# Supplementary material

## Methodology

## Statistical analysis

*TONADO®*

Analysis of the primary endpoints at 24 weeks was performed for all randomized patients who received at least one dose of treatment and had baseline and at least one post-baseline measurement at or before 24 weeks for any primary efficacy endpoint (full analysis set).

The mean changes from baseline in forced expiratory volume in 1 second ($FEV_1$) area under the curve from 0 to 3 hours ($AUC_{0–3}$) response, trough $FEV_1$ response, and St. George's Respiratory Questionnaire (SGRQ) total score were analyzed using a restricted maximum likelihood (REML)-based mixed-effect model repeated measures approach. Analyses included the fixed, categorical effects of treatment, test day, and treatment-by-test-day interaction, as well as the continuous, fixed covariates of baseline and baseline-by-test-day interaction. A spatial power covariance structure was used to model within-patient errors. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. Analyses were implemented using SAS version 9.2.

Transition Dyspnea Index (TDI) focal score was also analyzed using a REML-based mixed-effect model repeated measures approach.

A responder analysis on the SGRQ total score was performed, with patients classed as responders if their improvement in SGRQ total score was ≥4.0 units, and a logistic regression, which included the fixed categorical effect of treatment, was used to

calculate the odds ratio of responder between treatment groups. The same model was used to analyze TDI responders, with patients classed as responders if their TDI focal score was ≥1.0 unit, corresponding to an improvement from Baseline Dyspnea Index (BDI) baseline score of ≥1 unit.

*OTEMTO®*

The primary analyses were intent-to-treat analyses, performed on the full analysis set, defined as all patients who received at least one dose of study medication and had baseline and at least one post-baseline measurement for any of the primary endpoints. Changes from baseline in $FEV_1$ $AUC_{0–3}$, trough $FEV_1$, and SGRQ total score were analyzed using a REML-based mixed-effect model repeated measures approach, including the fixed categorical effects of treatment, test day, and treatment-by-test-day interaction, as well as the continuous fixed covariates of baseline and baseline-by-test-day interaction.

TDI focal score was also analyzed using the same REML-based mixed-effect model repeated measures approach.

A responder analysis on the SGRQ total score was performed, with patients classed as responders if their improvement in SGRQ total score was ≥4.0 units, and a logistic regression, which included the fixed categorical effect of treatment, was used to calculate the odds ratio of responder between treatment groups. The same model was used to analyze TDI responders, with patients classed as responders if their TDI focal score was ≥1.0 unit, corresponding to an improvement from BDI baseline score of ≥1.0 unit.

**Table S1** SGRQ total score and responder analysis after 12 weeks (OTEMTO®) and 24 weeks (TONADO®) by age subgroup

| | **12 weeks (OTEMTO®)** | | | **24 weeks (TONADO®)** | | |
|---|---|---|---|---|---|---|
| | **40−<65 years** | **65−<75 years** | **75−<85 years** | **40−<65 years** | **65−<75 years** | **75−<85 years** |
| **Adjusted mean (SE) SGRQ total score** | **SGRQ total score** | | | | | |
| Common baseline mean (SE) | 45.29 (0.67) | 40.35 (0.66) | 39.79 (1.09) | 45.49 (0.37) | 41.65 (0.41) | 40.65 (0.73) |
| Placebo | 44.17*** (0.79) | 40.56*** (0.74) | 40.40 (1.64) | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 40.00* (0.59) | 36.41 (0.62) | 37.62 (1.42) |
| Tiotropium 5 µg | 42.00* (0.75) | 37.96** (0.74) | 37.12 (1.47) | 39.42 (0.58) | 36.35 (0.62) | 36.32 (1.38) |
| Tiotropium + olodaterol 5/5 µg | 39.73 (0.75) | 34.67 (0.76) | 38.19 (1.27) | 38.03 (0.57) | 35.33 (0.59) | 34.66 (1.43) |

| % SGRQ responders | SGRQ responders | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 31.5 | 32.1 | 32.4 | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 47.5 | 42.4 | 39.8 |
| Tiotropium 5 µg | 44.4 | 37.7 | 42.5 | 50.0 | 47.3 | 46.9 |
| Tiotropium + olodaterol 5/5 µg | 54.4 | 53.9 | 42.6 | 60.5 | 54.0 | 56.2 |

