ARTICLE

Phase I Studies of Acebilustat: Biomarker Response and Safety in Patients with Cystic Fibrosis

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There is a significant unmet need for safe and effective anti-inflammatory treatment for cystic fibrosis. The aim of this study was to evaluate the safety of acebilustat, a leukotriene A4 hydrolase inhibitor, and its effect on inflammation biomarkers in patients with cystic fibrosis. Seventeen patients with mild to moderate cystic fibrosis were enrolled and randomized into groups receiving placebo or doses of 50 mg or 100 mg acebilustat administered orally, once daily for 15 days. Sputum neutrophil counts were reduced by 65% over baseline values in patients treated with 100 mg acebilustat. A modestly significant 58% reduction vs. placebo in sputum elastase was observed with acebilustat treatment. Favorable trends were observed for reduction of serum C-reactive protein and sputum neutrophil DNA in acebilustat-treated patients. No changes in pulmonary function were observed. Acebilustat was safe and well tolerated. The results of this study support further clinical development of acebilustat for treatment of cystic fibrosis.


Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Persistent neutrophilic lung inflammation is a major cause of morbidity and mortality in CF. Safe and effective anti-inflammatory treatment remains a significant unmet need. Acebilustat is a potential new anti-inflammatory treatment intended to target the excessive influx of neutrophils into the lungs of patients with CF.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ Whether once-daily oral acebilustat is tolerable and safe for further testing and whether it shows initial signs of pharmacologic or therapeutic effect in patients with CF. We address these questions by evaluating adverse events, lung function, and biomarkers related to inflammation and infection.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ We found that once-daily oral acebilustat showed promising trends in the reduction of both sputum and blood biomarkers related to inflammation without changing systemic or respiratory markers of infection. No change in lung function was observed. These results indicate that once-daily oral acebilustat is well tolerated, safe for further development, and may reduce both lung and systemic inflammation in patients with CF. A longer clinical trial may be required to observe changes in lung function.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ These findings support further clinical development of once-daily oral acebilustat as a new treatment with potential to address lung inflammation in patients with CF.

Persistent lung inflammation remains the major cause of morbidity and mortality for patients with cystic fibrosis (CF), and is characterized by excessive neutrophil influx into the airways that leads to tissue injury. The key mediators of neutrophilic insult in CF lungs include DNA and elastase. DNA expelled from neutrophils is a significant contributor to mucus thickening and airway obstruction.1,2 Neutrophil-derived elastase promotes lung tissue degradation and is strongly correlated with progressive lung function decline as well as acute pulmonary exacerbation.3–7 Elastase has also been shown to contribute to CF lung disease through a number of other mechanisms, including inactivation of the CF transmembrane conductance regulator and activation of the epithelial Na+ channel, both of which exacerbate the defect in ion transport conditions underlying CF.8,9 Paradoxically, excessive elastase released by neutrophils in CF airways also impairs host response to bacterial infection by inactivating many proteins important for host defense.10,11 Development of direct elastase inhibitors that are effective in humans has so far been elusive, perhaps because of the...
extraordinarily high local concentrations of elastase at the neutrophil surface.\textsuperscript{12}

