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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Background

- Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with reduced quality of life and life expectancy[1,2], accelerated decline in lung function[2], and increased healthcare costs[3,4]
- Despite the association between acute exacerbations and increased mortality in chronic obstructive pulmonary disease (COPD), current treatment options for acute exacerbations (AECOPD) are limited
- 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 reported to impact the treatment of AECOPD[5,6]
- Mitogen-activated protein kinase (MAPK) p38, a key regulator in the inflammation pathway, is activated in the lungs of patients with COPD, including upregulation during acute exacerbations[7,8]
- Inhibition of p38 in animal models of COPD, including steroid-resistant models, shows anti-inflammatory effects on local neutrophil response and mucus secretion
- Acumapimod is a potent, selective, oral, p38 MAPK inhibitor being investigated for the treatment of AECOPD, and has shown potent effect in suppression of endotoxin-induced pro-inflammatory cytokine production in man

Study objective

- To assess the preliminary proof of efficacy of single-dose acumapimod (BCT197) 20 or 75 mg versus placebo, and treatment effect after a second dose, given within 24 hours of diagnosis of an acute moderate/severe exacerbation of COPD

Study design & patients

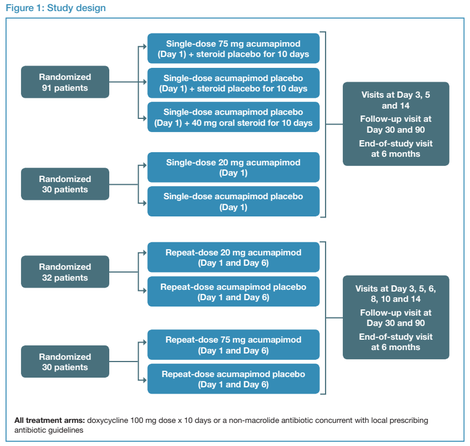
Study design

- 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
- Patients were randomized to single doses of acumapimod 20 mg or 75 mg on Day 1 or repeated doses of acumapimod 20 mg or 75 mg on Days 1 and 6 (**Figure 1**)
- Comparators were placebo and oral prednisone 40 mg daily for 10 days (**Figure 1**)

Figure 1: Study design



All treatment arms: doxycycline 100 mg dose x 10 days or a non-macrolide antibiotic concurrent with local prescribing antibiotic guidelines

Study endpoints

Primary endpoint:

- Improvement in forced expiratory volume in 1 second (FEV1) for acumapimod at Day 5 for single doses, and at Day 10 for repeated doses
  - The endpoint was analyzed with a linear model for repeated measurements, including all treatment groups and pooling placebo patients
  - The model included effects for baseline FEV1, treatment, day (Days 3, 5, 8, 10, 14 and 30), treatment-by-day interaction and baseline-by-day interaction
  - An unstructured covariance matrix was used

Secondary endpoints:

- Safety and tolerability (6-month follow up)
- Patient-reported outcomes (EXACT-PRO) analyzed with the same model as the primary endpoint
- Proportion of patients responding to treatment with acumapimod at Day 30
  - Treatment responders were defined as: no need to treat with oral steroids, no re-admission to hospital for COPD-related symptoms, no change in antibiotic therapy relating to COPD, or no need for treatment for a further exacerbation in the attending physicians' opinion throughout the duration of the study
- Length of hospital stay following initial admission

Exploratory endpoints:

- Biomarkers, including high sensitivity C-reactive protein (hsCRP) and fibrinogen levels

Patient demographics

- In total, 183 patients were randomized and 169 patients (92%) completed the acute treatment and 6 months follow-up study; four withdrew consent, four were lost to follow up and six died (unrelated to study drug)
- Baseline characteristics were similar among treatment groups (**Table 1**)
- Patients had a mean age of 62 years (range: 41–77 years) and mean body mass index of 26.5 kg/m^2 (range: 15.9–46.9 kg/m^2); all were Caucasian and 80% were male

Table 1: Baseline patient demographics

Characteristic		Treatment group						
		75 mg single-dose acumapimod (n=31)	Placebo (n=45)	40 mg prednisone (n=30)	20 mg single-dose acumapimod (n=25)	20 mg repeat-dose acumapimod (n=27)	75 mg repeat-dose acumapimod (n=25)	Total (n=183)
Age, years	Mean (SD)	60 (8.6)	61 (6.6)	63 (8.8)	62 (8.7)	61 (9.1)	64 (7.6)	62 (7.9)
	Range	44–75	46–75	45–77	43–77	41–76	40–76	41–77
Gender, n (%)	Male	23 (74)	32 (71)	26 (87)	21 (84)	23 (85)	21 (84)	146 (80)
	Female	8 (26)	13 (29)	4 (13)	4 (16)	4 (15)	4 (16)	37 (20)
Race, n (%)	Caucasian	31 (100)	45 (100)	30 (100)	25 (100)	27 (100)	25 (100)	183 (100)
Height, cm	Mean (SD)	166 (9.0)	168 (8.2)	167 (7.9)	168 (7.1)	168 (7.8)	168 (7.5)	168 (7.9)
	Range	147–187	153–185	151–186	155–181	150–182	150–186	147–187
Weight, kg	Mean (SD)	77.2 (19.6)	78.6 (20.1)	70.6 (13.3)	71.3 (15.2)	73.7 (14.7)	71.0 (16.8)	74.3 (17.3)
	Range	50.0–122.0	45.0–130.0	48.0–98.0	44.0–109.0	47.0–106.0	43.0–110.0	43.0–130.0
BMI, kg/m^2	Mean (SD)	28.1 (6.7)	27.8 (6.8)	25.4 (4.6)	25.1 (4.8)	26.1 (5.2)	25.2 (5.6)	26.5 (5.9)
	Range	17.4–46.7	16.2–46.9	17.4–33.5	16.6–35.6	17.5–36.5	15.9–35.5	15.9–46.9

