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 $\tau^2$ 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:

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

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

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

$$\begin{pmatrix}
\hat{\theta}_A^{AB} \\
\hat{\theta}_B^{BC} \\
\hat{\theta}_C^{CD} \\
\hat{\theta}_D^{AD} \\
\hat{\theta}_A^{BD}
\end{pmatrix} = 
\begin{pmatrix}
1 & -1 & 0 & 0 \\
0 & 1 & -1 & 0 \\
0 & 0 & 1 & -1 \\
1 & 0 & 0 & -1 \\
0 & 1 & 0 & -1
\end{pmatrix}
\begin{pmatrix}
\theta_A \\
\theta_B \\
\theta_C \\
\theta_D \\
\theta_A
\end{pmatrix} +
\begin{pmatrix}
\epsilon_1 \\
\epsilon_2 \\
\epsilon_3 \\
\epsilon_4 \\
\epsilon_5
\end{pmatrix}$$
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 $W = \text{diag}\left(\frac{1}{s_1^2}, \ldots, \frac{1}{s_m^2}\right)$ including the inverse variance weights. The network estimates are given by $\bar{\theta}^{nma} = H\bar{\theta}$, where

$$H = X(X^T W X)^+ X^T W$$

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

$$\text{COV}(\bar{\theta}^{nma}) = X(X^T W X)^+ X^T.$$

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

$$Q_{total} = (\bar{\theta} - \bar{\theta}^{nma})^T W(\bar{\theta} - \bar{\theta}^{nma}).$$

When a RE model is used rather than a FE model, the variance-covariance matrix changes. On the diagonal, $\tau^2$ has to be added to the variance terms for the individual arms but also to the off-diagonal elements. The off-diagonal elements correspond to the covariances between different arms of the same trial. Estimation of $\tau^2$ is often difficult as it cannot be directly observed. The corresponding degrees of freedom are a function of the number of studies and usually much fewer than those used to estimate the within trial variances.[3] The netmeta package also includes the
possibility to run RE models based on a graph theory approach to NMA. The additional between-
study variance is estimated as

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

with

$$
df = \sum_k (k - 1)n_k - (n - 1)
$$

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

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

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

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

$$
SE(\text{DCFB}) = \frac{(UCL - LCL)}{3.92},
$$

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 \( SE_{\text{CFB}} \) per arm as

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

where \( SE_{\text{CFB,T}}^2 \) and \( SE_{\text{CFB,C}}^2 \) represent SE of change from baseline in active treatment and
comparator arms, respectively.
If none of the above were reported, the SE was imputed from the average SD $\bar{SD}$ of the CFB per study arm, averaging over all reported and estimated SD in the corresponding networks of evidence as

$$SE(DCFB) = \bar{SD} \sqrt{\frac{1}{N_T} + \frac{1}{N_C}}.$$  

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

$$SE(ln(HR)) = (ln(UCL) - ln(LCL))/3.92,$$

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

$$SE(ln(RaR)) = \sqrt{\frac{1}{\hat{r}_T} + \frac{1}{\hat{r}_C}},$$

where $\hat{r}_T$ and $\hat{r}_C$ 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

