Mannino et al – Supplement

Methods

Screening, case-finding, and COPD diagnosis by spirometry

At Visit 0, patients underwent screening with the COPD-population screener: a five-item validated self-administered questionnaire designed to identify subjects at risk of having COPD\(^1\) and case-finding with the copd-6™ hand-held device (Vitalograph Ltd, Buckingham, UK) to screen for airflow limitation based on forced expiratory volume in 1 second (FEV\(_1\))/forced expiratory volume in 6 second <0.7. Although, this ratio was not a study inclusion criterion, it was used to identify patients for consideration into the study. At Visit 1, COPD diagnosis was established or confirmed using post-bronchodilation pulmonary functions tests (four puffs of albuterol). A post-bronchodilator FEV\(_1\)/forced vital capacity (FVC) <0.7 along with clinical assessment of the patient by the investigator supporting the introduction of COPD maintenance therapy was required pre-randomization. Post-bronchodilator spirometry was also performed at Visit 5, 4 weeks after terminating study drug, to confirm spirometric GOLD staging.\(^2\)

Pulmonary function testing

The intended primary endpoint was trough FEV\(_1\) after 12 weeks of treatment. Trough FEV\(_1\) was defined as the FEV\(_1\) measurement before the next inhalation of study drug and ~24 h after the last inhalation. Since the study was statistically underpowered this endpoint was reclassified as exploratory for these analyses.

Analyses

The statistical model for the exploratory treatment efficacy analysis included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, baseline FEV\(_1\) (pre-
bronchodilator FEV₁ at Visit 1) as covariates as well as baseline FEV₁-by-visit-interaction. Adjusted means of the primary endpoint were obtained from the primary model.

**Results**

**Treatment efficacy**

Exploratory analyses showed numerical improvements in trough FEV₁ with tiotropium compared with placebo at 12 weeks, with an adjusted mean±SE change from baseline of 0.095±0.039 L for tiotropium and 0.038±0.038 L for placebo. Similar patterns in trough FEV₁ were noted for trough FVC (Figure S2A–S2D). Data for mean daily FEV₁ and PEFR are shown in Table S3.

**Safety**

Tiotropium 18 μg was well tolerated by patients. A summary of adverse events (AEs) is provided in Table S5. No deaths were reported. Overall, 44.3% (62) of patients reported AEs; 28 (41.2%) on tiotropium and 34 (47.2%) on placebo. Severe AEs (ie, AEs that were incapacitating or caused inability to work or to perform usual activities) were reported by 5.0% (7) of patients; 5.9% (4) on tiotropium and 4.2% (3) on placebo. A treatment-related AE was reported by 0.7% (1) of patients on tiotropium (mild constipation). AEs leading to discontinuation were reported by 1.4% (2) of patients (1 patient with acute respiratory failure and COPD on tiotropium and 1 patient with lung neoplasm malignant on placebo). Serious AEs were reported by 4.3% (6) of patients (3 patients per treatment group); all required hospitalization. All serious AEs were reported by one patient each, except for COPD (2 patients in each treatment group) and acute respiratory failure (1 patient in each treatment group). No clinically notable mean changes in vital sign measurements occurred, and no trends were observed.
References


Table S1  Most frequently taken medication (>5% patients in any group) before entering the study, at baseline, and within ±7 days of randomization

<table>
<thead>
<tr>
<th>Medication</th>
<th>Placebo (n=72)</th>
<th>Tiotropium 18 μg (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before entering the study, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total taking medication</td>
<td>12 (16.7)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Short-acting beta adrenergics</td>
<td>9 (12.5)</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>9 (12.5)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>0 (0)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>4 (5.6)</td>
<td>3 (4.4)</td>
</tr>
<tr>
<td><strong>At baseline, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total taking medication</td>
<td>8 (11.1)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>7 (9.7)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>7 (9.7)</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td><strong>Within ±7 days of randomization, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total taking medication</td>
<td>25 (34.7)</td>
<td>31 (45.6)</td>
</tr>
<tr>
<td>Short-acting beta adrenergics</td>
<td>2 (2.8)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>12 (16.7)</td>
<td>11 (16.2)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>10 (13.9)</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Duration of antibiotic use, days, mean ± SD (median)</td>
<td>7.1±0.7 (7.0)</td>
<td>7.3±4.0 (8.0)</td>
</tr>
<tr>
<td>Corticosteroids, n (%)</td>
<td>22 (30.6)</td>
<td>26 (38.2)</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0 (0)</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>22 (30.6)</td>
<td>23 (33.8)</td>
</tr>
</tbody>
</table>

**Abbreviation:** SD, standard deviation.
Table S2 Duration of patients’ acute respiratory event at Visit 1 and symptoms reported

