Impact of Smoking Status on Improvements in Lung Function With Umeclidinium/Vilanterol Versus Fluticasone Propionate/Salmeterol in Patients With COPD

Background

In the US, 35%-50% of patients with chronic obstructive pulmonary disease (COPD) are current or former smokers. Improvements in lung function with anti-inflammatory treatments is limited in former smokers.

Primary use propitiates continued promotion of a continued anti-inflammatory and a long-acting (LA) bronchodilator (BD) for patients with COPD, irrespective of smoking status.

Evidence suggests that anti-inflammatory treatments for obstructive pulmonary disease (COPD) may improve lung function and respiratory muscle function in patients with COPD, irrespective of smoking status.

Consequently, the health benefits of UMEC/VI (SAL is preferred) for exacerbation-free survival in patients with COPD with a smoking status unknown or continuation to smoke or be ex-smoker is questionable.

An exploratory lung function assessment using the current smoking status continued smoking there is a need to assess if the use of UMEC/VI may improve lung function and respiratory muscle function in patients with COPD, irrespective of smoking status, as observed in smokers with COPD who actively smoke.

Therefore, a parallel-group, double-blind, randomized, placebo-controlled trial, the Global GOLD COPD trial, evaluated the efficacy and the safety of UMEC/VI (SAL is preferred) for exacerbation-free survival in patients with COPD with a smoking status unknown or continuation to smoke or ex-smoker in the previous 12 months.

The objective of the integrated analysis of two trials was to compare the efficacy and safety of UMEC/VI in current and former smokers with a low level of modification.

Methods

Study design

This was a post hoc analysis of the Global GOLD COPD trial (NCT03043967) who were treated with placebo or UMEC/VI (62.5/25 mcg twice daily) in a parallel-group, double-blind, randomized, placebo-controlled trial, the Global GOLD COPD trial, conducted at 100 centers in 25 countries from November 2016 to July 2017.

Patients

Eligible patients were aged ≥40 years with moderate to severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and with an FEV1 <50% predicted and a history of at least one exacerbation in the prior 12 months. Patients were randomized to receive UMEC/VI 62.5/25 mcg twice daily or placebo, with additional treatment with inhaled albuterol as needed via the ELIPTA® inhaler and FP/SAL 50/50 mcg administered twice daily via the Diskus® inhaler (NCT03043967).

Exclusions and assessments

Lung function was evaluated in current and former smokers using the 4-hour weighted mean forced expiratory volume in 1 second (FEV1), 24-hour weighted mean FEV1, and a 12-hour weighted mean FEV1 at day 94.

Secondary endpoints included trough FEV1, and the proportion of patients achieving an increase in trough FEV1 of ≥100 mL in the last 28 days of treatment at day 94.

Statistical analysis

All reported analyses were conducted in the ITT population, which included all randomized patients who received any study medication.

A 24-hour weighted mean FEV1 was calculated from the predicted and post-dose spirometry measurements at all visits 15 minutes and 3, 4, 5, 10, 15, 16, 18, 20, after the morning dose.

Baseline was the last of two assessments made within 14 days before study day 1.

An analysis of covariance (ANCOVA) model with covariates of study baseline, FEV1, and treatment was used.

Trough FEV1 was estimated using a mixed model repeated measures analysis with covariates of baseline FEV1, study day, day by baseline interaction and day by treatment interaction, where days non-randomly assigned.

Results

Patients

A total of 1,893 patients were included in the ITT population. 1,752 patients received UMEC/VI (98% current smokers) and 77 patients received FP/SAL (95% current smokers).

Baseline demographics and clinical characteristics by smoking status are shown in Table 1.

Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Current Smokers</th>
<th>Former Smokers</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean)</td>
<td>70.8 (11.1)</td>
<td>68.8 (11.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sex, % (M/F)</td>
<td>56.6 (43.4)</td>
<td>54.3 (45.7)</td>
<td>0.310</td>
</tr>
<tr>
<td>ETABLE, %</td>
<td>23.8 (76.2)</td>
<td>27.7 (72.3)</td>
<td>0.103</td>
</tr>
<tr>
<td>Smoking pack yrs</td>
<td>21.0 (16.5)</td>
<td>15.3 (12.8)</td>
<td>0.010</td>
</tr>
<tr>
<td>FEV1% pred (N=138)</td>
<td>45.0 (22.8)</td>
<td>47.7 (27.7)</td>
<td>0.256</td>
</tr>
</tbody>
</table>

Endpoints

Lung function

At day 94, UMEC/VI and FP/SAL resulted in improved 24-hour weighted mean FEV1, compared with baseline in current and former smokers (Figure 1).

The observed between-treatment mean difference was greater in current smokers compared with former smokers (101 ml vs. 64 ml, respectively).

Figure 1. Change from baseline in 0–24 hour weighted mean FEV1 at Day 94

Table 2. Subgroup analysis for endpoints reported for 22% and 25% of the patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UMEC/VI 178 mcg</th>
<th>FP/SAL 205 mcg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1% pred (N=368)</td>
<td>48.4 (22.8)</td>
<td>42.0 (29.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Conclusions

This randomized, double-blind, placebo-controlled trial showed that UMEC/VI 62.5/25 mcg given twice daily via the ELIPTA® inhaler and FP/SAL 50/50 mcg via Diskus® in patients with COPD, who are likely to continue smoking habits, may improve lung function compared with FP/SAL, regardless of smoking status.

These data are consistent with the plausibility of bronchodilation in the treatment for smoking-related COPD in this population and provide further evidence to support the Global initiative for chronic obstructive Lung Disease (GOLD) recommendation to use bronchodilator therapy in patients with COPD, regardless of smoking status.

Both treatments were well tolerated in current and former smoker subgroups.

These results support the hypothesis that smoking continues the benefits of LABA/LAMA in patients with COPD, potentially due to reduced stiffness resistance, and support the use of UMEC/VI 62.5/25 mcg to maintain long-term bronchodilation in risk-exposed patients with COPD, regardless of smoking status.

References


Disclosures

1. MJ, AL, and PR are employees of GlaxoSmithKline (GSK) and both GlaxoSmithKline, LLC is a direct competitor to both Eli Lilly and GSK. All other authors have nothing to disclose.

Aknowledgments

The Global GOLD COPD trial was funded by GlaxoSmithKline (GSK) and investigators and sites participating in the study. The study protocol and all amendments was approved by the relevant and the local institutional review boards for human research. The study authors and the corresponding author had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.