$$SE(ln(OR)) = \sqrt{\frac{1}{\hat{r}_T + N_T - \hat{r}_T} + \frac{1}{\hat{r}_C + N_C - \hat{r}_C}}.$$
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 FEV₁, 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                               | 1.19 (0.85, 1.68) p=0.3056         | NR                          | 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, 1.14) 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                               | 0.20 (-0.34, 0.75) p=0.4639  | 1.27 (0.74, 1.61) p=0.5370       | 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** |
|                | Placebo     | UMEC/VI     | Laba       | Placebo     | UMEC/VI     | Laba       |
|----------------|-------------|-------------|------------|-------------|-------------|------------|
| **ACL 400**    | 101.4 (69.01, 133.8) | -0.99 (-2.94, 0.97) | 1.08 (0.81, 1.45) | 0.18 (-0.21, 0.57) | 0.99 (0.67, 1.47) | -0.56 (-1.01, -0.10) |
|                | p≤0.0001    | p=0.3234    | p=0.5986   | p=0.3570    | p=0.9798    | p=0.0166   |
| **GLY 18**     | 127.53 (99.31, 155.75) | -2.01 (-3.76, -0.27) | 1.52 (1.16, 1.99) | 0.68 (0.32, 1.04) | 1.22 (0.76, 1.98) | -0.66 (-1.08, -0.24) |
|                | p≤0.0001    | p=0.0235    | p=0.0024   | p=0.0003    | p=0.4099    | p=0.0021   |
| **GLY 50**     | 97.67 (68.4, 126.93) | -1.26 (-2.95, 0.42) | 1.16 (0.89, 1.51) | 0.06 (-0.29, 0.41) | 1.15 (0.77, 1.71) | -0.84 (-1.41, -0.27) |
|                | p≤0.0001    | p=0.1413    | p=0.2717   | p=0.7386    | p=0.4852    | p=0.0040   |
| **TIO 18**     | 87.22 (65.35, 109.09) | -1.29 (-2.52, -0.07) | 1.17 (0.97, 1.41) | 0.34 (0.03, 0.64) | 1.23 (0.93, 1.62) | -0.55 (-0.83, -0.27) |
|                | p≤0.0001    | p=0.0386    | p=0.1097   | p=0.0310    | p=0.1438    | p=0.0001   |
| **UMEC/VI vs LABA monotherapies** |             |             |            |             |             |            |
| **VI 25**      | 95.76 (68.86, 122.66) | -0.37 (-1.85, 1.11) | 1.10 (0.89, 1.36) | 0.42 (0.13, 0.71) | 1.37 (1.07, 1.75) | -0.33 (-0.84, 0.17) |
|                | p≤0.0001    | p=0.625     | p=0.3996   | p=0.0045    | p=0.0111    | p=0.1904   |
| **FOR 9.6**    | 134.16 (105.93, 162.38) | -0.76 (-2.5, 0.98) | 1.35 (1.03, 1.76) | 0.48 (0.11, 0.84) | 0.94 (0.58, 1.52) | -0.34 (-0.76, 0.08) |
|                | p≤0.0001    | p=0.3912    | p=0.0294   | p=0.0104    | p=0.7961    | p=0.1115   |
| **FOR 10**     | NR          | -0.33 (-3.02, 2.37) | NR         | NR          | NR          | NR         |
| **FOR 12**     | 138.21 (106.21, 170.22) | -1.23 (-3.24, 0.78) | 1.11 (0.82, 1.5) | 0.22 (-0.17, 0.61) | 0.95 (0.64, 1.41) | -0.45 (-0.92, 0.02) |
|                | p≤0.0001    | p=0.2304    | p=0.4852   | p=0.2605    | p=0.8131    | p=0.0579   |
| **SAL 50**     | 140.19 (105.66, 174.72) | -1.80 (-3.44, -0.15) | 1.47 (1.15, 1.88) | 0.43 (0.14, 0.72) | 1.40 (1.04, 1.87) | -0.28 (-0.65, 0.09) |
|                | p≤0.0001    | p=0.0322    | p=0.0024   | p=0.0040    | p=0.0248    | p=0.1417   |
| **IND 150**    | 81.69 (41.23, 122.14) | -0.92 (-3.68, 1.85) | 1.01 (0.73, 1.39) | 0.11 (-0.23, 0.45) | 1.11 (0.74, 1.65) | -0.49 (-1.06, 0.08) |
|                | p≤0.0001    | p=0.5155    | p=0.9492   | p=0.5259    | p=0.6413    | p=0.0943   |
| **UMEC/VI vs placebo** | 207.78 (184.88, 230.67) | -3.21 (-4.59, -1.84) | 1.71 (1.39, 2.11) | 1.08 (0.82, 1.35) | 1.82 (1.39, 2.37) | -1.20 (-1.57, -0.83) |
|                | p≤0.0001    | p=0.0001    | p=0.0001   | p=0.0001    | p=0.0001    | p=0.0004   |
ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; HR, hazard ratio; LABA, long-acting β₂-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) |
|------------------|--------------------------------------|-------------------------------|-------------------------------------|-------------------------------|-----------------------------------------------------|
|                  | FE | RE | FE | RE | 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 | NR | NR | NR | NR | NR | NR | 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=0.9770 | 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, 0.01) 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 | 0.53 (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 |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| ACL 400  |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| GLY 15.6 |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| GLY 50   |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| TIO 5    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| TIO 18   |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| IND 27.5 |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| IND 150  |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| UMEC/VI vs LABA monotherapies |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| VI 25    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| FOR 12   |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| SAL 50   |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| IND 27.5 |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| IND 150  |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| UMEC/VI vs placebo |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |          |