**Notes:** *$P$<0.05, **$P$<0.01, ***$P$<0.001 compared to tiotropium + olodaterol 5/5 µg.

**Abbreviations:** NA, not applicable; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

**Table S2** TDI focal score and responder analysis after 12 weeks (OTEMTO®) and 24 weeks (TONADO®) by age subgroup

| | **12 weeks (OTEMTO®)** | | | **24 weeks (TONADO®)** | | |
|---|---|---|---|---|---|---|
| | **40−<65 years** | **65−<75 years** | **75−<85 years** | **40−<65 years** | **65−<75 years** | **75−<85 years** |
| **Adjusted mean (SE)** | **TDI focal score** | | | | | |
| Common baseline mean (SE) | 6.512 (0.080) | 6.641 (0.081) | 6.277 (0.137) | 6.529 (0.044) | 6.574 (0.050) | 6.467 (0.094) |
| Placebo | 0.371*** (0.212) | -0.239*** (0.206) | 0.328 (0.422) | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 1.712 (0.139) | 1.450** (0.151) | 1.239 (0.277) |
| Tiotropium 5 µg | 1.321 (0.205) | 0.859*** (0.209) | 1.599 (0.379) | 1.664 (0.137) | 1.542* (0.152) | 1.638 (0.272) |
| Tiotropium + olodaterol 5/5 µg | 1.722 (0.201) | 1.962 (0. 214) | 1.111 (0.326) | 1.974 (0.136) | 2.072 (0.147) | 1.670 (0.286) |
| **% TDI responders** | **TDI focal score responder analysis** | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 29.1 | 23.2 | 23.5 | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 51.8 | 45.7 | 39.6 |
| Tiotropium 5 µg | 45.8 | 33.5 | 52.5 | 52.2 | 47.4 | 53.5 |
| Tiotropium + olodaterol 5/5 µg | 52.7 | 60.4 | 40.7 | 53.7 | 58.5 | 47.3 |

**Notes:** **P*<0.05, ***P*<0.01, ****P*<0.001 compared to tiotropium + olodaterol 5/5 µg.

**Abbreviations:** NA, not applicable; SE, standard error; TDI, Transition Dyspnea Index.

**Table S3** Daytime rescue medication use (puffs/day) at 12 weeks (OTEMTO®) and 24 weeks (TONADO®) by age subgroup

| | **12 weeks (OTEMTO®)** | | | **24 weeks (TONADO®)** | | |
|---|---|---|---|---|---|---|
| **Adjusted weekly mean (SE)** | **40−<65 years** | **65−<75 years** | **75−<85 years** | **40−<65 years** | **65−<75 years** | **75−<85 years** |
| Placebo | 1.044*** (0.079) | 0.906 (0.086) | 0.647 (0.146) | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 1.034** (0.060) | 0.762 (0.057) | 0.804 (0.111) |
| Tiotropium 5 µg | 0.979*** (0.078) | 0.897 (0.086) | 0.714 (0.130) | 1.076** (0.058) | 0.899** (0.058) | 0.615 (0.111) |
| Tiotropium + olodaterol 5/5 µg | 0.580 (0.077) | 0.691 (0.088) | 0.523 (0.112) | 0.813 (0.058) | 0.636 (0.056) | 0.574 (0.118) |

**Notes:** ***P*<0.01, ****P*<0.001 compared to tiotropium + olodaterol 5/5 µg.

**Abbreviations:** NA, not applicable; SE, standard error.

**Table S4** Night-time rescue medication use (puffs/night) at 12 weeks (OTEMTO®) and 24 weeks (TONADO®) by age subgroup

| | **12 weeks (OTEMTO®)** | | | **24 weeks (TONADO®)** | | |
|---|---|---|---|---|---|---|
| **Adjusted weekly mean (SE)** | **40−<65 years** | **65−<75 years** | **75−<85 years** | **40−<65 years** | **65−<75 years** | **75−<85 years** |
| Placebo | 2.016*** (0.122) | 2.114*** (0.121) | 1.942* (0.263) | NA | NA | NA |
| Olodaterol 5 µg | NA | NA | NA | 1.611** (0.077) | 1.508* (0.085) | 1.280 (0.169) |
| Tiotropium 5 µg | 1.578*** (0.120) | 1.399 (0.121) | 1.378 (0.236) | 1.703*** (0.075) | 1.614*** (0.086) | 1.516* (0.164) |
| Tiotropium + olodaterol 5/5 µg | 0.987 (0.119) | 1.130 (0.125) | 1.076 (0.203) | 1.278 (0.075) | 1.207 (0.084) | 0.998 (0.178) |

