Efficacy and Safety of a Monoclonal Antibody Recognizing Interleukin-8 in COPD*

A Pilot Study

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Study objective: To investigate the efficacy and safety of a fully human monoclonal antibody recognizing the chemokine interleukin (IL)-8 in patients with COPD.

Design: Randomized, double-blind, parallel-group, placebo-controlled trial.

Setting: Eighteen clinics/hospitals in the United States.

Patients: One hundred nine patients with stable COPD.

Interventions: Three IV infusions of either monoclonal antibody recognizing IL-8 (800-mg loading dose; 400-mg subsequent doses) or active buffer solution administered monthly over a 3-month period.

Measurements and results: The differences in the transition dyspnea index (TDI) total score, the primary outcome measure, between fully human monoclonal IgG2 antibody directed against IL-8 and placebo were 0.8, 1.0, 0.8, and 0.3 at week 2 (p = 0.046) and months 1 to 3, respectively. At all time points, the proportion of patients achieving ≥ 1 point improvement in the TDI was greater for the monoclonal antibody group compared with the placebo group: 28% vs 11% at week 2 (p = 0.028). There were no significant differences observed for lung function, health status, 6-min walking distance, and adverse events between groups.

Conclusions: The results of this phase 2 study suggest that neutralization of IL-8 with monoclonal antibody therapy may improve dyspnea in patients with COPD. These results support the further investigation of monoclonal antibody therapy targeting IL-8 for the treatment of this disease.

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Key words: chemokine; interleukin-8; St. George Respiratory Questionnaire; transition dyspnea index

Abbreviations: ABX-IL8 = fully human monoclonal IgG2 antibody directed against interleukin-8; BDI = baseline dyspnea index; ELISA = enzyme-linked immunosorbent assay; IL = interleukin; SGRQ = St. George Respiratory Questionnaire; TDI = transition dyspnea index

In patients with COPD, the airflow limitation is typically progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Examination of sputum, BAL fluid, and/or bronchial biopsy specimens in patients with COPD have characterized the inflammation as infiltration of neutrophils, macrophages, and CD8+ T-lymphocytes. Various inflammatory mediators such as leukotriene B4 and the cytokines tumor necrosis factor-α and interleukin (IL)-8 have been implicated in the pathogenesis of COPD. For example, IL-8 and leukotriene B4 are elevated in sputum of patients with COPD, and both mediators...
are potent chemoattractants for neutrophils. Moreover, stimulated cultured human bronchial epithelial cells obtained by bronchoscopy biopsies produce significantly more IL-8 than unstimulated cells.

Although maintenance bronchodilators are considered the standard of care for treating the airflow limitation associated with COPD, there is increasing interest in concomitant treatment of the airway inflammation. Various anti-inflammatory agents have been used in patients with COPD, including both oral and inhaled corticosteroids as well as phosphodiesterase inhibitors. A novel approach to reduce the inflammatory process in COPD is to target directly the chemokines that attract and activate neutrophils. A fully human monoclonal IgG2 antibody directed against human IL-8 (ABX-IL8) has been developed. This monoclonal antibody blocks binding to IL-8 receptors on neutrophils and neutralizes IL-8–mediated neutrophil activation in vitro. Recently, Beeh and colleagues showed that pretreatment of sputum supernatant of 20 patients with COPD with an anti–IL-8 antibody led to a concentration-dependent inhibition of neutrophil chemotaxis. By binding and neutralizing IL-8, ABX-IL8 should theoretically reduce free serum and tissue levels of IL-8, and thus reduce the chemotactic gradient triggering neutrophil migration into the Airways and lung tissue. Additionally, ABX-IL8 should block IL-8–induced neutrophil activation and degranulation, preventing release of a potent mucin secretagogue, neutrophil elastase.

The purpose of this study was to examine the efficacy and safety of ABX-IL8 in symptomatic patients with COPD, all of whom had a component of chronic bronchitis. In this pilot study, we hypothesized that three infusions of ABX-IL8 administered monthly would reduce the severity of dyspnea compared with placebo treatment. Dyspnea was selected as the primary outcome measure because it is the major symptom of COPD; furthermore, the original and the updated Global Initiative for Chronic Obstructive Lung Disease guidelines emphasize that treatment should focus on relieving the symptoms of the disease. Secondary outcomes included health status, lung function, 6-min walking distance, and rescue use of albuterol.