*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

| Dual therapies | 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 | FE | RE |
| **Dual therapies** | | | | | | | | | | | | | | | | |
| UMEC/VI 62.5/25 | | | | | | | | | | | | | | | | |
| UMEC/VI 62.5/25 | | | | | | | | | | | | | | | | |
| ACL/ FOR 400/6 | | | | | | | | | | | | | | | | |
| ACL/ FOR 400/12 | | | | | | | | | | | | | | | | |
| GLY/ FOR 18/9.6 | | | | | | | | | | | | | | | | |
| GLY/ FOR (MDI) 18/9.6 | | | | | | | | | | | | | | | | |
| IND/ GLY 110/50 | | | | | | | | | | | | | | | | |
| TIO 18 + FOR 10 | | | | | | | | | | | | | | | | |
| TIO 18 + FOR 12 | | | | | | | | | | | | | | | | |
| LAMA monotherapies          | 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 |
|-----------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| **UMEC 62.5**               |                |                |                |                |                |                |
| -3.34 (-4.81, -1.86)        | -3.24 (-4.97, -1.52) | 1.45 (1.17, 1.8) | 1.44 (1.12, 1.85) | 0.76 (0.44, 1.08) | 0.76 (0.44, 1.08) | 1.37 (1.02, 1.74) | 1.39 (1.06, 1.88) | -0.83 (-1.39, -0.34) | 0.049 (0.23, 0.102) | 0.58 (0.40, 0.85) | 0.57 (0.36, 0.91) |
| p=0.0001                    | p=0.0002       | p=0.0007       | p=0.0001       | p=0.0001       | p=0.0078       | p=0.0087       | p=0.0345       | p=0.0001       | p=0.0551       | p=0.1013      | p=0.0001       | p=0.0187       |
| **UMEC 125**                |                |                |                |                |                |                |
| -1.41 (-2.96, 0.15)         | -1.34 (-3.09, 0.41) | 1.37 (1.09, 1.74) | 1.36 (1.04, 1.77) | 0.54 (0.17, 0.9) | 0.54 (0.17, 0.9) | 1.54 (1.12, 1.98) | 1.54 (1.14, 2.09) | -0.80 (-1.21, -0.44) | 0.0001         | 0.0001         | 0.43 (0.29, 0.64) |
| p=0.0763                    | p=0.1336       | p=0.0081       | p=0.0227       | p=0.0044       | p=0.0044       | p=0.0006       | p=0.0051       | p=0.0001       |                |              | p=0.0005       |
| **ACL 400**                 |                |                |                |                |                |                |
| -2.26 (-3.74, -0.77)        | -2.23 (-3.87, -0.59) | 1.57 (1.27, 1.95) | 1.58 (1.23, 2.03) | 0.90 (0.61, 1.19) | 0.90 (0.61, 1.19) | 1.83 (1.37, 2.43) | 1.83 (1.37, 2.43) | -0.79 (-0.96, -0.32) | 0.0001         | 0.0001         | 0.44 (0.27, 0.70) |
| p=0.0029                    | p=0.0078       | p=0.0001       | p=0.0003       | p=0.0001       | p=0.0001       | p=0.0001       | p=0.0001       |                |                |              |                |
| **GLY 18**                  |                |                |                |                |                |                |
| -1.18 (-2.30, 0.07)         | -1.20 (-2.48, 0.08) | 1.13 (0.94, 1.35) | 1.13 (0.92, 1.38) | 0.60 (0.40, 0.87) | 0.60 (0.40, 0.87) | 0.48 (1.08, 2.21) | 0.48 (1.08, 2.21) | 0.57 (-0.77, -0.37) | 0.0001         | 0.0001         | NR             |
| p=0.0371                    | p=0.0668       | p=0.1907       | p=02422        | p=0.029        | p=0.029        | p=0.0523       | p=0.0523       | p=0.54 (-0.82, -0.26) | 0.0001         | 0.0001         | NR             |
| **GLY 50**                  |                |                |                |                |                |                |
| -1.87 (-2.99, 0.76)         | -1.95 (-3.44, -0.45) | 1.49 (1.22, 1.81) | 1.48 (1.17, 1.87) | 0.75 (0.51, 0.98) | 0.75 (0.51, 0.98) | 1.58 (1.10, 2.11) | 1.58 (1.10, 2.11) | -0.30 (-0.63, -0.03) | 0.75 (0.53, 0.11) | 0.76 (0.68, 0.85) | 0.65 (0.31, 1.36) |
| p=0.0010                    | p=0.0106       | p=0.0011       | p=0.0012       | p=0.0013       | p=0.0013       | p=0.0013       | p=0.0013       |                |                |              |                |
