Treatment of acute exacerbations in COPD: an exploratory Phase II study of single and repeated doses of acumapimod (BCT197), an oral p38 inhibitor

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Abstract

Rationale:
Despite the association between acute exacerbations and increased mortality in chronic obstructive pulmonary disease (COPD), current treatment options for acute exacerbations (AECOPD) are limited. Mitogen-activated protein kinase (MAPK) p38, a key regulator in the inflammation pathway, is activated in the lungs of patients with COPD. Acumapimod is a potent, selective, oral, p38 inhibitor being investigated for the treatment of AECOPD.

Methods:
NCT01332097 was a Phase II, double-blind, randomized, placebo-controlled, study of patients with COPD (GOLD Stage II–IV) presenting with an acute exacerbation. Patients were randomized to single doses of 20mg/75mg acumapimod (Day 1) or repeated doses of 20mg/75mg acumapimod (Days 1 and 6). Comparators were placebo/40mg oral prednisone daily. Primary outcome: improvement in FEV1 versus placebo at Day 5 for single doses and Day 10 for repeated doses. Secondary endpoints included patient-reported outcomes (EXACT-PRO), length of hospital stay, safety (6-month follow up) and tolerability. Exploratory biomarkers were assessed.

Results:
In total, 169 (92%) patients completed the study; four withdrew consent, four were lost to follow up and six died (unrelated to study drug). Baseline characteristics were comparable. Dose-dependent improvement in FEV1 was observed, significant versus placebo, in the 75mg repeat-dose acumapimod group at Day 8 (difference vs placebo: 152mL; 95% CI: 21, 283; p=0.022). However, as the difference did not reach significance at Day 10, the primary endpoint was not met (Day 10: 124mL; -16, 263; p=0.082) (figure); none of the lower doses of acumapimod reached significance. In a post-hoc analysis, mean change in FEV1 AUC from baseline–Day 14 in the 75mg repeat-dose group was significantly higher versus placebo (p=0.02), prednisone (p=0.01) and 20mg single-dose acumapimod group (p=0.015). Dose-dependent trends in hsCRP, EXACT-PRO (rolling average AUC) and length of hospital stay were observed. Acumapimod was well tolerated with no incidences of acneiform skin rash at any dose and infrequent transient elevations in liver transaminases.

Conclusions:
Short-term treatment with the p38 inhibitor acumapimod showed clinically relevant improvement of 152mL increase in FEV1, versus placebo in AECOPD at Day 8, with dose-dependent trends in biochemical markers of inflammation, patient-reported outcomes and hospital stay. These data have been used to determine the acumapimod dose for the ongoing dose-ranging, Phase II AECOPD trial (NCT02700919). Acumapimod has the potential to provide well-tolerated clinical benefits in the treatment of AECOPD, which could lead to reduced healthcare burden and improved quality of life for these patients.

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Background
Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with increased mortality, morbidity, and healthcare costs.1–5 Acute exacerbations are the primary cause of hospitalizations in patients with COPD.6–9 The p38 mitogen-activated protein kinase (p38MAPK) pathway is activated in the lungs of patients with COPD, including upregulation during acute exacerbations.7,8 Acumapimod is a small molecule that inhibits p38MAPK, demonstrating anti-inflammatory and immunomodulatory properties.9

Study objective
An exploratory, double-blind, randomized, placebo-controlled, multicenter, adaptive parallel-group trial to assess the preliminary proof of efficacy of single-dose acumapimod (BCT197) 20 or 75 mg versus current treatment options for AECOPD (antibiotics, bronchodilators and systemic corticosteroids)1,4 do not adequately address the inflammatory component of AECOPD, and corticosteroid resistance is frequently observed.1,4

Study design & patients
Study design
An exploratory double-blind, randomized, placebo-controlled, multicenter adaptive parallel-group trial.

Patients
Adult patients (aged 40–80 years) with a diagnosis of COPD (Stage II to IV according to the Global Initiative for Chronic Obstructive Lung Disease) and who presented with an exacerbation were enrolled for Chronic Obstructive Lung Disease) and who presented with an exacerbation were enrolled.