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=72)</th>
<th>Tiotropium 18 μg (n=68)</th>
<th>Total (n=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of acute respiratory event, days, mean ± SD</td>
<td>3.7±1.6</td>
<td>4.1±1.8</td>
<td>3.9±1.7</td>
</tr>
<tr>
<td>Qualifying events for study inclusion, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of previous shortness of breath</td>
<td>56 (77.8)</td>
<td>56 (82.4)</td>
<td>112 (80.0)</td>
</tr>
<tr>
<td>New shortness of breath</td>
<td>15 (20.8)</td>
<td>11 (16.2)</td>
<td>26 (18.6)</td>
</tr>
<tr>
<td>Limiting activities due to new or increased shortness of breath</td>
<td>58 (80.6)</td>
<td>52 (76.5)</td>
<td>110 (78.6)</td>
</tr>
<tr>
<td>Additional symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>62 (86.1)</td>
<td>63 (92.6)</td>
<td>125 (89.3)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>45 (62.5)</td>
<td>52 (76.5)</td>
<td>97 (69.3)</td>
</tr>
<tr>
<td>Nasal symptoms</td>
<td>47 (65.3)</td>
<td>46 (67.6)</td>
<td>93 (66.4)</td>
</tr>
<tr>
<td>New or increased wheeze</td>
<td>42 (58.3)</td>
<td>43 (63.2)</td>
<td>85 (60.7)</td>
</tr>
<tr>
<td>Chest discomfort related to breathing</td>
<td>29 (40.3)</td>
<td>30 (44.1)</td>
<td>59 (42.1)</td>
</tr>
<tr>
<td>New or increased night-time awakenings</td>
<td>32 (44.4)</td>
<td>37 (54.4)</td>
<td>69 (49.3)</td>
</tr>
<tr>
<td>New or increased limiting activities</td>
<td>50 (69.4)</td>
<td>47 (69.1)</td>
<td>97 (69.3)</td>
</tr>
<tr>
<td>Elevated body temperature</td>
<td>2 (2.8)</td>
<td>1 (1.5)</td>
<td>3 (2.1)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
Table S3 Descriptive statistics for mean daily FEV₁ and mean daily PEFR over time and change from baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Change from baseline, mean ± SD</th>
<th>Tiotropium 18 μg</th>
<th>Change from baseline, mean ± SD</th>
<th>Total</th>
<th>Change from baseline, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Mean daily FEV₁, L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63</td>
<td>1.66±0.75</td>
<td>60</td>
<td>1.54±0.60</td>
<td>123</td>
<td>1.61±0.68</td>
</tr>
<tr>
<td>Week 2</td>
<td>58</td>
<td>1.56±0.68</td>
<td>48</td>
<td>1.48±0.51</td>
<td>106</td>
<td>1.53±0.61</td>
</tr>
<tr>
<td>Week 4</td>
<td>51</td>
<td>1.51±0.61</td>
<td>44</td>
<td>1.43±0.47</td>
<td>95</td>
<td>1.47±0.55</td>
</tr>
<tr>
<td>Week 12</td>
<td>58</td>
<td>1.41±0.74</td>
<td>53</td>
<td>1.38±0.66</td>
<td>111</td>
<td>1.39±0.70</td>
</tr>
<tr>
<td>Last 7 days of treatment</td>
<td>72</td>
<td>1.40±0.70</td>
<td>68</td>
<td>1.34±0.59</td>
<td>140</td>
<td>1.37±0.65</td>
</tr>
<tr>
<td>Mean daily PEFR, L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>63</td>
<td>264.6±109.6</td>
<td>60</td>
<td>249.2±103.5</td>
<td>123</td>
<td>257.1±106.5</td>
</tr>
<tr>
<td>Week 2</td>
<td>58</td>
<td>273.3±103.5</td>
<td>48</td>
<td>255.1±96.0</td>
<td>106</td>
<td>265.1±100.1</td>
</tr>
<tr>
<td>Week 4</td>
<td>51</td>
<td>250.9±99.9</td>
<td>44</td>
<td>255.2±98.1</td>
<td>95</td>
<td>252.9±98.6</td>
</tr>
<tr>
<td>Week 12</td>
<td>58</td>
<td>261.2±129.9</td>
<td>53</td>
<td>249.3±115.9</td>
<td>111</td>
<td>255.5±123.0</td>
</tr>
<tr>
<td>Last 7 days of treatment</td>
<td>72</td>
<td>253.4±115.8</td>
<td>68</td>
<td>249.6±108.7</td>
<td>140</td>
<td>251.5±112.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** FEV₁, forced expiratory volume in 1 second; PEFR, daily peak expiratory flow rate; SD, standard deviation.
Table S4 Descriptive statistics for the Work Productivity and Activity Impairment Questionnaire: Respiratory Symptoms (WPAI:RS) over time and change from baseline. The employment section of the questionnaire was only completed by patients who were currently in employment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Tiotropium 18 μg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>Change from baseline, mean ± SD</td>
</tr>
<tr>
<td>Percent of days employed over 12-week treatment period</td>
<td>72</td>
<td>32.4±43.8</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140</td>
</tr>
<tr>
<td>Number of days of lost work</td>
<td>16</td>
<td>8.95±11.27</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Percent work time missed during the preceding 7 days due to a problem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25</td>
<td>8.7±18.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.8±23.5</td>
<td>–</td>
</tr>
<tr>
<td>Week 2</td>
<td>23</td>
<td>9.3±26.3</td>
<td>−0.1±31.8</td>
</tr>
<tr>
<td>Week 4</td>
<td>23</td>
<td>5.9±19.2</td>
<td>−3.5±29.2</td>
</tr>
<tr>
<td>Week 12</td>
<td>20</td>
<td>6.6±22.6</td>
<td>−0.7±27.2</td>
</tr>
<tr>
<td>Percent overall work impairment during the preceding 7 days due to a problema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>25</td>
<td>27.9±27.5</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35.8±25.3</td>
<td>–</td>
</tr>
<tr>
<td>Week 2</td>
<td>23</td>
<td>23.1±25.2</td>
<td>−7.2±21.9</td>
</tr>
<tr>
<td>Week 4</td>
<td>23</td>
<td>20.7±20.5</td>
<td>−9.7±19.7</td>
</tr>
<tr>
<td>Week 12</td>
<td>20</td>
<td>19.0±21.9</td>
<td>−15.5±26.2</td>
</tr>
<tr>
<td>Percent activity impairment during the preceding 7 days due to a problem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>69</td>
<td>54.8±29.3</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54.8±28.2</td>
<td>–</td>
</tr>
<tr>
<td>Week 2</td>
<td>68</td>
<td>42.9±28.8</td>
<td>−11.6±26.4</td>
</tr>
<tr>
<td>Week 4</td>
<td>67</td>
<td>42.1±29.1</td>
<td>−13.0±27.4</td>
</tr>
<tr>
<td>Week 12</td>
<td>65</td>
<td>38.6±27.7</td>
<td>−16.9±26.7</td>
</tr>
</tbody>
</table>