**Notes:** *$P$<0.05, **$P$<0.01, ***$P$<0.001 compared to tiotropium + olodaterol 5/5 µg.

**Abbreviations:** NA, not applicable; SE, standard error.

**Figure S1** Age distribution at baseline for OTEMTO® (A) and TONADO® (B).

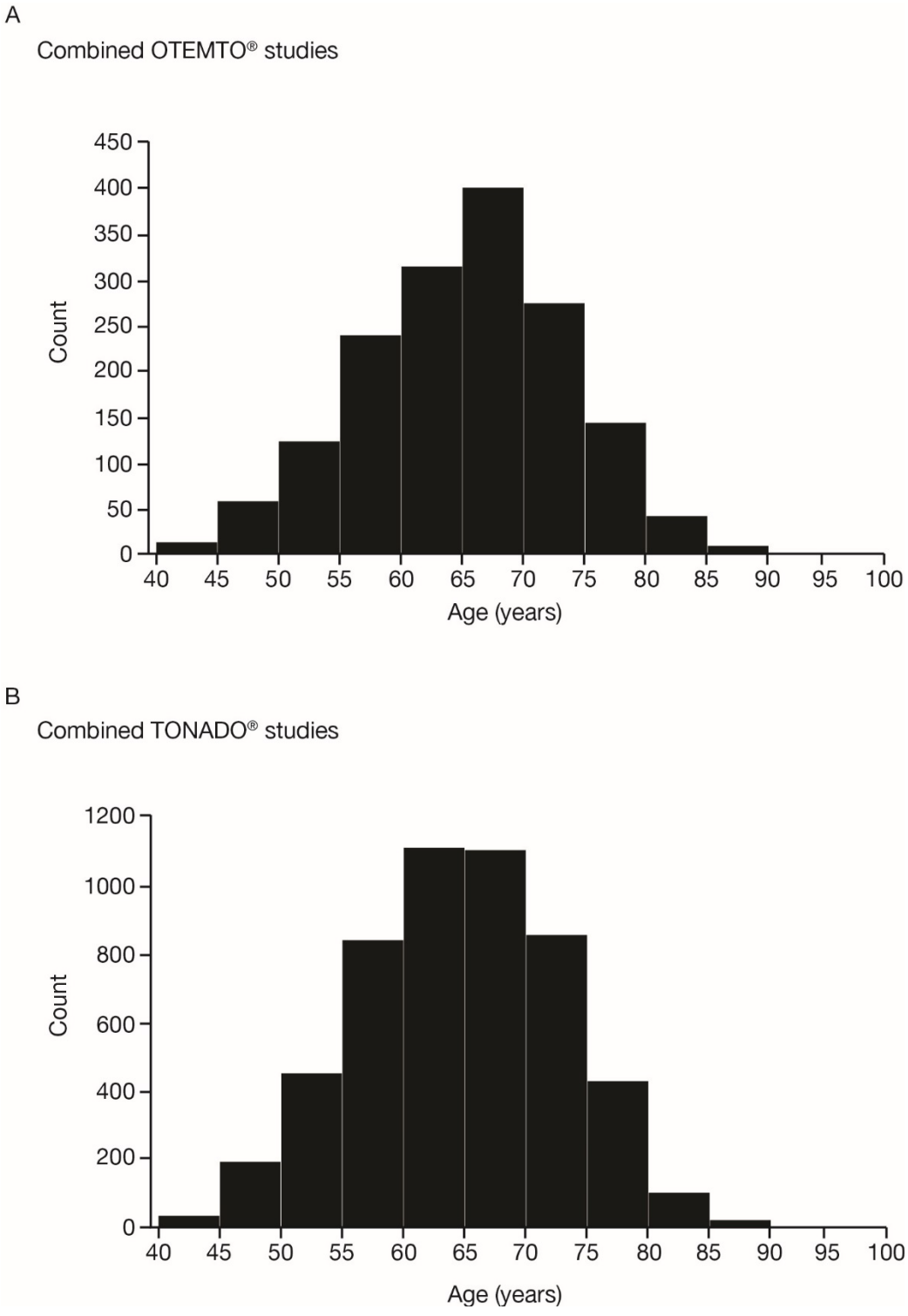

**Figure S2** Adjusted mean (SE) SGRQ total score at (A) Week 12 (OTEMTO®) and (B) Week 24 (TONADO®) by age group.

**Abbreviations:** CI, confidence interval; O, olodaterol; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; T, tiotropium.

