aclidinium; CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

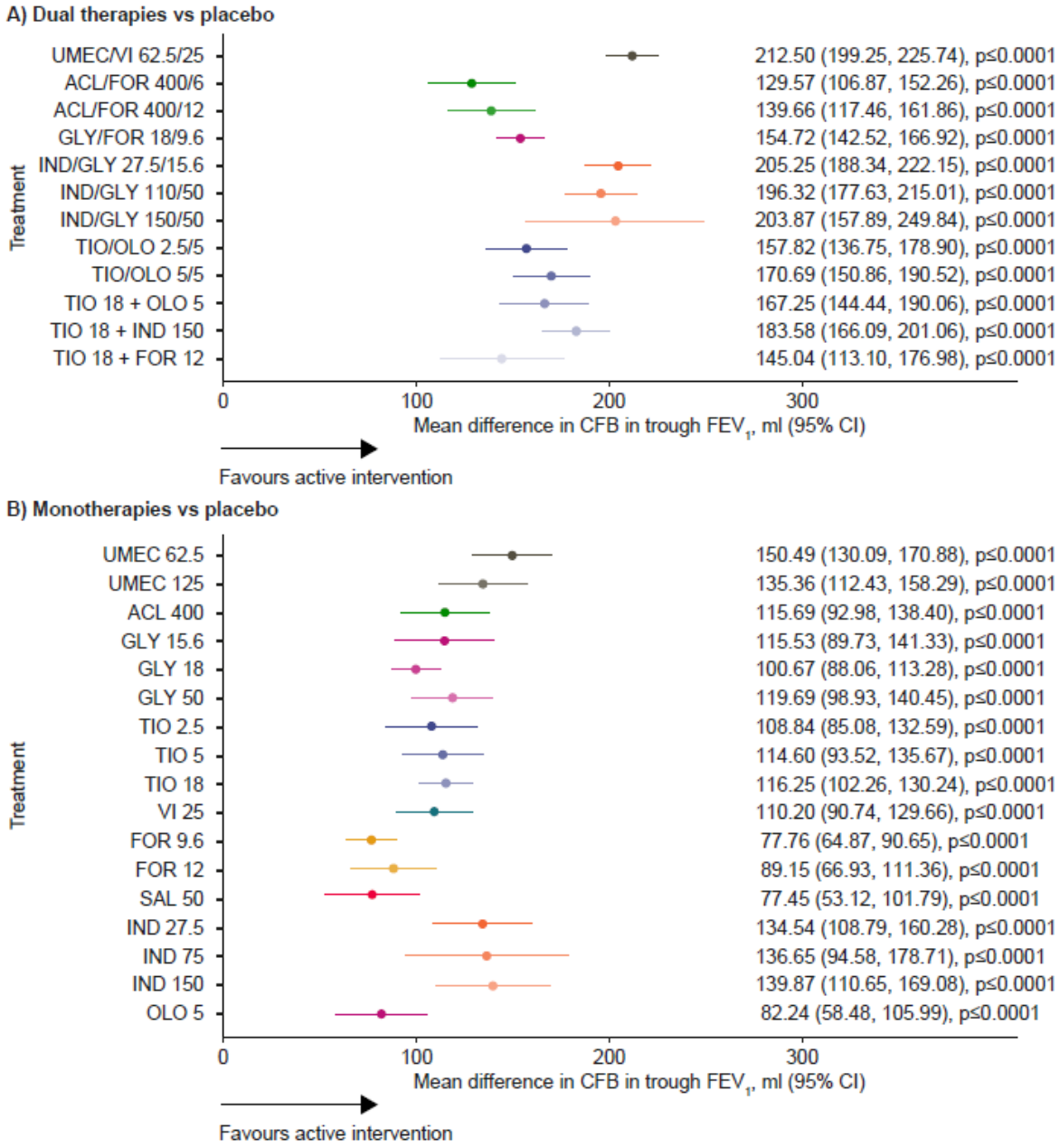
Supplementary Figure S3. Fixed effects model of mean difference in change from baseline in trough FEV_1 with (A) dual and (B) monotherapy versus placebo at 24 weeks



Assessment of heterogeneity/inconsistency: I^2=35.33%; Q=44.84; p=0.0305.

