Background

- Frequent rescue use is associated with an increased risk of COPD exacerbations and hospitalizations.1,2
- Assessment of rescue medication use may therefore be a useful marker of disease severity in both clinical trials and routine clinical practice.

In this post hoc analysis of the Early MACS (MAXimizing bronchodilator for improving COPD stability) trial, it was hypothesized that patients with higher rescue medication use were more symptomatic. The objective was to explore the relationship between baseline rescue medication use and daily Evaluating Respiratory Symptoms COPD (E-RS) total score, the risk of a clinically important deterioration (CID), and the risk of a composite exacerbation and study treatment withdrawal endpoint.

Methods

- In the double-blind, parallel-group EMAX trial, patients with symptomatic COPD and no exacerbation risk not receiving inhaled corticosteroids were randomized 1:1:1 to umecclidinivalerander (UMEC/VI) 62.5-25 mcg once daily, UMEC 62.5 mcg once daily, or salmeterol (SAL) 50 mcg twice daily for 24 weeks.3
- E-RS and rescue medication use were recorded daily and analyzed at a priori at 4-weekly intervals. E-RS scores were stratified post hoc by rescue medication use (puffs/day) quartiles at baseline and at Weeks 21-24 to reflect the relationship between rescue medication use and symptoms at each time point.
- The composite CID endpoint was defined prospectively as a first moderate or severe exacerbation, and/or a COPD Assessment Test (CAT) deterioration (≥2 points from baseline), and/or a self-reported deterioration of Transition Dyspnea Index (SDI-TI) deterioration (≥1 point from baseline), and/or a Statistician's Respiratory Questionnaire (SGRQ) deterioration (≥4 points overall baseline).
- Hazard ratios (HR) were calculated to assess the effect of the relationship between baseline rescue medication use on CID, and an exacerbation and study treatment withdrawal combined endpoint (defined post hoc) up to Day 168.
- CID HR were calculated using Cox proportional hazards models with covariates of treatment, number of bronchodilators per day during run-in, geographical region, baseline rescue medication use quartile, baseline CAT score, baseline SGRQ score and Baseline Dyspnea Index focal score.
- For the exacerbation/study treatment withdrawal composite endpoint, HR were calculated with a Cox proportional hazards model with covariates of treatment, number of bronchodilators per day during run-in and geographical region.

Results

- Symptom burden by rescue use

- Patients with higher baseline rescue medication use (puffs/day) had a greater symptom burden at baseline according to mean E-RS total score (Figure 1).
- Although rescue medication use decreased from baseline during the treatment period in all treatment arms, the relationship between mean rescue medication use (puffs/day) and mean E-RS total score was maintained at Weeks 21–24 (Figure 2).
- No differences were observed between treatment arms.

- On-treatment rescue use by baseline rescue use

- There was a trend towards higher on-treatment rescue medication use at Weeks 21–24 in patients with high baseline rescue medication use (puffs/day) (Table 2).

- CID and exacerbation/study withdrawal by baseline rescue use

- The risk of a CID and the risk of the composite endpoint for an exacerbation or study treatment withdrawal were significantly lower for patients with baseline rescue medication use <0.2 puffs/day versus ≥1.5 puffs/day (Figure 1).

- Table 2: CID and exacerbation/study withdrawal by baseline rescue medication use quartile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UMEC/VI (n=605)</th>
<th>UMEC (n=608)</th>
<th>SAL (n=604)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean daily rescue medication use (puffs/day)</td>
<td>2.4 (1.7)</td>
<td>2.3 (1.7)</td>
<td>2.4 (1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>CID</td>
<td>2 (0–3)</td>
<td>2 (0–3)</td>
<td>2 (0–3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Exacerbation/study treatment withdrawal</td>
<td>15 (0–30)</td>
<td>19 (0–30)</td>
<td>23 (0–60)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions

- Mean daily rescue medication use is associated with mean daily symptom burden in patients with COPD.
- Higher baseline rescue medication use is associated with an increased risk of CID and exacerbation/study treatment withdrawal.
- These findings support the use of rescue medication use as a marker of symptom burden and risk of disease worsening in clinical practice and as an endpoint in clinical trials.