Materials and Methods

Patients

Patients > 50 years of age with a diagnosis of COPD and a history of chronic bronchitis were recruited. Inclusion criteria were as follows: ≥ 20 pack-year smoking history; grade 1 or higher for breathlessness on the modified Medical Research Council scale; and a baseline FEV1 ≥ 30% and ≤ 70% of predicted and < 70% of FVC. Exclusion criteria were as follows: an increase in FEV1 > 30% or > 300 mL, whichever was greater, at 30 min following two puffs (180 μg) of inhaled albuterol; postbronchodilator FEV1 > 70% of predicted; any history of asthma, bronchiectasis, cystic fibrosis, or α-antitrypsin deficiency, or congestive heart failure; any clinically significant comorbid disease; use of daytime supplemental oxygen; and any recent (within 2 months of screening) COPD exacerbation or pneumonia requiring hospitalization or emergency department treatment; or recent history of a respiratory tract infection (within 2 weeks of screening).

Concomitant use of inhaled long-acting β-agonists and inhaled short-acting bronchodilators (ipratropium bromide and β-agonists) were allowed, but were withheld for 12 h and 6 h, respectively, prior to each study visit. Use of systemic corticosteroids was not allowed during the study except to treat an exacerbation. Inhaled corticosteroids, oral β-agonists, and theophylline preparations were discontinued 3 weeks prior to the first infusion.

Study Design

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 18 centers in the United States. The Institutional Review Board at each center approved the protocol. Informed written consent was obtained. Patients were randomized 1:1 to receive ABX-IL8 (concentration of 10 mg/mL; 10 mM sodium phosphate; 138 mM sodium chloride; pH 6.0) or active buffer solution (10 mM sodium phosphate; 138 mM sodium chloride; pH 6.0) as placebo administered by IV infusion. The volume of fluid administered was the same for both active and placebo treatments. Randomization was performed centrally, and patients were stratified by bronchodilator response and by FEV1 ≤ 40% or ≥ 40% of predicted.

There were eight visits: the screening period (one visit), the treatment period (baseline, week 2, month 1, month 2, month 3); and the follow-up period (month 4 and month 5). All treatments were administered by IV infusion over 30 min; a loading dose (800 mg) was administered at the baseline visit (month 0), followed by two doses of 400 mg administered monthly thereafter (month 1 and month 2). The dosing regimen was selected on the basis of unpublished clinical trial data supporting its safety in patients with rheumatoid arthritis and in patients with psoriasis.

Outcome Measures

Dyspnea was measured using the baseline dyspnea index (BDI) at the initial visit and the transition dyspnea index (TDI) at all subsequent visits. The BDI is a discriminative instrument that measures the severity of breathlessness at a baseline state; the TDI is an evaluative instrument that measures the changes in breathlessness compared to the baseline or initial visit. Both instruments include three components that affect the severity of dyspnea with activities of daily living: functional impairment, magnitude of task, and magnitude of effort. The primary outcome measure was the TDI total score, which represents the sum of scores for the three components (range, −9 to +9). The BDI and TDI have been used widely in randomized clinical trials to evaluate the efficacy of bronchodilator medications, long-acting β-agonist and inhaled corticosteroid combination, pulmonary rehabilitation, and inspiratory muscle training. Secondary outcomes included change from baseline in pre-
bronchodilator and postbronchodilator FEV₁, the St. George Respiratory Questionnaire (SGRQ), 32 6-min walking distance, and use of albuterol as rescue therapy. Spirometry was measured at each visit using the Koko spirometer (PDS Research; Louisville, CO). The SGRQ and 6-min walk were assessed at baseline and at each monthly visit. Lung volumes were measured by body plethysmography at baseline and again at the 3-month visit using available equipment at each testing site. Patients maintained a diary of daily use of albuterol as rescue therapy.

A COPD exacerbation was defined in the protocol as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.”33 All reported COPD exacerbations were reviewed prior to unblinding, and only those that met this definition were included in the analysis.