| **TIO 18**                  |                |                |                |                |                |                |
| -1.93 (-2.86, 1.00)         | -1.92 (-2.97, 0.87) | 1.47 (1.27, 1.70) | 1.47 (1.24, 1.73) | 0.75 (0.51, 0.98) | 0.75 (0.51, 0.98) | 1.46 (1.12, 1.83) | 1.46 (1.12, 1.83) | -0.66 (-0.83, -0.40) | 0.74 (0.54, 0.49) | 0.47 (0.25, 0.83) | 0.46 (0.25, 0.83) |
| p=0.0001                    | p=0.0003       | p=0.0001       | p=0.0001       | p=0.0011       | p=0.0011       | p=0.0054       | p=0.0054       |                |                |              |                |
| **LABA monotherapies**      |                |                |                |                |                |                |
| **VI 25**                   |                |                |                |                |                |                |
| -2.86 (-4.20, 1.51)         | -2.84 (-4.35, 1.34) | 1.57 (1.29, 1.91) | 1.56 (1.25, 1.95) | 0.66 (0.37, 0.96) | 0.66 (0.37, 0.96) | 1.33 (1.07, 1.71) | 1.33 (1.07, 1.71) | -0.87 (-1.21, -0.52) | 0.0001         | 0.0001         | NR             |
| p=0.0001                    | p=0.0002       | p=0.0001       | p=0.0001       | p=0.0001       | p=0.0001       | p=0.0085       | p=0.0085       |                |                |              |                |
| **FOR 9.6**                 |                |                |                |                |                |                |
| -2.44 (-3.56, 1.13)         | -2.45 (-3.73, 1.17) | 1.27 (1.06, 1.52) | 1.27 (1.04, 1.55) | 0.61 (0.24, 0.97) | 0.61 (0.24, 0.97) | 1.94 (1.41, 2.66) | 1.94 (1.41, 2.66) | -0.88 (-1.14, -0.58) | 0.0001         | 0.0001         | NR             |
| p=0.0001                    | p=0.0002       | p=0.0019       | p=0.0010       | p=0.0010       | p=0.0010       | p=0.0085       | p=0.0085       |                |                |              |                |
| **FOR 10**                  |                |                |                |                |                |                |
| -2.89 -2.88                 | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             | NR             |
|       | FOR 12       | SAL 50     | IND 150     |
|-------|--------------|------------|-------------|
|       | (-5.14, -0.63) | (-3.58, -0.48) | (-4.68, 0.10) | p=0.012                  |
|       | p=0.0223     | p=0.0102   | p=0.0605    |
|       | 1.53 (1.22, 1.91) | 1.18 (0.91, 1.52) | 1.72 (1.34, 2.20) | p≤0.0001       |
|       | p=0.0002     | p=0.2043   | p=0.0001    |
|       | 1.54 (1.19, 1.99) | 1.17 (0.85, 1.59) | 1.69 (1.26, 2.20) | p≤0.0001       |
|       | 0.86 (0.57, 1.15) | 0.66 (0.28, 1.03) | 0.97 (0.72, 1.23) | p≤0.0001       |
|       | p=0.0011     | p=0.0006   | p=0.0004    |
|       | 0.86 (0.57, 1.15) | 0.66 (0.28, 1.03) | 0.97 (0.72, 1.23) | p≤0.0001       |
|       | 1.92 (1.52, 2.42) | 1.3 (0.99, 1.71) | 1.66 (1.25, 2.20) | p=0.0005       |
|       | p≤0.0001     | p=0.0613   | p=0.0001    |
| p=0.0223 | 1.9 (1.43, 2.54) | 1.3 (0.89, 1.89) | 1.64 (1.15, 2.35) | p=0.0069       |
|       | p=0.0001     | p=0.1682   | p=0.0001    |
|       | -0.89 (-1.1, -0.67) | -0.88 (-1.11, -0.65) | -0.65 (-0.98, -0.32) | p≤0.0001       |
|       | p=0.0011     | p=0.0001   | p=0.0001    |
|       | -0.75 (-1.08, -0.41) | -0.92 (-1.44, -0.39) | -0.71 (-1.18, -0.24) | p=0.791       |
|       | p=0.0001     | p=0.0001   | p=0.0001    |
|       | 0.94 (0.76, 1.16) | 0.59 (0.29, 1.23) | 0.59 (0.25, 1.39) | p=0.553       |
|       | p=0.791     | p=0.2304   | p=0.1426    |
|       | 0.96 (0.71, 1.30) | 0.73 (0.48, 1.11) | 0.72 (0.42, 1.24) | p=0.236       |
|       | p=0.791     | p=0.1426   | p=0.236    |