A logical approach to treating CF lung inflammation is to reduce the excessive migration of neutrophils into the lungs, thereby reducing release of both neutrophil-derived DNA and elastase in the airways. Identifying the primary drivers of neutrophil influx and activation in the CF lung is the subject of much current research.\textsuperscript{13,14} One such candidate is leukotriene B4 (LTB4), a potent lipid mediator of neutrophil migration and activation.\textsuperscript{15} LTB4 is produced by the action of the enzyme leukotriene A4 hydrolase (LTA4H) on the intermediate arachidonic acid product leukotriene A4.\textsuperscript{16} LTB4 has recently been identified as a requisite mediator of neutrophil swarming behavior and serves as a neutrophil-to-neutrophil relay signal in order to amplify an initial inciting inflammatory signal, such as formyl peptides.\textsuperscript{16,17} LTB4 signaling from neutrophils also initiates a cascade of cytokines and chemokines that further amplify and sustain inflammation as well as perpetuate further neutrophil recruitment.\textsuperscript{18,19} Furthermore, LTB4 has been shown to stimulate neutrophils to release elastase, and conversely elastase can stimulate accumulation of LTB4.\textsuperscript{20,21} Consistent with these findings, generation of LTB4 is increased in the lungs of patients with CF and correlates with disease severity.\textsuperscript{22,23} Taken together, these findings suggest that, once incited, neutrophils may form a self-sustaining inflammatory cycle of LTB4 generation and neutrophil recruitment that results in persistent and excessive release of neutrophilic DNA and elastase into the airways of patients with CF. Breaking this cycle by intervening in the production of LTB4 is an attractive target for treatment of CF airway inflammation.

We hypothesized that reducing LTB4 production via selective inhibition of LTA4H would provide measurable and potentially beneficial anti-inflammatory effects. Acebilustat (CTX-4430) is a direct and selective inhibitor of LTA4H in development as a once-daily oral anti-inflammatory treatment for CF. Pharmacokinetics and pharmacodynamics of acebilustat in healthy volunteers and patients with CF, reported separately, indicate that 50 mg and 100 mg once-daily oral doses of acebilustat significantly reduce LTB4 production, and, thus, are potentially effective doses for anti-inflammatory treatment of CF. Here, we report the results for biomarkers and safety from a first-in-human phase I clinical study in patients with CF treated for 15 days with 50 mg or 100 mg once-daily oral acebilustat or matched placebo.

### METHODS

#### Study design

This study was carried out using a randomized, double-blind, placebo-controlled dose escalation design, with study treatment administered orally once daily for 15 days.\textsuperscript{24} Adult male and female patients with CF aged 18–55 years and having percent predicted forced expiratory volume 1 (FEV1) $\geq$ 50% and $\leq$ 90% as well as body mass index of at least 17.0 Kg/m$^2$ were eligible to participate in this study. Assessments were performed on day -1 (1 day before the first dose of study treatment) to study day 2 (day after first study treatment), on study days 7–9 for interim evaluation, on study days 14–16 (day after last study treatment) for end of treatment evaluation, and for follow-up on day 22, as shown in Figure 1. The protocol and informed consent documents were reviewed by the Office for Research Ethics Committees Northern Ireland and all patients provided informed consent.

Two study cohorts were enrolled with a planned cohort size of nine, consisting of three placebo-treated and six acebilustat-treated patients. In the first cohort, nine patients were randomized to receive either 50 mg acebilustat or matching placebo capsule. After an escalation review of the safety data from the first cohort, a second cohort was enrolled and patients were randomized to receive either 100 mg acebilustat or matching placebo capsule. Due to lack of additional available patients, the second cohort was stopped at a total enrollment of eight patients. For all analyses, the placebo-treated patients from each dosing cohort were combined as a unified group called “placebo.”

#### Study procedures

Induced sputum samples were collected on study days -1 (baseline), 2 (day after first dose), 9 (acebilustat steady state), 16 (day after last dose), and 22 (follow-up), as shown in Figure 1. Sputum induction was performed at the clinical sites based on previously described methods.\textsuperscript{25} Specimens were collected and processed at the clinical sites and split into two subsamples after gentle mechanical homogenization. One subsample was immediately processed for cell counting and bacterial culture, and the other subsample was further processed and preserved for soluble and cellular markers, including neutrophil elastase and DNA.\textsuperscript{26,27} Lung clearance index was performed on study days -1 (baseline), 7, and 16 (end of treatment) using the SF6 multiple breath washout method, as previously described.\textsuperscript{28} Raw data from multiple breath washout tests were read centrally by a single observer blinded to treatment, as per recent recommendations.\textsuperscript{29}