Safety was assessed at each study visit by recording of adverse events, complete blood tests, and urinalysis. Blood samples were obtained prior to and 30 min after completion of dosing at each dosing visit for measuring plasma levels of ABX-IL8. Serum was obtained at baseline and at each monthly visit for measurement of IL-8 levels and at baseline and from month 3 through month 5 for detection of human anti-human antibodies to ABX-IL8.

Concentrations of total IL-8 in serum samples collected at baseline were determined by the QuantiGlo Human IL-8 Chemiluminescent Immunoassay (R&D Systems; Minneapolis, MN), as described by the manufacturer. For determination of ABX-IL8 in serum samples, an enzyme-linked immunosorbent assay (ELISA) was developed at Abgenix, Inc. (Fremont, CA). Briefly, 96-well ELISA plates were coated with recombinant human IL-8. After blocking and washing steps, samples were diluted in 10% normal serum and added to the plates. After removal of unbound material, horseradish peroxidase-labeled mouse-anti-human IgG2 was added. Excess enzyme conjugate was removed by washing, and K-BLUE substrate (Neogen Corporation; Lexington, KY) was added to the wells. Enzyme reaction was stopped by the addition of 2 mol/L sulfuric acid, and the absorbance was measured at 450 nm. In addition, detection of human anti-human antibody response in serum samples was accomplished using a sandwich ELISA assay.

Statistical Analysis

Efficacy analyses were performed on the modified intent-to-treat populations that included all randomized patients with at least one TDI assessment. A sample size of 65 patients per group was considered sufficient based on a mean difference of 1 U in the TDI total score (considered the minimal clinically important difference)34,35 at the 5% significance level with a power of 80% assuming a SD of 2.0 U in the TDI. The TDI total score was analyzed using an analysis of variance model with treatment and sites as the main factors. In addition, the proportions of patients achieving a TDI total score of ≥1 was compared between ABX-IL8 and placebo groups using the χ² test.

Change from baseline in secondary end points was analyzed in patients with both baseline and posttreatment values using an analysis of covariance model with treatment and sites as main factors and the baseline value as the covariate. Other between-group comparisons used the χ² test unless the number of patients in one or more cells of the frequency table was less than five, in which case the Fisher exact test was used. If patients received disallowed concomitant medication (eg, corticosteroids, theophylline, leukotriene-receptor antagonists) to treat a COPD exacerbation, then the lowest of the pre-exacerbation or postexacerbation score was imputed during the time the patient was receiving the disallowed medication. The proportion of patients with treatment-emergent COPD exacerbation was compared between ABX-IL8 and placebo using the χ² test. Safety analyses were based on data collected from all randomized patients. Baseline characteristics of the placebo and ABX-IL8–treated groups were compared using either an unpaired t test or χ² test. Values are reported as mean ± SEM; p < 0.05 was considered statistically significant.

Results

Patient Disposition

One hundred nineteen patients were randomized to one of two treatment groups (Table 1). Ten patients (7 patients receiving placebo, and 3 patients receiving ABX-IL8) withdrew from the study prior to the first scheduled administration of the study drug. These patients did not have a TDI assessment, and are therefore not included in the efficacy analyses. The remaining 109 patients constitute the modified intent-to-treat population. Overall, 99 patients (91%) received all three infusions of the study medication.

Patient Characteristics

There were no significant differences in any of the baseline characteristics between the two treatment groups (Table 2). The mean values for the baseline serum IL-8 concentrations were 37 ± 13 pg/mL in the placebo group and 25 ± 5 pg/mL in the ABX-IL8 group (p = 0.39). Due to the inability of the assay to discriminate between free or ABX-IL8 bound IL-8, concentrations of IL-8 following treatment with ABX-IL8 were not determined.

Pharmacokinetics

The serum concentration-time profile for ABX-IL8 following administration of monthly doses of the antibody is shown in Figure 1. Stable trough serum concentrations were maintained throughout the treatment period. Trough concentrations achieved

