**Background**

- In COPD clinical trials, differential withdrawal rates between treatment groups can cause bias due to the healthy survivor population increasing with time. This may lead to an underestimation of the benefit of investigational treatment.

- Treatment differences in exacerbation rate reduction have been shown to decrease over time as a result of early treatment withdrawal.1–4

  - A composite endpoint of exacerbation and treatment withdrawal has been developed to compensate for the impact of early treatment withdrawal on exacerbation outcomes.1–4

- This post hoc analysis of the Early MAximization of bronchodilator for improving COPD stability (EMAX) trial examined whether there were differential withdrawal rates between treatment groups and if a composite endpoint of exacerbation and study withdrawal would better capture treatment benefits than the individual endpoints.

**Methods**

- The 24-week, double-blind, parallel-group EMAX trial randomized patients with symptomatic COPD and low exacerbation risk not receiving inhaled corticosteroids to UMEC/VI (50/50) mg once daily, UMEC 62.5 mg once daily, or salmeterol (SAL) 50 mcg twice daily for 24 weeks. Patients were limited to a maximum of one or two long-acting muscarinic antagonists (LAMA) or long-acting β2-agonists (LABA) monotherapy before screening and during run-in.1–5

- Time to first moderate or severe exacerbation was analyzed prior to time to study treatment withdrawal and the composite endpoint of time to first moderate or severe exacerbation and time to study treatment withdrawal were analyzed post hoc.

- Hazard ratios (HRs) and 95% confidence intervals were calculated using a Cox proportional hazards model with covariates of treatment, number of bronchodilators, exacerbation risk not receiving inhaled corticosteroids, and study treatment withdrawal may better capture treatment benefits than the individual endpoints.

- The analyses were conducted using the intent-to-treat (ITT) population.

**Results**

**Table 1: Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UMEC/VI (N=809)</th>
<th>UMEC (N=804)</th>
<th>SAL (N=804)</th>
<th>Total (N=2425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.6 (8.5)</td>
<td>64.9 (8.5)</td>
<td>64.6 (8.5)</td>
<td>64.6 (8.5)</td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>371 (46)</td>
<td>327 (41)</td>
<td>342 (42)</td>
<td>688 (41)</td>
</tr>
<tr>
<td>Current smoker at screening, n(%)</td>
<td>366 (46)</td>
<td>286 (36)</td>
<td>413 (51)</td>
<td>1265 (52)</td>
</tr>
<tr>
<td>Smoking pack-years, mean (SD)</td>
<td>46.5 (27.7)</td>
<td>47.5 (23.5)</td>
<td>48.1 (25.3)</td>
<td>48.4 (26.3)</td>
</tr>
<tr>
<td>COPD duration, years, mean (SD)</td>
<td>6.8 (6.0)</td>
<td>7.8 (6.9)</td>
<td>6.3 (6.7)</td>
<td>7.3 (6.8)</td>
</tr>
<tr>
<td>Moderate COPD exacerbations in prior year*, n(%)</td>
<td>12 (1.5)</td>
<td>12 (1.5)</td>
<td>14 (1.8)</td>
<td>38 (1.6)</td>
</tr>
<tr>
<td>Predominant FEV1 predicted, mean (SD)</td>
<td>76.9 (12.5)</td>
<td>75.9 (12.0)</td>
<td>76.7 (12.5)</td>
<td>76.7 (12.7)</td>
</tr>
<tr>
<td>% reversibility to salbutamol, mean (SD)</td>
<td>10.1 (3.8)</td>
<td>10.2 (3.2)</td>
<td>9.7 (3.6)</td>
<td>10.0 (3.3)</td>
</tr>
<tr>
<td>Maintenance miss, n(%)</td>
<td>250 (31)</td>
<td>250 (31)</td>
<td>248 (31)</td>
<td>748 (31)</td>
</tr>
<tr>
<td>Rescue asthma, (oral, mean (SD))</td>
<td>2.2 (2.4)</td>
<td>2.1 (2.0)</td>
<td>2.2 (2.5)</td>
<td>2.2 (2.5)</td>
</tr>
<tr>
<td>Baseline CAT score, mean (SD)</td>
<td>19.1 (5.5)</td>
<td>19.3 (5.2)</td>
<td>19.2 (5.6)</td>
<td>19.2 (5.6)</td>
</tr>
</tbody>
</table>

- Baseline characteristics were similar between treatment groups (Table 1).