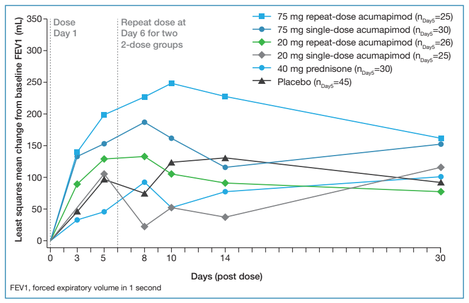
BMI, body mass index; SD, standard deviation

Results

Lung function (primary endpoint)

- All treatment groups showed an improvement in FEV1 from baseline on Day 5 (**Figure 2**)
  - There was no evidence of an improvement over placebo for the acumapimod 75 mg group (p=0.27), the acumapimod 20 mg group (p=0.92) or the acumapimod 20 mg repeat-dose group (p=0.51)
  - The largest improvement over baseline was observed for the acumapimod 75 mg repeat-dose group, resulting in an improvement over placebo of 100 mL (95% confidence interval [CI]: −2, 202; p=0.056)
  - The primary endpoint was not met on Day 5
- There was no statistically-significant improvement in FEV1 between acumapimod and placebo groups at Day 10; thus, the primary endpoint was not met (difference vs. placebo: 124 mL; 95% CI: −16, 263; p=0.082) (**Figure 2**)
- *Post-hoc* analysis:
  - Significant dose-dependent improvement in FEV1 with acumapimod 75 mg repeat dose versus placebo at Day 8 (difference vs. placebo: 152 mL; 95% CI: 21, 283; p=0.022)
    - Improvement was clinically meaningful (>100 mL improvement vs. placebo) and consistent with the duration of most AECOPD
  - Mean change in FEV1 area under the curve (AUC) from baseline to Day 14 in the acumapimod 75 mg repeat-dose group was significantly higher than that for placebo (p=0.02), prednisone (p=0.01) and 20 mg single-dose acumapimod (p=0.015) groups, supporting the dose-dependency and the benefit over 14 days, which covers the expected duration of a COPD exacerbation

Figure 2: Clinically meaningful improvements in FEV1 with acumapimod versus standard of care and placebo



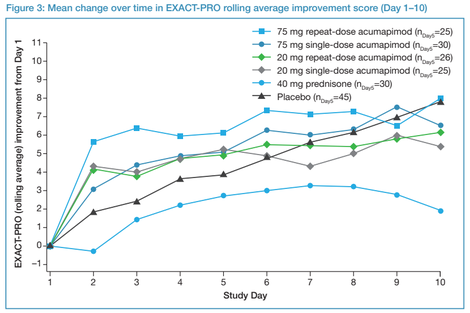
FEV1, forced expiratory volume in 1 second

Patient-reported outcomes

- No statistically-significant difference between acumapimod and placebo groups on most days in the rolling average† improvement score (RAIS) on EXACT-PRO (**Figure 3**)
- Dose-dependent improvements in patient-reported outcomes (EXACT-PRO) were observed as early as Day 3
- On Day 3, the RAIS was higher for the acumapimod 75 mg single-dose and 75 mg repeat-dose groups versus placebo (4.90 and 6.46 vs. 2.23)
- The lowest improvement score was observed for prednisone on all days

†Rolling average refers to a 3-day rolling average

Figure 3: Mean change over time in EXACT-PRO rolling average improvement score (Day 1–10)



Response to treatment

- All patients receiving single doses of acumapimod (75 mg and 20 mg) were considered responders* (**Table 2**)
- Patients receiving placebo had a 91.1% response rate
- Patients receiving repeat-dose acumapimod 20 mg or 75 mg had response rates of 88.0% and 87.5%, respectively

Table 2: Proportion of patients responding to treatment

	Treatment group					
	75 mg single-dose acumapimod (n=31)	Placebo (n=45)	40 mg prednisone (n=30)	20 mg single-dose acumapimod (n=25)	20 mg repeat-dose acumapimod (n=27)	75 mg repeat-dose acumapimod (n=25)
Number assessed	31	45	29	25	25	24
Responders*, n (%)	31 (100)	41 (91.1)	26 (89.7)	25 (100)	22 (88)	21 (87.5)