<table>
<thead>
<tr>
<th>Patient Disposition*</th>
<th>Placebo</th>
<th>ABX-IL8</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>60</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Discontinuations before dosing, No.</td>
<td>7 (12)</td>
<td>3 (5)</td>
<td>0.32</td>
</tr>
<tr>
<td>( % of randomized)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MITT, No. ( % of randomized)</td>
<td>53 (88)</td>
<td>56 (95)</td>
<td></td>
</tr>
<tr>
<td>Completed month 3, No.</td>
<td>46 (87)</td>
<td>53 (90)</td>
<td></td>
</tr>
<tr>
<td>( % of MITT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuations, No. ( % of MITT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>5 (8)</td>
<td>1 (2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>ND</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>ND</td>
</tr>
<tr>
<td>Unavailable for follow-up</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Data are presented as No. unless otherwise indicated. MITT = modified intent-to-treat; ND = not determined.
during the dosing intervals were $47 \pm 18 \mu g/mL$, $39 \pm 14 \mu g/mL$, and $42 \pm 17 \mu g/mL$, for study months 1, 2, and 3, respectively. Due to administration of a loading dose, higher maximum serum concentrations were achieved following administration of the first dose of the antibody relative to those observed during the subsequent dosing intervals. Maximum serum concentrations achieved during

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22015/)

**Table 2—Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 53)</th>
<th>ABX-IL8 (n = 56)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>63 (1.0)</td>
<td>65 (1.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Female, %</td>
<td>53</td>
<td>38</td>
<td>0.11</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 (1.3)</td>
<td>171 (1.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>COPD duration, yr</td>
<td>5.3 (0.7)</td>
<td>7.4 (0.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>FEV$_1$, L</td>
<td>1.2 (0.06)</td>
<td>1.3 (0.06)</td>
<td>0.86</td>
</tr>
<tr>
<td>FEV$_1$, % of predicted</td>
<td>42 (1.7)</td>
<td>42 (1.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>FEV$_1$/FVC</td>
<td>0.5 (0.02)</td>
<td>0.5 (0.01)</td>
<td>0.94</td>
</tr>
<tr>
<td>Bronchodilator response, %†</td>
<td>39</td>
<td>30</td>
<td>0.33</td>
</tr>
<tr>
<td>Smoking history, pack-years</td>
<td>73.5 (4.7)</td>
<td>63.4 (4.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Active smokers, %</td>
<td>40</td>
<td>39</td>
<td>0.97</td>
</tr>
<tr>
<td>Inhaled anticholinergic therapy, %</td>
<td>53</td>
<td>46</td>
<td>0.77</td>
</tr>
<tr>
<td>Inhaled long-acting β-agonist, %</td>
<td>38</td>
<td>46</td>
<td>0.56</td>
</tr>
<tr>
<td>Baseline dyspnea index</td>
<td>5.6 (0.4)</td>
<td>5.6 (0.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>SGRQ</td>
<td>47.6 (2.6)</td>
<td>50.0 (2.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>Six-minute walk distance, m</td>
<td>401.1 (13.4)</td>
<td>400.3 (13.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>Serum IL-8, pg/mL</td>
<td>37 (13)</td>
<td>25 (5)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM) unless otherwise indicated.
†Percentage of patients with increase in FEV$_1$ $\geq 12\%$ and $\geq 200 \text{ mL}$ at 30 min after inhalation of two puffs (180 μg) of albuterol.
each dosing interval were 229 ± 67 µg/mL, 151 ± 41 µg/mL, and 145 ± 38 µg/mL for study months 0, 1, and 2, respectively.

Outcome Measures

The results of the TDI total scores, lung function, health status, 6-min walking distance, and IL-8 levels at the various visits are reported in Table 3.

Dyspnea

Patients who received ABX-IL8 had an increase in the TDI total score at 2 weeks, which persisted throughout the 3-month treatment period (Fig 2). In contrast, the mean TDI scores for the patients who received placebo initially declined with a gradual improvement noted at 3 months. The differences in the mean TDI scores between ABX-IL8–treated patients and placebo-treated patients were 0.8, 1.0, 0.8, and 0.3 at week 2 (p = 0.046) and month 1, month 2, and month 3, respectively (Fig 2). The benefit of ABX-IL8 waned during the follow-up period, consistent with the elimination of the drug (Fig 2). The proportion of patients who achieved a TDI score ≥ 1 was higher in ABX-IL8–treated patients compared with placebo-treated patients at all time points (Fig 3). However, the only statistically significant difference occurred at week 2 (28% vs 11%; p = 0.03). There were no differences in the TDI response based on baseline FEV1 percentage of predicted, bronchodilator response, or smoking status.