**Table 2: Study treatment withdrawal**

<table>
<thead>
<tr>
<th>Treatment status, n (%)</th>
<th>UMEC/VI (N=809)</th>
<th>UMEC (N=804)</th>
<th>SAL (N=804)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment withdrawn</td>
<td>96 (12)</td>
<td>131 (16)</td>
<td>124 (16)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>9 (1)</td>
<td>16 (2)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>2 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Primary reason for study treatment withdrawal, n(%)</td>
<td>12 (1.5)</td>
<td>16 (2.0)</td>
<td>12 (1.5)</td>
</tr>
</tbody>
</table>

- Time to study treatment withdrawal and the composite endpoint of time to first moderate or severe exacerbation and time to study treatment withdrawal were analyzed post hoc.

- Hazard ratios (HRs) and 95% confidence intervals were calculated using a Cox proportional hazards model with covariates of treatment, number of bronchodilators, exacerbation risk not receiving inhaled corticosteroids, and study treatment withdrawal may better capture treatment benefits than the individual endpoints.

- The analyses were conducted using the intent-to-treat (ITT) population.

**Figure 1** Kaplan-Meier curve for time to study treatment withdrawal

**Figure 2** Risk reduction with UMEC/VI versus UMEC or SAL for each of the three endpoints

**Figure 3** Kaplan-Meier curve for time to first moderate/severe exacerbation

**Figure 4** Kaplan-Meier curve for time to first on-treatment moderate/severe exacerbation

**Conclusions**

- The ITT population included 2425 patients baseline characteristics were similar between treatment groups (Table 1).

- **Study treatment withdrawal**

  - The proportion of patients withdrawing was lower with UMEC/VI compared with either monotherapy in the ITT population (Figure 1, Table 2).

  - The risk of study treatment withdrawal was significantly lower with UMEC/VI versus UMEC (45% reduction) and SAL (27% reduction) (Figure 2).

- **Time to first moderate or severe exacerbation**

  - On treatment, a moderate or severe exacerbation was experienced by a smaller proportion of patients receiving UMEC/VI compared with UMEC or SAL in the ITT population (Figure 3).

  - Interestingly, the reduction in risk of study treatment withdrawal was greater for UMEC/VI compared with UMEC versus UMEC alone but the reduction in risk of exacerbation was greater for UMEC/VI versus UMEC alone.

- **Composite time to first study treatment withdrawal or first moderate/severe exacerbation**

  - A smaller proportion of patients receiving UMEC/VI withdrew from study treatment or had a moderate/severe exacerbation compared with UMEC or SAL in the ITT population (Figure 4).

  - The risk of a composite endpoint event was significantly reduced with UMEC/VI versus SAL by 36%, but not UMEC (19% reduction) (Figure 2).

- **Baseline characteristics**

  - The ITT population included 2425 patients baseline characteristics were similar between treatment groups (Table 1).

  - **Study treatment withdrawal**

    - The proportion of patients withdrawing was lower with UMEC/VI compared with either monotherapy in the ITT population (Figure 1, Table 2).

    - The risk of study treatment withdrawal was significantly lower with UMEC/VI versus UMEC (45% reduction) and SAL (27% reduction) (Figure 2).

  - **Time to first moderate or severe exacerbation**

    - On treatment, a moderate or severe exacerbation was experienced by a smaller proportion of patients receiving UMEC/VI compared with UMEC or SAL in the ITT population (Figure 3).

    - Interestingly, the reduction in risk of study treatment withdrawal was greater for UMEC/VI compared with UMEC versus UMEC alone but the reduction in risk of exacerbation was greater for UMEC/VI versus UMEC alone.

  - **Composite time to first study treatment withdrawal or first moderate/severe exacerbation**

    - A smaller proportion of patients receiving UMEC/VI withdrew from study treatment or had a moderate/severe exacerbation compared with UMEC or SAL in the ITT population (Figure 4).

    - The risk of a composite endpoint event was significantly reduced with UMEC/VI versus both UMEC (23% reduction) and SAL (22% reduction) (Figure 2).

**References**

4. RAMAX Ltd, Bramhall, Cheshire, UK; Respiratory Medicine and Allergy, Lund University, Lund, Sweden; Precision Approach Ltd, contingent worker on assignment of GSK; Skipton, Northampton, UK; Biberfeld, Västerås, Sweden; Respiratory Clinical Sciences, GSK, Kattedal, NL; Mannaz/Clinical Sciences, GSK, Kattedal, NL, Utrecht and Parisian School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Utrecht and Maastricht, Philippus-Umc/Region Maastricht, Germany; summary on the Senior Center for Lung Research (SCL) funded by Liam Campbell, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK.

**Disclosures**

- The authors reported no relevant conflicts of interest, including financial relationships with or ownership of companies or organizations that might influence their work. For disclosures, please see the Disclosures section on the journal website.