ACL, aclidinium; CAT, COPD Assessment Test, CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; HR, hazard ratio; LABA, long-acting β₂-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

| Active comparator       | 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) |
|-------------------------|-------------------------------------|-----------------------------|------------------------------------|-----------------------------|-----------------------------------------------------|
|                         | FE                                  | RE                          | FE                                  | RE                          | FE                                                  | RE                                                  |
| Dual therapies          |                                     |                             |                                     |                             |                                                     |                                                     |
| UMEC/VI 62.5/25         | -3.92 [-5.31, -2.54]                | -3.92 [-5.31, -2.54]        | 1.78 (1.45, 2.18)                  | 1.78 (1.45, 2.18)           | 1.11 (0.87, 1.40)                                  | 1.11 (0.82, 1.40)                                  | 2.39 (1.88, 3.04)                                 | 2.39 (1.88, 3.04)                                 | -0.7 (-1.31, 0.09)                                 |
|                         | p=0.0001                            | p=0.0001                    | p=0.0001                            | p=0.0001                    | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0234                                           |
| ACL/FOR 400/12          | NR                                  | NR                          | 1.89 (1.39, 2.57)                  | 1.89 (1.39, 2.57)           | 0.89 (0.41, 1.38)                                  | 0.90 (0.31, 1.49)                                  | 2.82 (2.06, 3.85)                                 | 2.82 (2.06, 3.85)                                 | NR                                                 |
|                         |                                     |                             | p=0.0001                            | p=0.0001                    | p=0.0003                                           | p=0.0003                                           |                                                     |                                                     |                                                     |
| ACL/FOR 400/6           | NR                                  | NR                          | 1.68 (1.23, 2.28)                  | 1.68 (1.23, 2.28)           | NR                                                 | NR                                                 | 2.91 (2.12, 3.98)                                 | 2.91 (2.12, 3.98)                                 | NR                                                 |
|                         |                                     |                             | p=0.0001                            | p=0.0001                    |                                                     |                                                     | p=0.0001                                           | p=0.0001                                           |                                                     |
| IND/GLY 27.5/15.6       | -4.99 [-6.61, -3.38]                | -4.99 [-6.61, -3.38]        | 2.41 (1.87, 3.10)                  | 2.41 (1.87, 3.10)           | 1.62 (1.26, 2.02)                                  | 1.62 (1.22, 2.02)                                  | 2.52 (1.96, 3.25)                                 | 2.52 (1.96, 3.25)                                 | -1.20 (-1.45, -0.94)                              |
|                         | p=0.0001                            | p=0.0001                    | p=0.0001                            | p=0.0001                    | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           |
| IND/GLY 110/50          | -5.17 [-6.81, -3.52]                | -5.17 [-6.81, -3.52]        | 2.03 (1.47, 2.81)                  | 2.03 (1.47, 2.81)           | 1.27 (1.04, 1.5)                                   | 1.29 (0.98, 1.59)                                  |                                                     |                                                     |                                                     |
|                         | p=0.0001                            | p=0.0001                    | p=0.0001                            | p=0.0001                    | p=0.0001                                           | p=0.0001                                           |                                                     |                                                     |                                                     |
| IND/GLY 150/50          | NR                                  | NR                          | NR                                  | NR                          | NR                                                 | NR                                                 | NR                                                 | NR                                                 | NR                                                 |
|                         |                                     |                             |                                     |                             |                                                     |                                                     |                                                     |                                                     |                                                     |
| TIO/OLO 2.5/5           | -3.89 [-5.46, -2.33]                | -3.89 [-5.46, -2.33]        | 2.04 (1.53, 2.73)                  | 2.04 (1.53, 2.73)           | 1.61 (1.23, 2.03)                                  | 1.61 (1.19, 2.03)                                  |                                                     |                                                     |                                                     |
|                         | p=0.0001                            | p=0.0001                    | p=0.0001                            | p=0.0001                    | p=0.0001                                           | p=0.0001                                           |                                                     |                                                     |                                                     |
| TIO/OLO 5/5             | -4.72 [-6.29, -3.16]                | -4.72 [-6.29, -3.16]        | 2.51 (1.88, 3.36)                  | 2.51 (1.88, 3.36)           | 1.62 (1.25, 2.00)                                  | 1.62 (1.2, 2.04)                                   |                                                     |                                                     |                                                     |
|                         | p=0.0001                            | p=0.0001                    | p=0.0001                            | p=0.0001                    | p=0.0001                                           | p=0.0001                                           |                                                     |                                                     |                                                     |
| TIO/18 + FOR 12         | -3.41 [-6.95, -0.48]                | -3.41 [-6.95, -0.48]        | 0.71 (-0.09, 1.51)                 | 0.71 (-0.09, 1.51)          | 0.72 (-0.14, 1.58)                                  | 0.72 (-0.14, 1.58)                                  |                                                     |                                                     |                                                     |
|                         | p=0.0554                            | p=0.0554                    | p=0.0802                            | p=0.0802                    |                                                     |                                                     |                                                     |                                                     |                                                     |
| TIO/18 + IND 150        | -5.41 [-7.50, -3.32]                | -5.41 [-7.50, -3.32]        | 1.64 (1.19, 2.28)                  | 1.64 (1.19, 2.28)           | 1.41 (0.98, 1.94)                                  | 1.41 (0.88, 1.94)                                  | 2.67 (1.87, 3.82)                                 | 2.67 (1.87, 3.82)                                 | -1.05 (-1.43, -0.66)                              |
|                         | p=0.0001                            | p=0.0001                    | p=0.0028                            | p=0.0028                    | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0001                                           | p=0.0058                                           |