Lung Function

The mean changes in FEV1 from baseline for both treatment groups were < 20 mL throughout the treatment period. No significant changes were observed for total lung capacity or functional residual capacity within a group or between groups.

Health Status

At the end of the treatment period (month 3), patients treated with ABX-IL8 had a change of -4.0 ± 2.0 U (n = 51) in the SGRQ compared with a change of -2.1 ± 2.7 U (n = 51) for those who received placebo (Δ 1.9; p = 0.68).

Other Outcomes

The mean change from baseline in the 6-min walking test throughout the treatment period was < 20 m (p = 0.2) for either treatment group. At baseline, the placebo and ABX-IL8 treatment groups averaged 3.9 ± 0.6 puffs per day and 3.4 ± 0.4 puffs per day of rescue albuterol, respectively. The differences between ABX-IL8–treated and placebo-
treated patients in the change from baseline in the average number of puffs per day of rescue albuterol were small (−0.1 puffs, −0.2 puffs, −0.4 puffs, and −0.1 puffs per day at week 2, month 1, month 2, and month 3 visits, respectively), and were not statistically significant.

Safety and Adverse Events

ABX-IL8 and placebo infusions were well tolerated by all subjects. There were no significant infusion-related reactions reported, and no infusions were stopped because of an adverse event.

The percentage of patients experiencing adverse events was similar in the two treatment groups (Table 4). Five placebo-treated patients (respiratory failure, COPD exacerbation, hypersonnia, angina, and headache) and one ABX-IL8–treated patient (pneumonia) discontinued because of an adverse event (p = 0.11). The three most common adverse events considered drug related were COPD exacerbation, lower-extremity edema, and congestive heart failure.

There were no significant changes observed in WBC or RBC counts or blood chemistries in either treatment group throughout the study. No human anti-human antibody response was detected during the study in any patients.

Discussion

There are no current guidelines or recommendations for selection of the most appropriate primary
outcome measure for evaluating biological agents for the treatment of COPD. In a study of monoclonal anti-IgE antibody therapy in patients with asthma, Milgrom and colleagues\textsuperscript{36} used the asthma symptom score for assessing efficacy. These investigators found significant improvements in this outcome, but no significant change in FEV\(_1\) at 12 weeks with either a high dose or a low dose of the monoclonal antibody. We also selected a symptom outcome, dyspnea reflected by activities of daily living as measured by the TDI, to evaluate efficacy in our study for several reasons. First, the Confronting COPD International telephone survey documented that dyspnea is the major complaint of patients with COPD.\textsuperscript{21} Second, the Global Initiative for Chronic Obstructive Lung Disease guidelines\textsuperscript{1,18} have emphasized that the treatment of patients with COPD should be directed toward relief of symptoms. Third, there is no rationale that a monoclonal antibody directed against a chemokine should enhance lung function, a traditional metric used to assess efficacy in trials involving bronchodilator medications.

The major findings of this pilot study were as follows: (1) ABX-IL8 reduced the severity of dyspnea as measured with the TDI compared with placebo; (2) there were no significant differences in lung function, health status, or rescue albuterol use between treatment groups; (3) the infusions of ABX-IL8 were well tolerated; and (4) adverse events were similar between the treatment and placebo groups. The TDI total score was selected to measure the changes in the severity of breathlessness in this study for two reasons: (1) it has been used widely in clinical trials, and (2) it has been shown to be responsive to a variety of interventions involving patients with COPD.\textsuperscript{21–31} Our results showed that ABX-IL8 provided relief of dyspnea that was evident at 2 weeks after the first infusion and persisted for a 2-month period (Fig 2). However, only the difference in the TDI total score at 2 weeks between treatment groups achieved statistical significance. The early onset of the effect could be a result of the higher loading dose (800 mg) and the higher maximum serum concentration in the first dosing interval. After 2 months, there was a steady decline in the TDI total score that may be related to the lower doses of the monoclonal antibody. At the end of the follow-up period, the TDI total score for ABX-IL8–treated patients had returned to baseline, whereas the placebo-treated patients slowly improved. The loss of drug benefit during the follow-up period is consistent with the decreased drug exposure. In addition, it is possible that reduction in IL-8 could lead to a compensatory increase in proinflammatory mediators that could diminish the efficacy of ABX-IL8 over time.