#### Statistical analysis

For the analysis of total white blood cell (WBC) counts, neutrophil counts, elastase, and DNA in sputum, specimens taken after the end of treatment (day after final treatment) were compared with specimens taken at baseline (day prior to first treatment). These data are presented as percentage change from baseline for each individual patient, then compared as the combined group of all patients receiving acebilustat (treated, including both the 50 mg and 100 mg
dose groups) vs. placebo and also by individual treatment groups (placebo, 50 mg acebilustat, and 100 mg acebilustat). Samples for sputum microbiology were examined from study days -1 (baseline), 2 (day after first dose), 9 (interim), 16 (end of treatment), and 22 (follow-up), and analyzed longitudinally or by comparing colony-forming units (CFUs) at the end of treatment (day after final treatment) to baseline (day before first treatment).

Two systemic markers of inflammation were studied; serum C-reactive protein (CRP) and circulating neutrophil count. Blood samples collected on study day 14 (day before final treatment) were compared with specimens taken at baseline (day prior to first treatment). Treatment was stopped early for one patient in the placebo group due to increased CRP on study day 8. Therefore, this placebo patient is omitted from all analyses other than safety, yielding a placebo group of four.

Statistical comparison of the full treated group to placebo was carried out using an unpaired parametric one-tailed *t*-test with 95% confidence level. For statistical comparison of the acebilustat dose groups to placebo, a one-way analysis of variance was carried out using Dunnett’s multiple comparison test with a 90% confidence level. For results with at least modest statistical significance (\(P = 0.05\); 95% confidence), the \(P\) value is reported in the results and figures. Nonsignificant values are reported as “*ns*”. Data for all analyses included in this study were graphed and statistical analyses were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com).

**RESULTS**

A total of 17 patients with CF entered the study and were randomized to study treatment. Of the 17 patients participating in the study, 4 were female and 13 were male. The study patients ranged in age from 21–39 years old, in body weight from 51.0–98.3 kg, and in body mass index from 19.60–27.90 kg/m\(^2\). A total of 16 patients completed the study. One patient in the placebo group discontinued participation in the study prior to dosing on day 8 due to an adverse event of elevated serum CRP. Therefore, this patient was excluded from the analyses other than safety, resulting in a placebo group size of four. Hematology measures were not taken for one patient in the 100 mg acebilustat dose group on day 14, therefore, this patient is excluded from the analysis of peripheral blood neutrophils resulting in a 100 mg dose group of 5 and a combined treated group size of 11 for analysis of peripheral blood neutrophil count. In some cases, such as for sputum WBC and neutrophil cell counts, data for specific samples were missing or not obtainable and the group size reflects the lack of analyzable data for these samples.

**Inflammation biomarkers**

Decreases were observed in all sputum inflammation biomarkers for the acebilustat-treated patients compared with their own baselines and to the placebo group. Notably, large dose-dependent reductions from baseline were observed in sputum WBC and neutrophil counts in the acebilustat-treated patients, as shown in Figure 2. For sputum WBC, there was a 31% reduction from baseline in the acebilustat-treated group (\(n = 11\)) and a 60% reduction from baseline in the 100 mg acebilustat group (range, 12–100% reduction; \(n = 5\)). Additionally, four of six patients in the 50 mg acebilustat group and four of five patients in the 100 mg acebilustat group showed reductions from their own baseline in sputum WBC count. For sputum neutrophils, there was a 34% reduction from baseline in the acebilustat treated group (\(n = 11\)) and a 65% reduction from baseline in the 100 mg acebilustat group (range, 23–100% reduction; \(n = 5\)). Four of the five analyzable patients treated with 100 mg acebilustat showed reductions of at least 48% in sputum neutrophils. In contrast, placebo-treated patients showed an overall increase from baseline on both sputum WBC (62% increase from baseline; \(n = 4\)) and neutrophils (56% increase from baseline; \(n = 4\)).