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

**p-values:**
- p<0.001: **p=0.0001**
- p<0.005: **p=0.001**
- p<0.01: **p=0.01**
- p<0.05: **p=0.05**
- p<0.1: **p=0.1**
- p<1: **p=1**

**Note:**
- NR: Not reported.
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; FEV₁, forced expiratory volume in 1 second; LABA, long-acting β₂-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, 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    | %   |
| Lipworth, 2018[30] 24 weeks            | 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 |
|                                        | GLY 18 | 474   | 250 | 52.7 | 474   | 34  | 7.2  | 474   | 5    | 1.1  | 474   | 25  | 5.3  | 480   | 63  | 13.1 |
|                                        | FOR 9.6 | 480   | 256 | 53.3 | 480   | 40  | 8.3  | 480   | 5    | 1.0  | 480   | 24  | 5.0  | 483   | 66  | 13.7 |
|                                        | PBO     | 235   | 131 | 55.7 | 235   | 19  | 8.1  | 235   | 6    | 2.6  | 235   | 10  | 4.3  | 238   | 38  | 16.0 |
| Singh, 2015[31] (OTEMTO 1) 12 weeks   | TIO+OLO 5/5 | 203   | 91  | 44.8 | 203   | 10  | 4.9  | NR     | NR   | NR   | 202   | 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  | NR     | NR   | NR   |
|                                        | TIO 5   | 203   | 90  | 44.3 | 203   | 6   | 3.0  | NR     | NR   | NR   | 203   | 3   | 1.5  | NR     | NR   | NR   |
|                                        | PBO     | 204   | 105 | 51.5 | 204   | 11  | 5.4  | NR     | NR   | NR   | 204   | 13  | 6.4  | NR     | NR   | NR   |
| Singh, 2015[31] (OTEMTO 2) 12 weeks   | TIO+OLO 5/5 | 202   | 87  | 43.1 | 202   | 6   | 3.0  | NR     | NR   | NR   | 202   | 1   | 0.5  | NR     | NR   | NR   |
|                                        | TIO+OLO 2.5/5 | 202   | 92  | 45.5 | 202   | 4   | 2.0  | NR     | NR   | NR   | 202   | 4   | 2.0  | NR     | NR   | NR   |
|                                        | TIO 5   | 203   | 93  | 45.8 | 203   | 12  | 5.9  | NR     | NR   | NR   | 203   | 7   | 3.4  | NR     | NR   | NR   |
|                                        | PBO     | 202   | 93  | 46   | 202   | 4   | 2.0  | NR     | NR   | NR   | 202   | 10  | 5.0  | NR     | NR   | NR   |
| Vogelmeier, 2008[32] 24 weeks          | FOR 10  | 210   | 72  | 34.3 | NR     | NR   | NR   | NR     | NR   | NR   | 210   | 25  | 11.9 | 210   | 0    | 0.0  |
|                                        | TIO 18  | 221   | 79  | 35.7 | NR     | NR   | NR   | NR     | NR   | NR   | 221   | 13  | 5.9  | NR     | NR   | NR   |
|                                        | TIO 18 + FOR 10 | 207   | 70  | 33.8 | NR     | NR   | NR   | NR     | NR   | NR   | 207   | 25  | 12.1 | 207   | 0    | 0.0  |
|                                        | PBO     | 209   | 82  | 39.2 | NR     | NR   | NR   | NR     | NR   | NR   | 209   | 30  | 15.0 | 209   | 1    | 0.5  |
| Maleki-Yazdi, 2014[33] 24 weeks        | UMEC/VI 62.5/25 | 454   | 202 | 44   | 454   | 16  | 4.0  | 454   | 1    | 0.2  | 454   | 18  | 4.0  | 454   | 53  | 12.0 |
|                                        | TIO 18  | 451   | 190 | 42   | 451   | 17  | 4.0  | 451   | 1    | 0.2  | 451   | 14  | 3.0  | 451   | 63  | 14.0 |