Note: aIncludes both time lost and degree of impairment.

Abbreviation: SD, standard deviation.
Table S5  Adverse event overall summary (treated set), expressed as number of patients (%)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo (n = 72)</th>
<th>Tiotropium 18 μg (n = 68)</th>
<th>Total (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>34 (47.2)</td>
<td>28 (41.2)</td>
<td>62 (44.3)</td>
</tr>
<tr>
<td>Severe&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (4.2)</td>
<td>4 (5.9)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Investigator defined drug−related</td>
<td>0 (0.0)</td>
<td>1 (1.5)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other significant</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
<td>1 (1.4)</td>
<td>1 (1.5)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (4.2)</td>
<td>3 (4.4)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Fatal</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Immediately life−threatening</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Disability/incapacitated</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Requiring hospitalization</td>
<td>3 (4.2)</td>
<td>3 (4.4)</td>
<td>6 (4.3)</td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Notes: <sup>a</sup>Iincapacitating or caused inability to work or to perform usual activities. <sup>b</sup>A patient may be counted in more than one seriousness criterion.
Figure S1 Patient disposition

266 patients for study eligibility assessed

Reason for screen failure:
- 102 inclusion criteria:
  - 98 FEV₁/FVC > 0.7
  - 4 other
- 6 exclusion criteria
- 5 administrative reasons
- 13 unknown

140 patients randomized for treatment

72 patients received placebo
Premature discontinuation:
- 1 adverse event (lung neoplasm malignant)
- 3 administrative reasons:
  - 2 refused to continue medication
  - 1 other reason

68 patients received tiotropium 18 µg
Premature discontinuation:
- 1 adverse event (acute respiratory failure, COPD)
- 1 administrative reason:
  - 1 refused to continue medication

68 (94.4%) completed the study
66 (97.1%) completed the study
Figure S2 (A) Mean ± SD and (B) adjusted mean ± SE change from baseline (BL) for trough forced expiratory volume in 1 second (FEV₁) over time and (C) mean ± SD and (D) adjusted mean ± SE change from BL for trough forced vital capacity (FVC) for over time. Change from baseline results are from a mixed-model analysis of repeated measures. Fixed effects included: treatment, visit, treatment-by-visit interaction, baseline, and baseline-by-visit interaction; patients were considered random and a spatial power covariance structure was used.
**Figure S3** Descriptive statistics (mean ± SD) for the COPD Assessment Test™ (CAT) and Functional Assessment of Chronic Illness Therapy (FACIT) - Short Form scores for dyspnea and functional limitation over time (A, C, and E, respectively) and change from baseline (B, D, and F, respectively). For the CAT only patients with a COPD diagnosis before study entry were assessed.