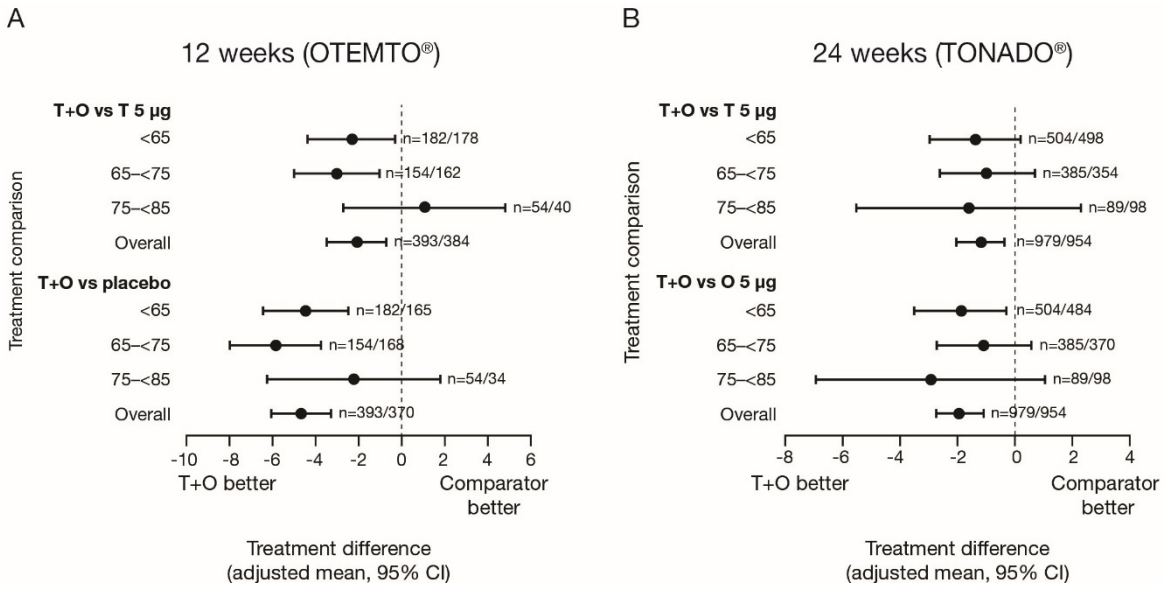

**Figure S3** SGRQ total score responder analysis at (A) Week 12 (OTEMTO®) and (B) Week 24 (TONADO®) by age group.

**Abbreviations:** CI, confidence interval; O, olodaterol; SGRQ, St. George's Respiratory Questionnaire; T, tiotropium.

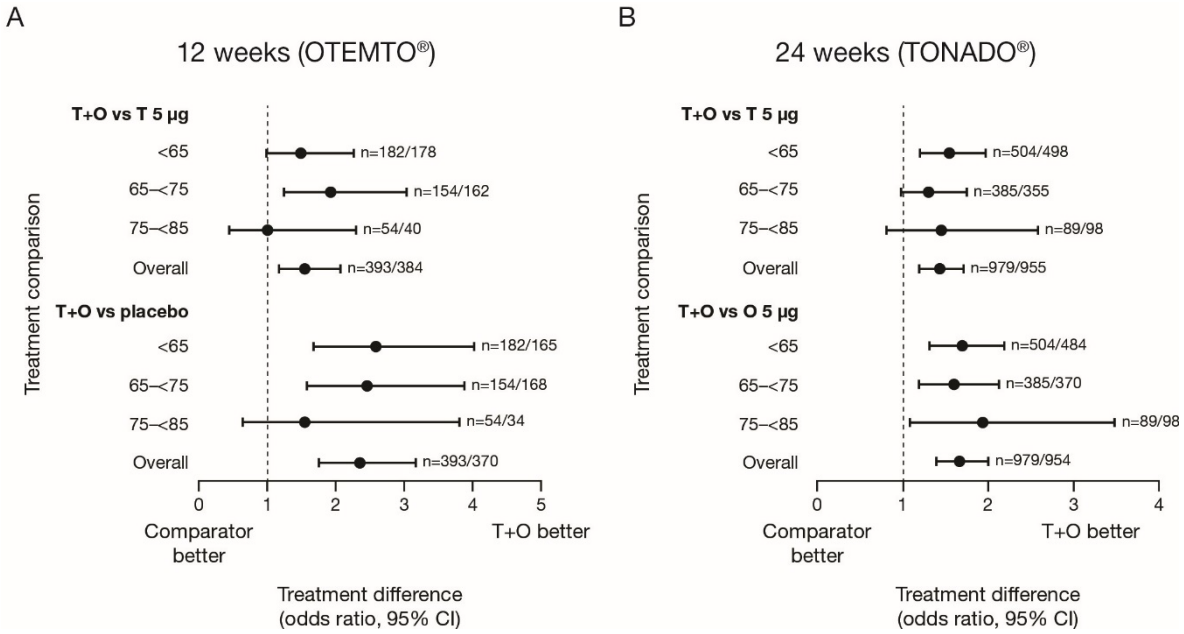

**Figure S4** Adjusted mean (SE) TDI focal score for each treatment group by age from (A) baseline to Week 12 (OTEMTO®) and (B) baseline to Week 24 (TONADO®).