*Responders were defined as: no need to treat with oral steroids, no re-admission to hospital for COPD-related symptoms, no change in antibiotic therapy relating to COPD, or no need for treatment for a further exacerbation in the attending physicians' opinion

Changes in high-sensitivity C-Reactive Protein (hsCRP)

- Changes in hsCRP were observed to be greater in BCT197 dose groups than in placebo groups during the period of acumapimod exposure. Reduction in hsCRP from baseline to Day 5 was 28% placebo; 51% 20mg acumapimod single-dose; 59% 20 mg acumpaimod repeat-dose; 61% 75 mg acumpaimod single-dose; 72% 75 mg acumpaimod repeat-dose. Prednisone was 74%.

Safety/tolerability

- Over half the patients (54%) experienced ≥1 adverse event (AEs) during the study (**Table 3** summarises most frequent events occurring in ≥3% of patients)
  - The most common AE was COPD exacerbation (**Table 4**)
  - Nasopharyngitis was also commonly reported
- Thirteen patients experienced 15 serious AEs (SAEs) excluding death, none of which were suspected to be related to acumapimod (**Table 4**)
  - COPD was the SAE for 10 patients (six on placebo and four on acumapimod); three patients were hospitalized twice for COPD exacerbations
  - All SAEs were moderate in severity, except for one case of bladder cancer
- There were two cases of pruritic rash in the 75mg repeat-dose, but no cases of the typical acneiform skin rash that has been associated with p38 inhibitors were observed at any dose in this study
- One patient had blood creatinine levels outside the normal range reported as an AE
- There were six deaths over the 6-month study duration, four in the acumapimod and two in the prednisone groups, none of which were considered related to the study drug

Table 3: Summary of adverse events

AE summary, n (%)	Treatment group					
	75 mg single-dose acumapimod (n=31)	Placebo (n=45)	40 mg prednisone (n=30)	20 mg single-dose acumapimod (n=25)	20 mg repeat-dose acumapimod (n=27)	75 mg repeat-dose acumapimod (n=25)
AEs	12 (39)	26 (58)	16 (53)	13 (52)	15 (56)	16 (64)
SAEs	1 (3)	4 (9)	3 (10)	1 (4)	2 (7)	2 (8)
Treatment-related SAEs	0	0	0	0	0	0
Deaths	1 (3)	0	2 (7)	1 (4)	1 (4)	1 (4)

AEs, adverse events; SAEs, serious adverse events

Table 4: Adverse events occurring in ≥3% of patients in any group

AEs, n (%)	Treatment group					
	75 mg single-dose acumapimod (n=31)	Placebo (n=45)	40 mg prednisone (n=30)	20 mg single-dose acumapimod (n=25)	20 mg repeat-dose acumapimod (n=27)	75 mg repeat-dose acumapimod (n=25)
COPD	1 (3)	12 (27)	5 (17)	4 (16)	5 (19)	6 (24)
Fecal occult blood	3 (10)	3 (7)	3 (10)	5 (20)	4 (15)	0
Nasopharyngitis	2 (7)	2 (4)	3 (10)	4 (16)	4 (15)	1 (4)
Pneumonia	0	1 (2)	1 (3)	0	1 (4)	2 (8)
Dizziness	2 (7)	0	0	0	0	3 (12)
Headache	1 (3)	3 (7)	3 (10)	1 (4)	1 (4)	0
Diarrhea	1 (3)	2 (4)	0	0	1 (4)	2 (8)
Dyspepsia	0	0	0	1 (4)	1 (4)	0
Hypertension	1 (3)	1 (2)	2 (7)	1 (4)	1 (4)	0
Acute cardiac failure	1 (3)	0	1 (3)	0	0	0

AEs, adverse events; COPD, chronic obstructive pulmonary disease

Conclusions

- FEV1 improvement versus placebo at Days 5 and 10 was not met (primary endpoint), but a clinically-relevant and statistically-significant FEV1 improvement with 75-mg repeat-dose acumapimod over placebo at Day 8 did occur (*post-hoc* analysis)
- FEV1 improvements were associated with dose-dependent trends in biochemical markers of inflammation, patient-reported outcomes and hospital stay
- Acumapimod was well tolerated with a manageable, generally favorable safety profile
- AEs observed with p38 inhibitors class (liver toxicity and acneiform skin rash) were not observed in this study
- These data have been used to determine the acumapimod doses for an ongoing dose-ranging, Phase II acute exacerbation in COPD trial (NCT02700919)
- Acumapimod is well tolerated, and has clinically-meaningful benefits with improved quality of life and reduced burden on healthcare

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Jackie Parkin & Alastair MacKinnon are employees of Mereo BioPharma Group Plc

Baldur Magnusson is an employee of Novartis

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