| Calverley, 2018[34] 52 weeks           | TIO/OLO 5/5 | 3939  | 2920 | 74  | 3939  | 810 | 21.0 | NR     | NR   | NR   | 3939  | 219 | 6.0  | 3939  | 219 | 6.0  |
|                                        | TIO 5   | 3941  | 2937 | 75  | 3941  | 822 | 22.0 | NR     | NR   | NR   | 3941  | 302 | 8.0  | 3941  | 302 | 8.0  |
| Kerwin, 2017[49] (A2349) 12 weeks      | 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 |
|                                        | UMEC/VI 62.5/25 | 340   | 150 | 44.1 | 340   | 21  | 6.2  | NR     | NR   | NR   | 340   | 11  | 3.2  | -     | -    | -    |
|                                        | 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 |
|                                        | 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 |
| Study                         | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 |
|-------------------------------|-------------|-------------|-------------|-------------|
| Kerwin, 2017 (A2350)         | UMEC/VI 62.5/25 | UMEC/VI 62.5/25 | UMEC 62.5 | SAL 50 |
| Maltais, 2019 (22)           | 24          | 24          | 8           | 12         |
| Feldman, 2017 (25)           | 8           | 8           | 8           | 12         |
| Kalberg, 2016 (36)           | 12          | 12          | 12          | 12         |
| Riley, 2018 (37)             | 12          | 12          | 12          | 12         |
| Treatment Period 1: | Treatment Period 2: | Duration wash out: | 3.0 Duration wash out: |
|-------------------|-------------------|-------------------|----------------------|
| 18                | 18                | 4                 | 2.0                  |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 570 | 20 | 3.5 | 570 | 39 | 6.8 | 570 | 2 | <1.0 |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| TIO 18     | 561      | 230.0    | 41 | 564| NR | NR | NR | NR | NR | 564 | 10 | 1.8 | 564 | 35 | 6.2 | 564 | 0 | 0.0  |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 570 | 14 | 2.5 | 570 | 37 | 6.5 | 570 | 2 | <1.0 |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| TIO 18     | 570      | 229.1    | 40.2| 570| NR | NR | NR | NR | NR | 570 | 14 | 2.5 | 570 | 37 | 6.5 | 570 | 2 | <1.0 |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 226 | 3 | 1.3 | 226 | 14 | 6.2 | 226 | 0 | 0.0  |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| IND 150    | 221      | 75       | 33.9| 221| 5   | 2.2 | NR | NR | NR | 221 | 4  | 1.8 | 221 | 13 | 5.8 | 223 | 0 | 0.0  |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 729 | 93 | 167 | 729 | 33 | 5.0 | 741 | 59 | 8.0  |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| 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  |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 217 | 20 | 9.0 | 217 | 54 | 25.0 | 217 | 1 | 0.5  |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| 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  |
| TIO 18     | 215      | 133      | 62 | 215 | 15  | 7.0  | 215 | 4  | 2.0 | 215 | 15 | 7.0 | 215 | 49 | 23.0 | 215 | 1 | 0.5  |