ACL, aclidinium; CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

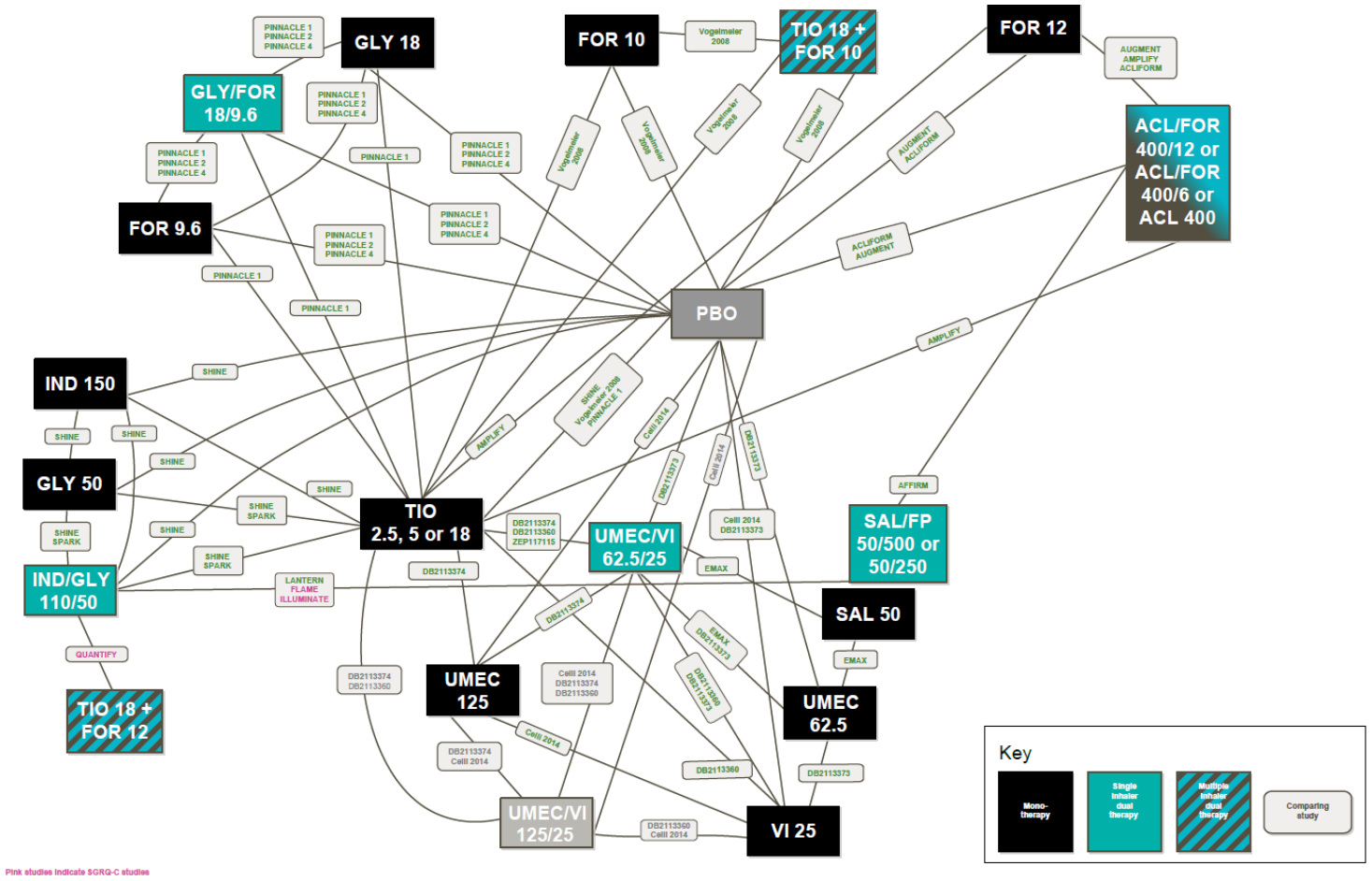
Supplementary Figure S4. Fixed effects model of mean difference in change from baseline in trough FEV_1 of (A) dual and (B) monotherapy versus placebo at 12 weeks



Assessment of heterogeneity/inconsistency: I^2=38.64%; Q=81.48, p=0.0033.