**Abbreviations:** CI, confidence interval; O, olodaterol; SE, standard error; T, tiotropium; TDI, Transition Dyspnea Index.

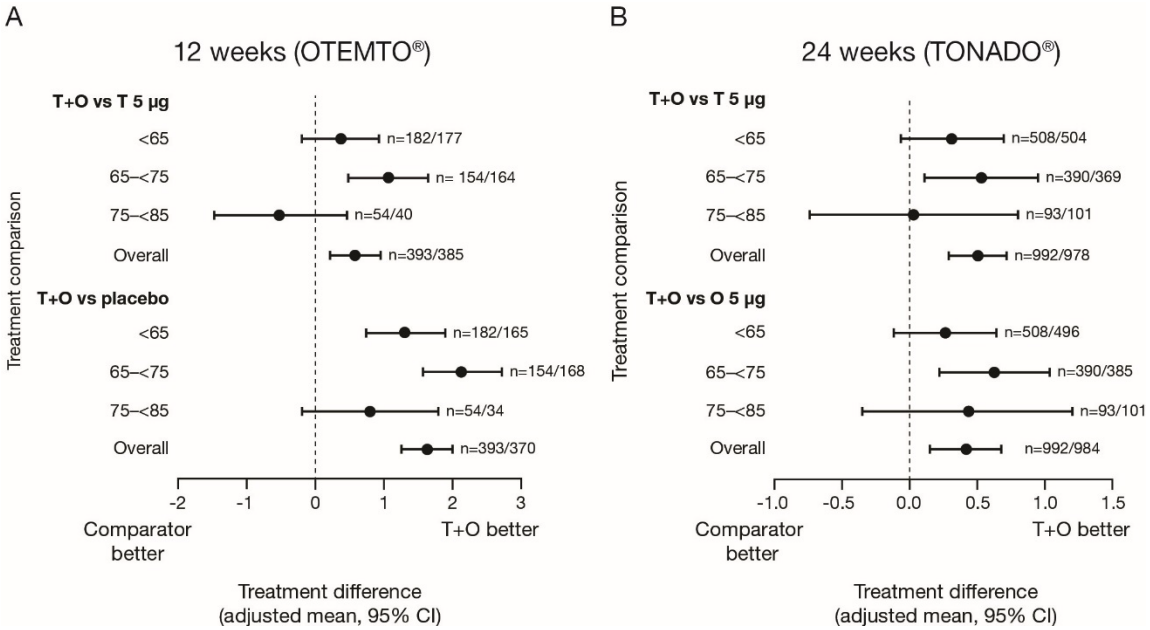

**Figure S5** TDI focal score responder analysis at (A) Week 12 (OTEMTO®) and (B) Week 24 (TONADO®) by age group.

**Abbreviations:** CI, confidence interval; O, olodaterol; T, tiotropium; TDI, Transition Dyspnea Index.