Table 1: Baseline patient demographics

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean (SD)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Placebo (n=45)</td>
<td>166 (9.0)</td>
<td>147–187</td>
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<tr>
<td>20 mg (n=25)</td>
<td>168 (8.2)</td>
<td>153–185</td>
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<tr>
<td>75 mg (n=30)</td>
<td>167 (7.9)</td>
<td>151–186</td>
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<tr>
<td>75 mg repeat-dose (n=25)</td>
<td>168 (7.1)</td>
<td>155–181</td>
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<tr>
<td>20 mg repeat-dose (n=25)</td>
<td>168 (7.8)</td>
<td>150–182</td>
</tr>
<tr>
<td>75 mg repeat-dose (n=25)</td>
<td>168 (7.5)</td>
<td>150–186</td>
</tr>
<tr>
<td>20 mg repeat-dose (n=25)</td>
<td>168 (7.9)</td>
<td>147–187</td>
</tr>
</tbody>
</table>

Table 2: Proportion of patients responding to treatment

Treatment group | Proportion (%) | 95% CI | p-value
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Placebo (n=45)</td>
<td>31 (70)</td>
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<tr>
<td>20 mg (n=25)</td>
<td>29 (78)</td>
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<td>75 mg (n=30)</td>
<td>69 (24)</td>
<td>40–88</td>
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</tr>
<tr>
<td>75 mg repeat-dose (n=25)</td>
<td>69 (26)</td>
<td>40–90</td>
<td></td>
</tr>
<tr>
<td>20 mg repeat-dose (n=25)</td>
<td>69 (26)</td>
<td>40–90</td>
<td></td>
</tr>
<tr>
<td>75 mg repeat-dose (n=25)</td>
<td>69 (28)</td>
<td>40–90</td>
<td></td>
</tr>
<tr>
<td>20 mg repeat-dose (n=25)</td>
<td>69 (28)</td>
<td>40–90</td>
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</table>

Results
Lung function (primary endpoint)
All treatment groups showed an improvement in FEV1 from baseline on Day 3 (Figure 3).

Response to treatment
Table 2: Proportion of patients responding to treatment

Changes in high-sensitivity C-reactive protein (hsCRP)
Figure 4 shows the changes in hsCRP from baseline to Day 14 for the different treatment groups. Reduction in hsCRP from baseline to Day 14 was significantly higher for the 75 mg repeat-dose group than placebo (p=0.02), prednisone (p=0.01) and 75 mg single-dose acumapimod (p=0.02).

SAEs
One patient had blood creatinine levels outside the normal range reported as an AE.

Table 3: Adverse events occurring in ≥1% of patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=45)</th>
<th>20 mg (n=25)</th>
<th>75 mg (n=30)</th>
<th>75 mg repeat-dose (n=25)</th>
<th>20 mg repeat-dose (n=25)</th>
<th>75 mg repeat-dose (n=25)</th>
<th>20 mg repeat-dose (n=25)</th>
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<tbody>
<tr>
<td>AE</td>
<td>12 (39)</td>
<td>3 (12)</td>
<td>16 (53)</td>
<td>15 (56)</td>
<td>22 (88)</td>
<td>16 (64)</td>
<td>18 (72)</td>
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<tr>
<td>SAE</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (10)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>0</td>
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</tbody>
</table>

Conclusions
Acumapimod is well tolerated, and has clinically-meaningful benefits with improved quality of life and reduced burden on healthcare.

References

Acknowledgments
The authors and all of the study investigators and participants.

Disclosures
I. Strâmbu reports personal and other fees received from Arensia Exploratory Medicine while the study was ongoing. J. Parkin reports being a member of the Board of Directors of Mereo BioPharma Group Plc. B. Magnusson reports being an employee of Mereo.

Figure 1: Study design.

Figure 2: Primary endpoint summary.

Figure 3: Mean change over time in EXACT-PRO (rolling average) improvement from Day 1.

Figure 4: Changes in high-sensitivity C-reactive protein (hsCRP).