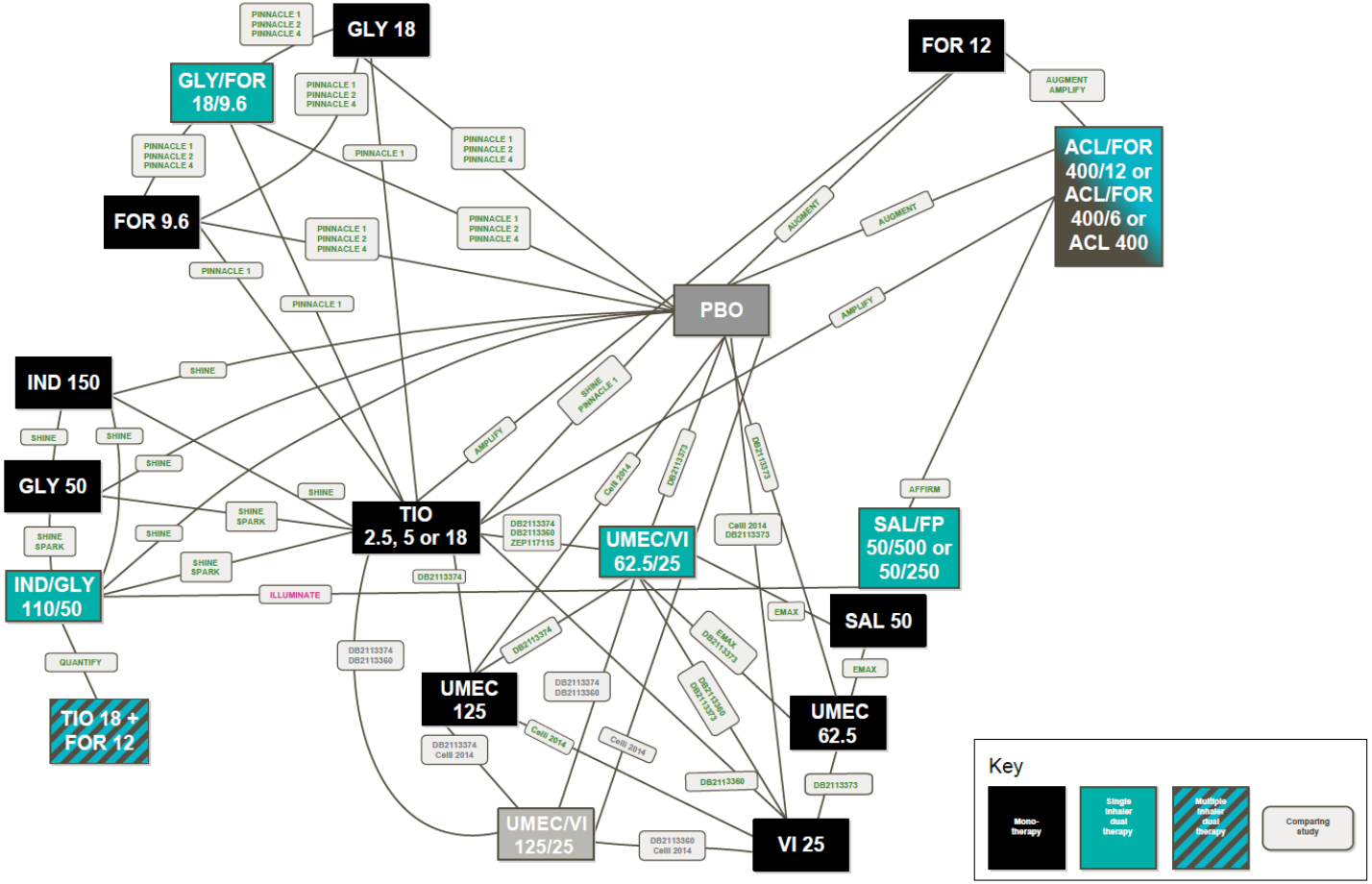
ACL, aclidinium; CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S5. Networks of evidence informing SGRQ total score analysis at 24 weeks



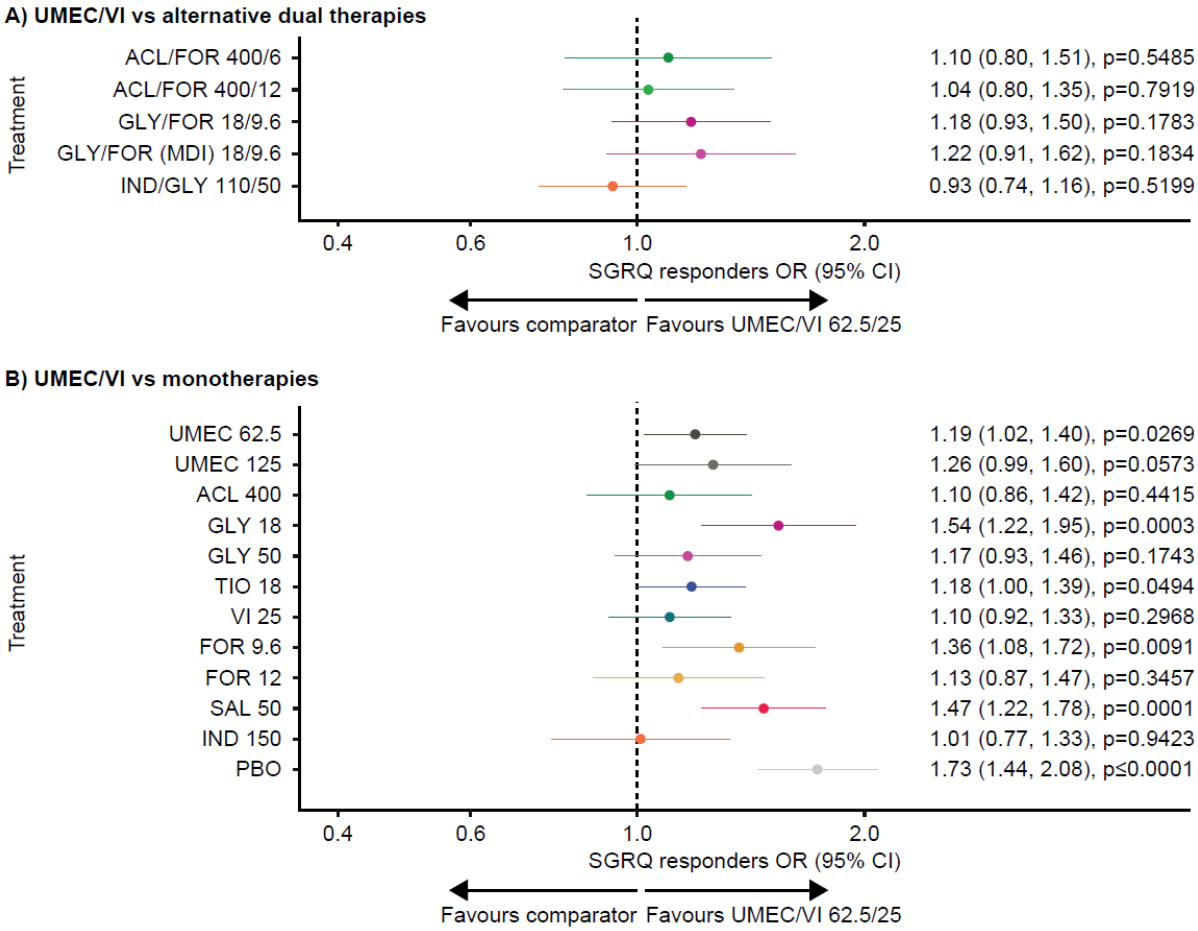
ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S6. Networks of evidence informing SGRQ responder analysis at 24 weeks



ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

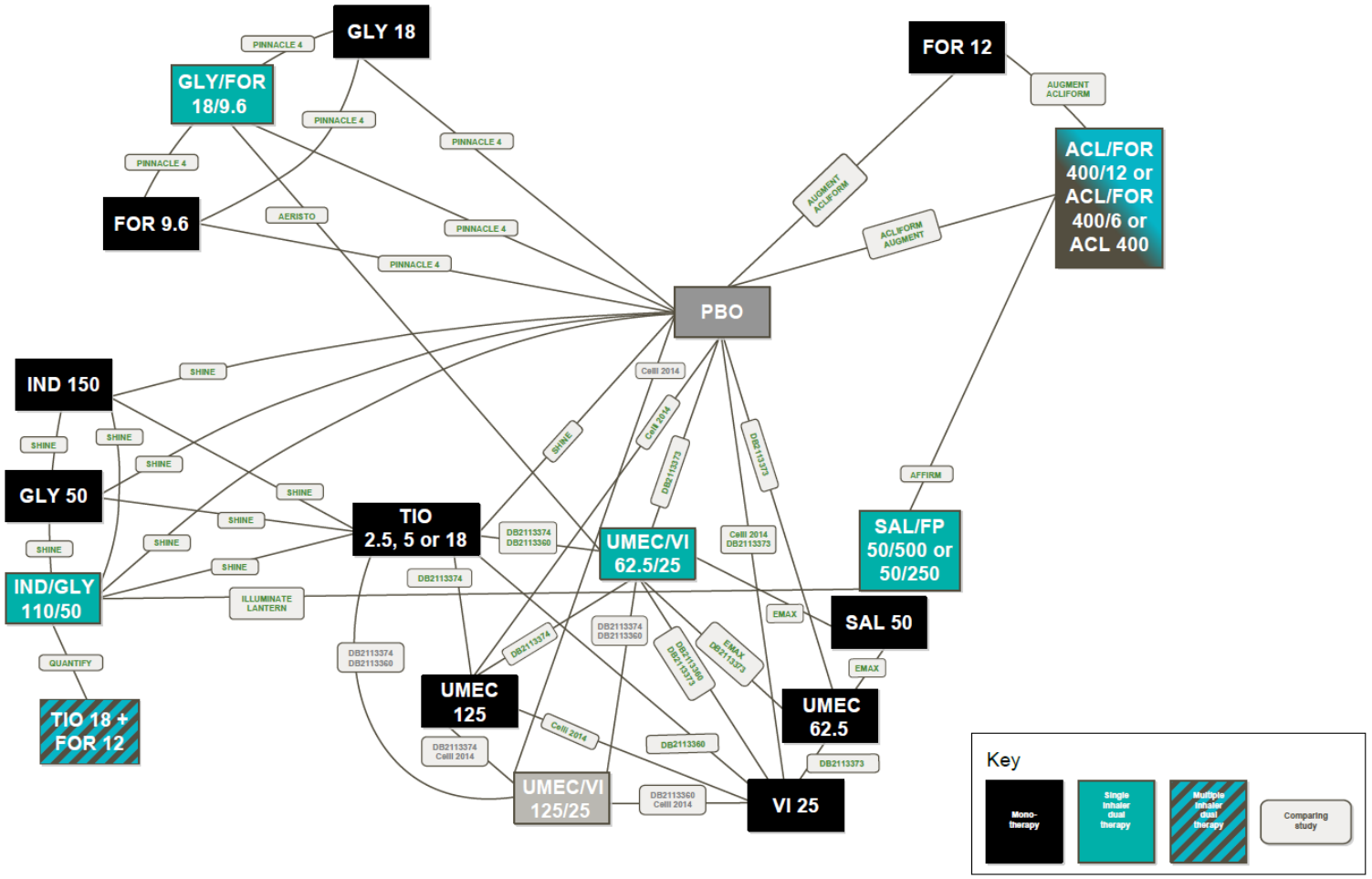
Supplementary Figure S7. Fixed effects model of SGRQ responders OR of UMEC/VI versus (A) dual and (B) monotherapy at 24 weeks



Assessment of heterogeneity/inconsistency: I^2=25.20%; Q=24.07; p=0.1529.