This effect of ABX-IL8 raises interesting questions about the perplexing and challenging problem of breathlessness experienced by patients with COPD. Clearly, the improvements in breathlessness were not due to enhanced lung function. Whether any reduced infiltration of neutrophils as expected with ABX-IL8 could influence airway and/or tissue receptor activity that modulates the perception of dyspnea is speculative. However, vagal-mediated receptors and nerve fibers are located in the lung and transmit afferent information to the CNS. Moreover, previous studies\textsuperscript{10,12,26} have demonstrated that inhaled corticosteroids alone and in combination with long-acting \(\beta\)-agonists reduce the severity of dyspnea in patients with COPD. Thus, it is reasonable to postulate that an anti-inflammatory effect may influence breathlessness, although the exact mechanism(s) are not understood.

The improvement in the TDI total score with ABX-IL8 compared with placebo was 1-U difference at 1 month, and approached this level (differences in TDI scores of 0.8) at 2 weeks and at 2 months. The magnitude of this benefit is considered clinically meaningful,\textsuperscript{34,35} and was comparable to the reported improvements in TDI total scores with individual bronchodilator therapy or with combination medications.\textsuperscript{12,22–25} There were no significant changes in spirometry, lung volumes, health status, or the 6-min walking distance with either treatment or between groups. Although ABX-IL8 treatment was associated with a greater improvement in the total score of the SGRQ than with placebo, the difference (\(\Delta 1.9\) U) did not achieve the 4-U level considered clinically meaningful.\textsuperscript{32} However, at least 6 months of treatment may be required to demonstrate the expected benefits in health status with pharmacologic therapy.\textsuperscript{23,38} Rescue albuterol use was slightly lower (range, –0.1 to –0.4 puffs per day) in the active-treated group.

### Table 4—Adverse Event Summary

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo (n = 60), No. (%)</th>
<th>ABX-IL8 (n = 59), No. (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 adverse event</td>
<td>35 (58)</td>
<td>42 (71)</td>
<td>0.142</td>
</tr>
<tr>
<td>≥1 drug-related adverse event*</td>
<td>8 (13)</td>
<td>12 (20)</td>
<td>0.307</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0.491</td>
</tr>
<tr>
<td>Lower-extremity edema</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>0.491</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0.491</td>
</tr>
<tr>
<td>≥1 severe or maximal adverse event</td>
<td>6 (10)</td>
<td>3 (5)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

*The three most frequent drug-related adverse events.
compared to placebo. It is possible that the concomitant use of long-acting β-agonists and ipratropium bromide may have limited the utility of this end point.

Treatment with ABX-ILS was both safe and well tolerated. Importantly, there were no infusion reactions; adverse events, including COPD exacerbations, were similar between treatment and placebo groups. Moreover, no patients had detectable antibodies to ABX-ILS.

There are two major limitations with this clinical trial. First, the dose of ABX-ILS may have been suboptimal to demonstrate efficacy. The dose was selected based on the highest doses administered in previous phase two trials in patients with other inflammatory diseases (rheumatoid arthritis and psoriasis) in which IL-8 is elevated (unpublished data). The dosing regimen in this study resulted in trough serum concentrations of ABX-ILS (approximately 40 µg/mL) that exceeded the concentration required to inhibit IL-8 binding to neutrophils in vitro by 90% (approximately 0.12 µg/mL). However, it is likely that the concentration of ABX-ILS in the airway was substantially lower than serum and may not have been sufficient to fully inhibit IL-8 activity. Second, treatment was administered for only 3 months. Additional doses may be required over a longer time period (eg, ≥ 1 year) to more completely evaluate the benefit/safety profile of ABX-ILS.

To the best of our knowledge, this is the first report of a trial of monoclonal antibody therapy targeted against an important chemokine in patients with COPD. So far, there are two reports of using monoclonal antibodies in the treatment of asthma. With COPD, So far, there are two reports of using targeted against an important chemokine in patients.

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REFERENCES
17 Nadel JA. Role of neutrophil elastase in hypersecretion during COPD exacerbations, and proposed therapies. Chest 2000; 117:3865—3898
19 Fletcher CM, Elmes PC, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. BMJ 1959; 1:257—266
26 Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 μg)/salmeterol (50 μg) combined in the diskus inhaler for the treatment of COPD. Chest 2003; 124:834—843