| Treatment | Perio 1: | Perio 2: | NR | NR | NR | NR | NR | NR | NR | 214 | 5 | 2.0 | 214 | 1 | <1.0 | 214 | 15 | 7.0  |
|------------|----------|----------|----|----|----|----|----|----|----|-----|----|----|----|----|----|----|----|----|
| 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  |
| Study                  | Treatment 1 | Treatment 2 | Treatment 3 | Treatment 4 | Treatment 5 | Treatment 6 | Treatment 7 | Treatment 8 | Treatment 9 | Treatment 10 | Treatment 11 | Treatment 12 | Treatment 13 | Treatment 14 | Treatment 15 | Treatment 16 |
|------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| GSK CSR* (DB21133 60) | 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* (DB21133 73) | 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]  | 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 | ACL/FOR 400/12 | 466 265 56.9 466 33 7.1 NR NR NR 466 34 7.3 466 79 17.0 466 1 0.2 | 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]    | IND/GLY 110/50 | 1678 1459 86.9 1678 308 18.4 1678 45 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]      | 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]       | 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 | 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 |
| D'Urzo, 2014[44]      | 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, 2017[45]      | ACL/FOR 400/12 | 335 215 64.2 335 19.09 5 5.7 335 2 0.6 338 21 6.3 338 66 20.0 335 1 0.3 | ACL/FOR 400/12 | 335 215 64.2 335 19.09 5 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 17.98 2 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 5.0 337 1 0.3 340 16 4.7 340 72 21.0 337 3 0.9 | ACL 400 | 337 210 62.3 337 16.85 5 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 |
|                        | 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 11.95 2 3.6 332 3 0.9 337 21 6.3 337 101 30.0 332 0 0.0 |
|                        | 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 | 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 |
| Study                          | Drug 1 | Drug 2 | Drug 3 | Drug 4 | Drug 5 | Drug 6 | Drug 7 | Drug 8 | Drug 9 | Drug 10 |
|-------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|
| **Ferguson, 2016[46]**        |        |        |        |        |        |        |        |        |        |         |
| FLIGHT 1                      |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| GLY 16                        |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Mahler, 2015[47]** (FLIGHT 1 & FLIGHT 2, pooled) | 52 |        |        |        |        |        |        |        |        |         |
| 2015                          |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| GLY 16                        |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Mahler, 2015[47]** (FLIGHT 1) | 12 |        |        |        |        |        |        |        |        |         |
| 2015                          |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| GLY 16                        |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Mahler, 2015[47]** (FLIGHT 2) | 12 |        |        |        |        |        |        |        |        |         |
| 2015                          |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| GLY 16                        |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Siler, 2016[48]**           |        |        |        |        |        |        |        |        |        |         |
| FLIGHT 1                      |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| UMECTIVI 62.5/25              |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Kerwin, 2017[49]**          |        |        |        |        |        |        |        |        |        |         |
| FLIGHT 1                      |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| UMECTIVI 62.5/25              |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Donohue, 2016[50]**         |        |        |        |        |        |        |        |        |        |         |
| FLIGHT 1                      |        |        |        |        |        |        |        |        |        |         |
| 2016                          |        |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| ACL/FOR 400/12                |        |        |        |        |        |        |        |        |        |         |
| FOR 12                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| **Martinez, 2017[51]** (PINAACL E-1) | 24 |        |        |        |        |        |        |        |        |         |
| 2017                          |        |        |        |        |        |        |        |        |        |         |
| 2018                          |        |        |        |        |        |        |        |        |        |         |
| GLY/FOR 18/9.6                |        |        |        |        |        |        |        |        |        |         |
| TIO 18                        |        |        |        |        |        |        |        |        |        |         |
| PBO                           |        |        |        |        |        |        |        |        |        |         |
| Study                     | Treatment Description       | 510 | 286 | 56.1 | 510 | 36 | 7.1 | 510 | 7 | 1.4 | 510 | 25 | 4.9 | 510 | 80 | 15.7 | 510 | 1 | 0.2 |
|--------------------------|----------------------------|-----|-----|------|-----|----|-----|-----|---|-----|-----|----|-----|-----|----|------|-----|---|----|
| **Donohue, 2017[51]**    | 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]**    | IND/GLY 110/50             | 474 | 261 | 55.1 | 474 | 22 | 4.6 | NR  | 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 | 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 | 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 | 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 | NR  | 232 | 10 | 4.3 | 232 | 45 | 19.2 | 232 | 0 | 0.0 |
| **Buhl, 2015[52]**       | IND/GLY 110/50             | 476 | 208 | 43.7 | 476 | 30 | 6.3 | NR  | 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 | NR  | 458 | 27 | 5.9 | 458 | 52 | 11.4 | 458 | 3 | 0.7 |
| **Tashkin, 2009[53]**    | TIO 18 + FOR 12            | NR  | NR  | NR  | NR  | NR | NR | NR  | NR | NR | NR  | 124 | 6  | 5.0 | 124 | 18 | 15.0 | NR  | NR | NR  |
| **Frichth, 2018[54]**   | IND/GLY 110/50             | 248 | 62  | 25   | 248 | 9  | 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  | 9   | NR  | NR | NR | NR  | 250 | 3  | 1.2 | 250 | 13 | 5.2  | 250 | 1 | <1.0 |
| **Celli, 2014[55]**     | 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]**     | UMEC/VI 62.5/25            | 358 | 99  | 28   | 358 | 7  | 2.0 | NR  | 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 | NR  | 358 | 5  | 1.0 | 358 | 18 | 5.0  | 358 | 2 | 0.6 |
| **Donohue, 2015[57]**   | 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]**   | 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] | | TIO 18 + IND 150 | 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 |
| 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 |
| ZuWallac, 2014[62] (ANHELT O 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 |
| ZuWallac, 2014[62] (ANHELT O 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] (TOMANO 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 |
|               | TIO 5 | TIO/OLO 2.5/5 | TIO/OLO 5/5 |
|---------------|-------|---------------|-------------|
| 506           | 376   | 74.3          | 506         |
| 93            | 18.4  | 506           | 7           |
| 1.4           | 506   | 51            | 10.1        |
| 506           | 96    | 19.0          | NR          |
| NR            | NR    | NR            | NR          |

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.

*Available from clinicalstudydatarequest.com.*
Supplementary Figure S1. Network of evidence informing trough FEV\textsubscript{1} analysis at (A) 24 and (B) 12 weeks.

A) 24 weeks

B) 12 weeks
ACL, aclidinium; FEV₁, 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 FEV₁ with UMEC/VI versus (A) dual therapy and (B) monotherapy at 12 weeks

Assessment of heterogeneity/inconsistency: I²=38.64%; Q=81.48; p=0.0033.

ACL, aclidinium; CFB, change from baseline; CI, confidence interval; FEV₁, 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 FEV₁ 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; FEV₁, 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.