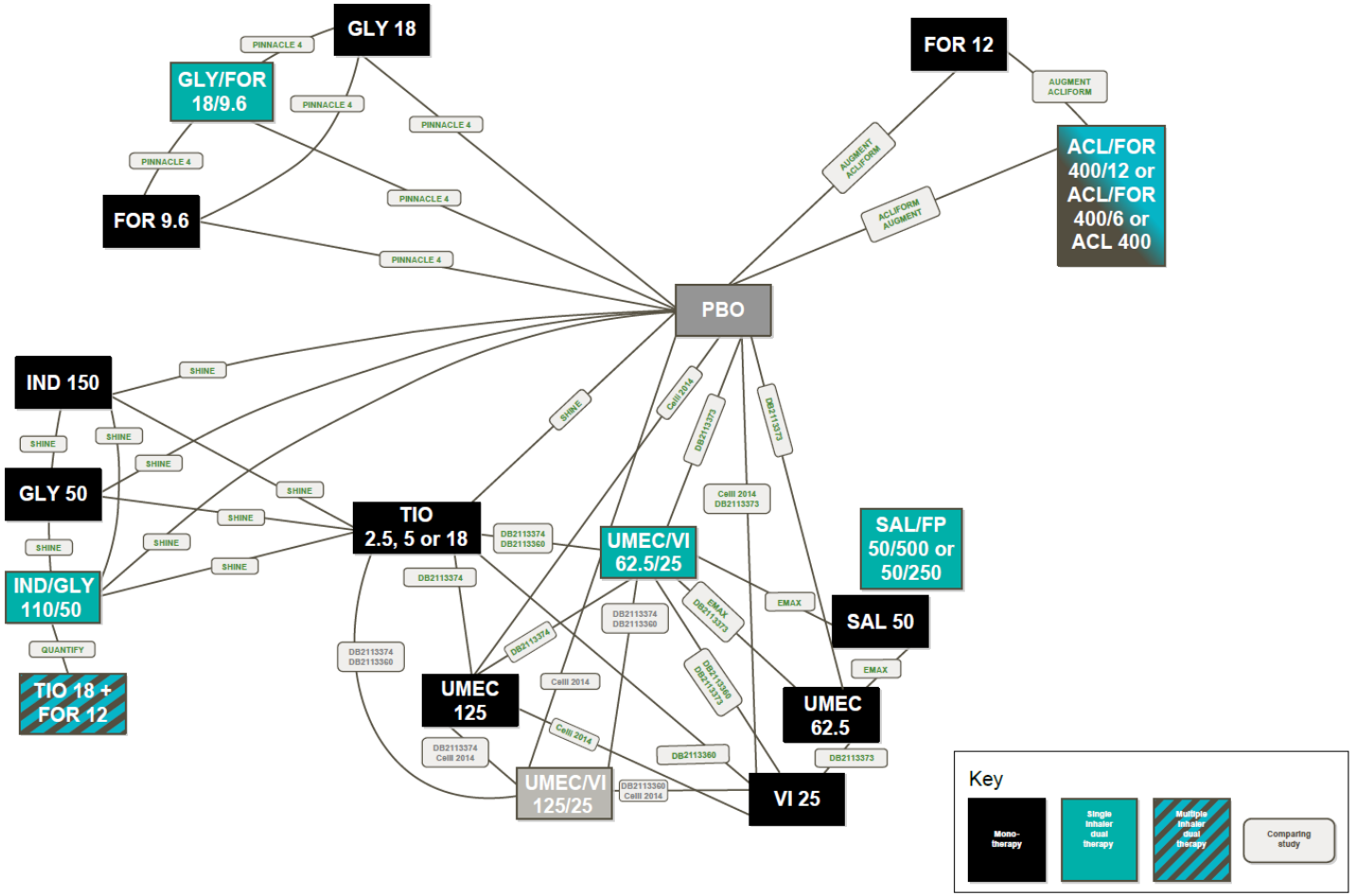
ACL, aclidinium; CI, confidence interval; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; OR, odds ratio; PBO, placebo; SAL, salmeterol; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S8. Networks of evidence informing TDI focal score analysis at 24 weeks



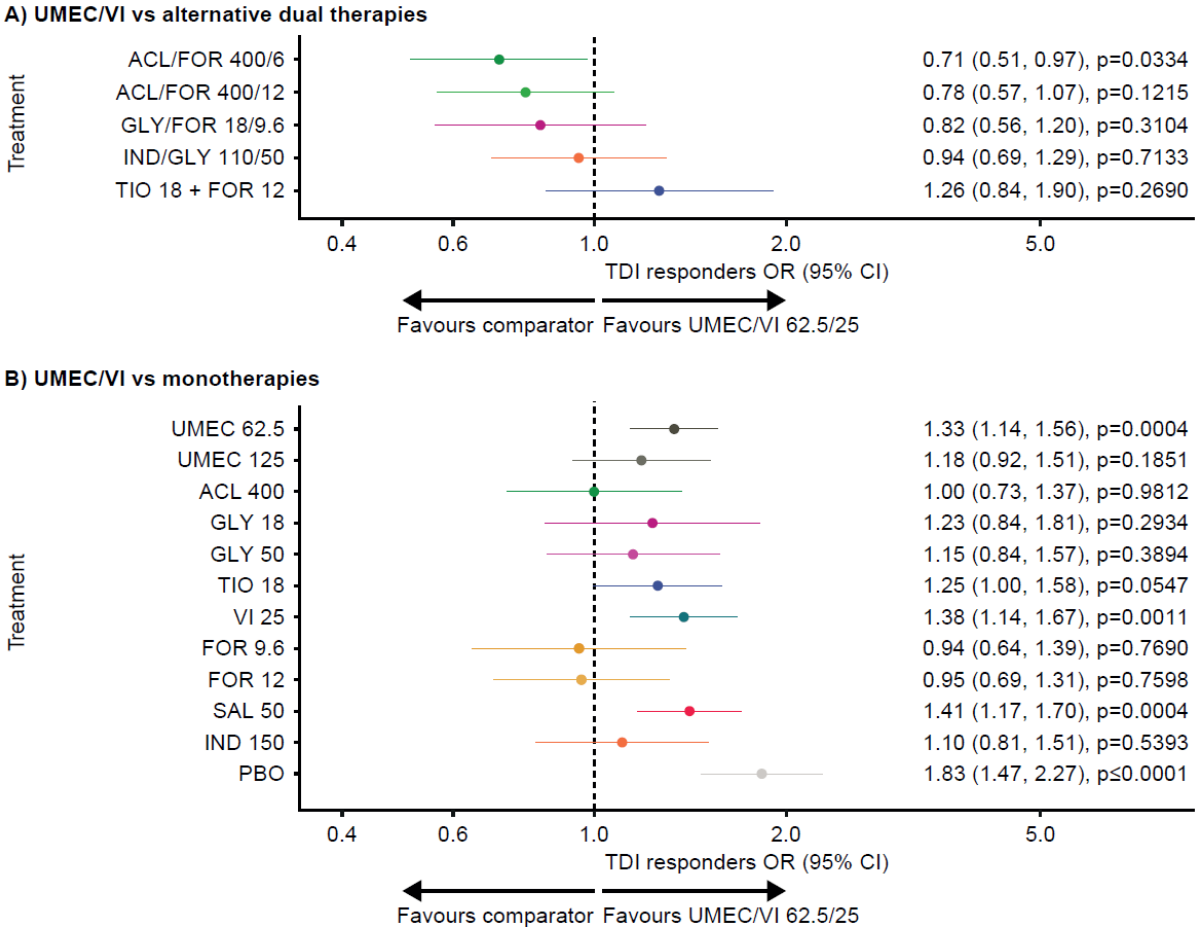
ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TDI, transitional dyspnoea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S9. Networks of evidence informing TDI responder analysis at 24 weeks



ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TDI, transitional dyspnoea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

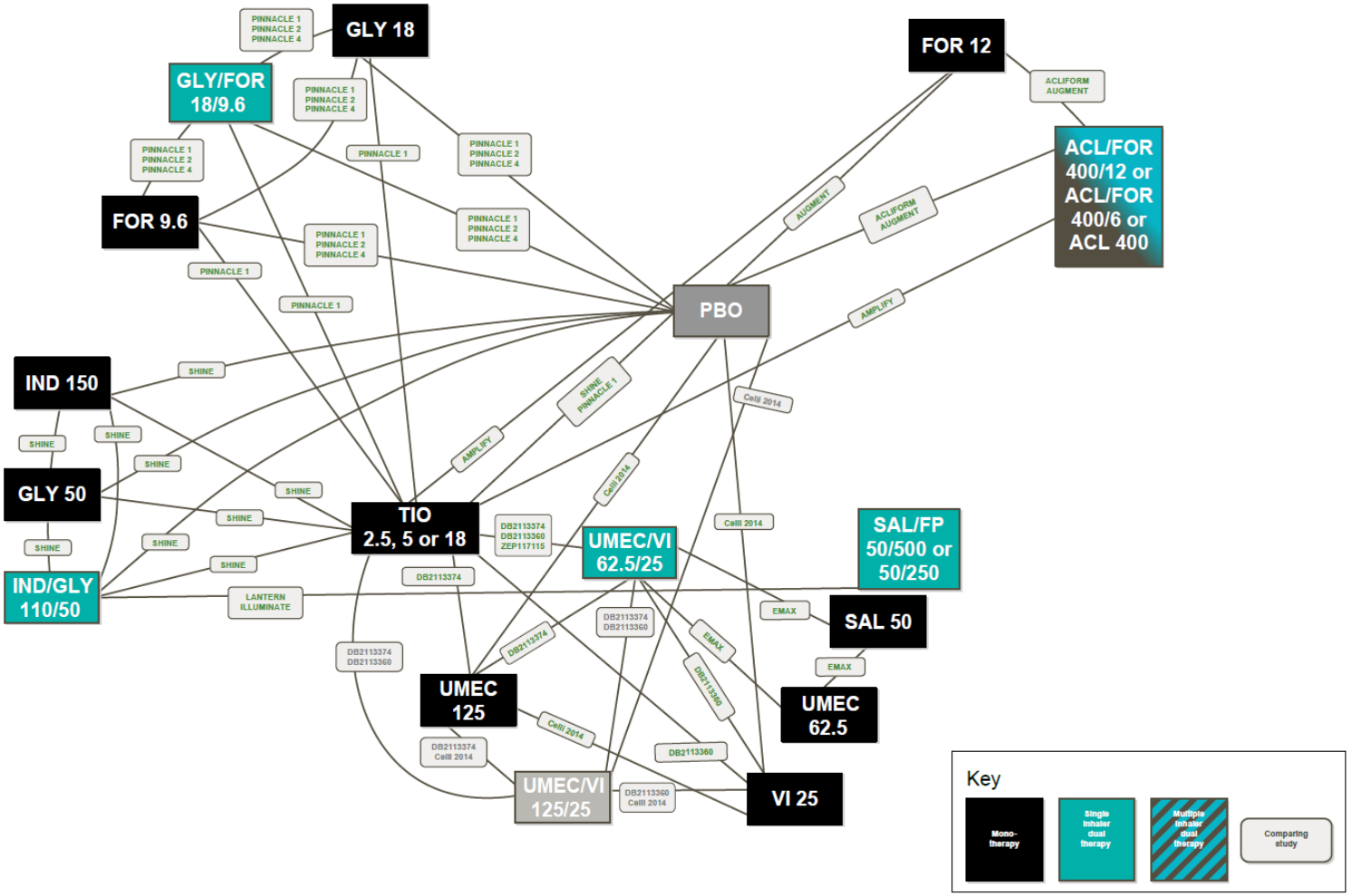
Supplementary Figure S10. Fixed effects model of TDI responders OR with UMEC/VI versus (A) dual and (B) monotherapy at 24 weeks



Assessment of heterogeneity/inconsistency: I^2=36.01%; Q=15.63; p=0.1108.

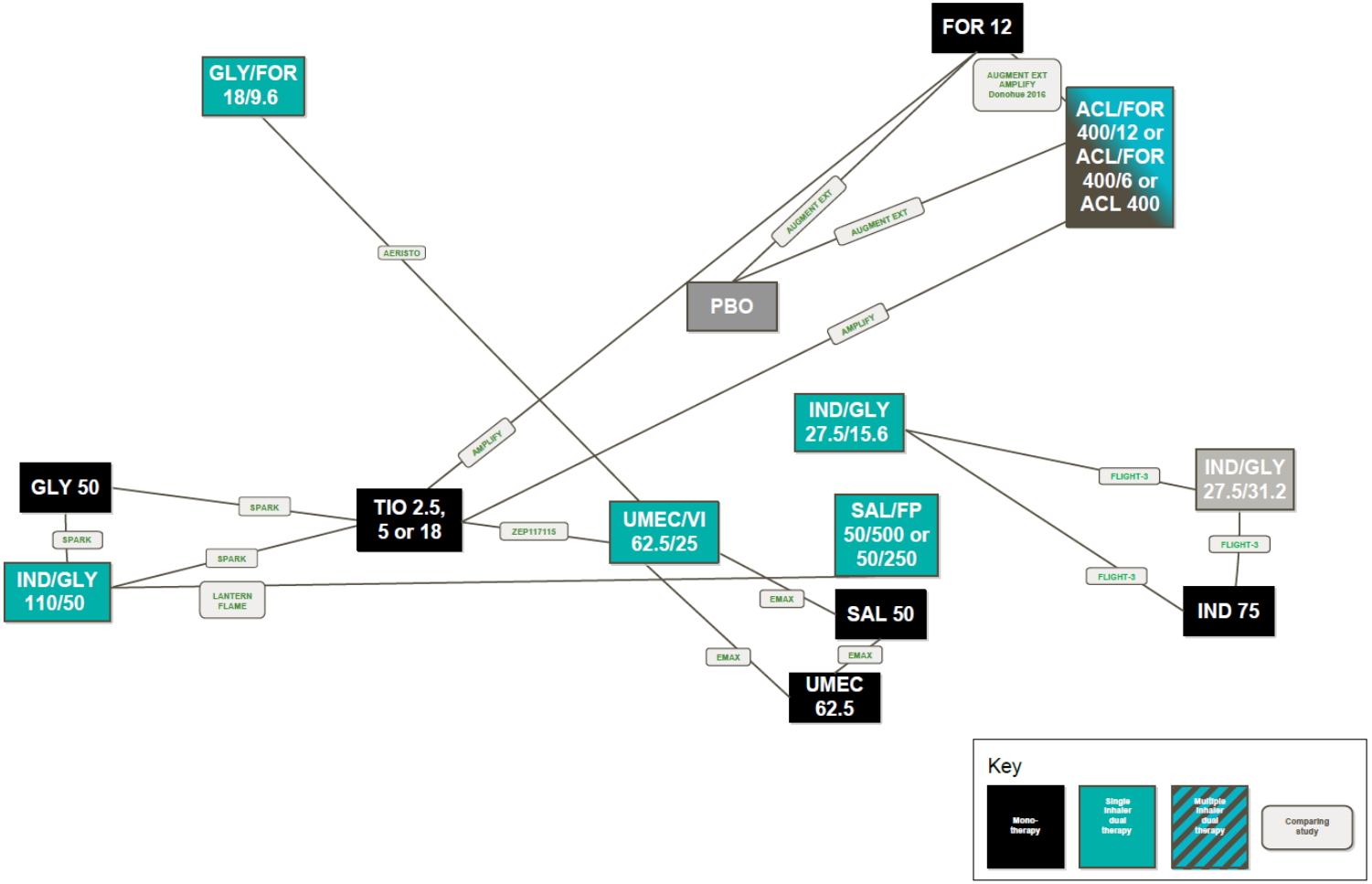
ACL, aclidinium; CI, confidence interval; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; OR, odds ratio; PBO, placebo; SAL, salmeterol; TDI, transitional dyspnoea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S11. Networks of evidence informing rescue medication use analysis at 24 weeks



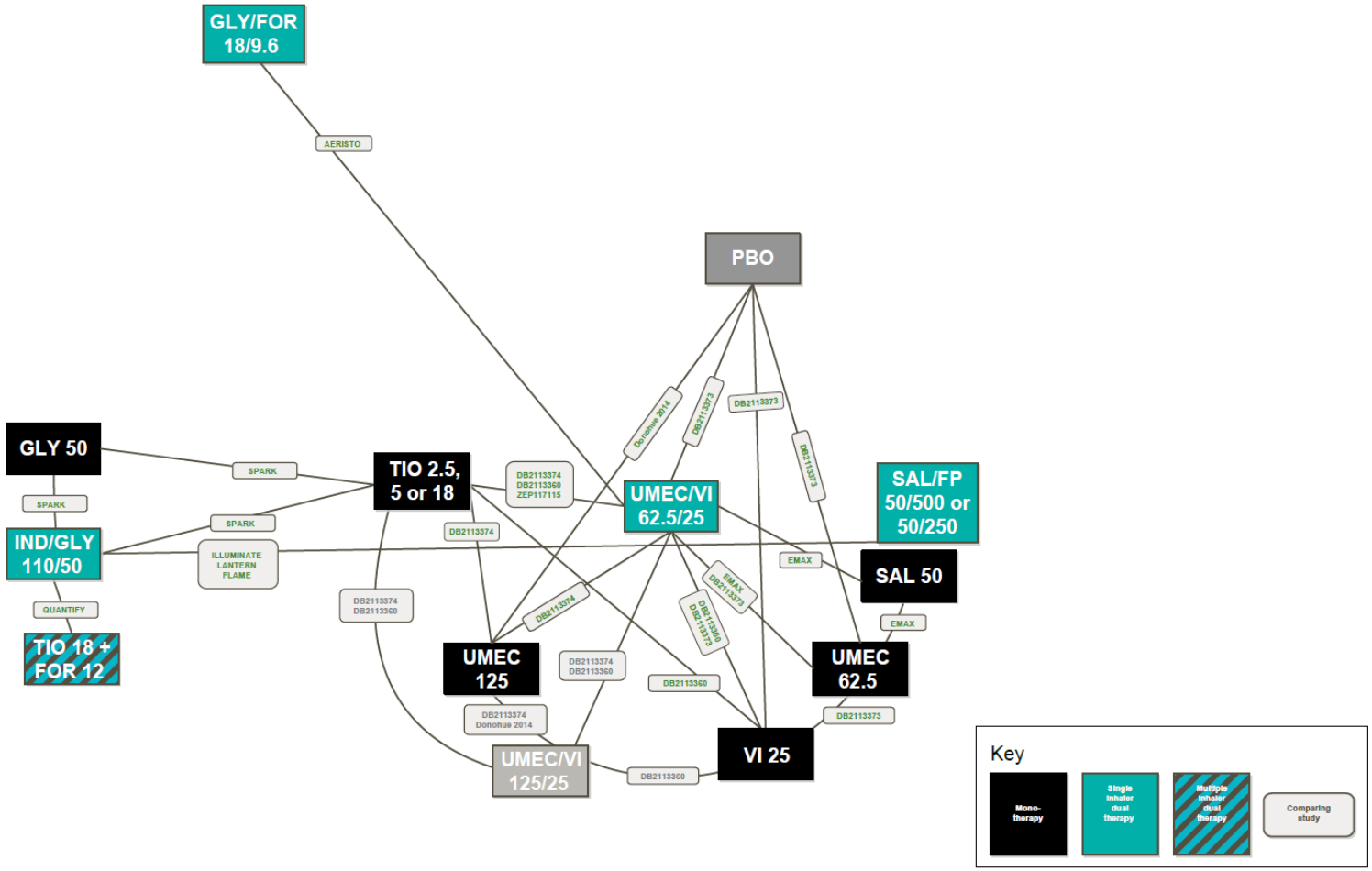
ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TDI, transitional dyspnoea index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S12. Networks of evidence informing annualised moderate/severe exacerbation analysis



ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

Supplementary Figure S13. Networks of evidence informing time to first exacerbation analysis



ACL, aclidinium; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; PBO, placebo; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.