Positive treatment trends were also observed for sputum DNA and sputum elastase in this study (Figure 3), with a substantial proportion of treated subjects showing a decrease from baseline and compared with placebo. There was a modestly significant 58% reduction in elastase in the treated group compared with placebo (\(P < 0.05\), one-tailed *t*-test). There was no clear dose dependence for either marker; however, there was a trend toward proportions of patients showing reductions with higher acebilustat doses.

There was an overall increase from baseline CRP of \(+2.7 ± 5.3\) mg/L (mean ± SD, \(n = 4\)) in patients treated with placebo, whereas for the acebilustat-treated patients there was an overall decrease from baseline CRP of \(-1.2 ± 6.2\) mg/L (\(n = 12\)). This difference was not statistically significant and there was no clear dose dependence. Circulating neutrophil counts did not change from baseline (\(7.4 ± 3.1; n = 11\)) to end of treatment (\(7.0 ± 3.1; n = 11\)) within the acebilustat-treated
Figure 3 Sputum DNA and elastase at end of treatment. Sputum DNA (top) and elastase (bottom) measures taken at end of treatment (study day 16). Results are expressed as percentage of baseline value (mean ± SD) for each individual patient (shown as markers in the graphs). Analysis was performed in two ways: combined acebilustat-treated group (50 mg and 100 mg) vs. placebo (left), and as separate dose groups placebo, 50 mg and 100 mg acebilustat (right).

At the end of treatment, the acebilustat-treated group was also not different from the placebo group (6.3 ± 3.3; n = 4).

Sputum microbiology
Treatment with 50 or 100 mg acebilustat for 15 days did not elicit a discernable pattern of change from baseline or a difference in pattern from placebo in the longitudinal data for either total bacterial load or total observed genera, as shown in Figure 4. Change from baseline CFUs in the treated and placebo groups was examined by comparing samples from end of treatment (day after last dose) to baseline (day before first dose) and the results are depicted in Figure 5. No difference from baseline to end of treatment in total bacterial CFU in the acebilustat-treated groups or vs. placebo was observed. Apparent reduction in the mean total bacterial load in the acebilustat-treated group compared with the placebo group are largely driven by one particularly large increase in the placebo group and are not thought to reflect a reduction in total bacterial load with acebilustat treatment.

Overall, six genera were observed across all treatment groups: pseudomonas, hemophilus, staphylococcus, streptococcus, Rothia, and Burkholderia. Two additional genera were observed sporadically and only in the group treated with 100 mg acebilustat: actinomycosis and lactobacillus. There was no increase or decrease in presence or quantity of any genera during 15 days of treatment with placebo or 50 or 100 mg/day acebilustat.

Lung function
No clear changes in percent predicted FEV1, forced vital capacity, FEV_{25-75}, or lung clearance index were observed between baseline and end of treatment with 50 or 100 mg acebilustat, as shown in Figure 6.

Safety
Acebilustat was well tolerated in this study. Overall, 45 adverse events were reported for 14 of 17 patients in this study: five of six patients treated with 50 mg acebilustat, six of six patients treated with 100 mg acebilustat, and three of five patients treated with placebo. A summary of safety data is presented in Table 1. The most common treatment emergent adverse events were headache, oropharyngeal pain, abdominal pain, cough, increased sputum, and hemoptysis. These adverse events were mild or moderate in severity.
and were considered unrelated or unlikely to be related to acebilustat. There were no serious adverse events related to acebilustat. One serious adverse event of acute pulmonary exacerbation of CF was reported in a subject who received acebilustat 50 mg. However, the symptoms started about 4 weeks after receiving the last dose of acebilustat. Therefore, this serious adverse event was assessed by the clinical site investigator as being unlikely related to the investigational product.

DISCUSSION

The biomarker results suggest that acebilustat is pharmacologically active at the exposures achieved with once daily oral doses of 50 mg and 100 mg, and this is consistent with the pharmacokinetic and pharmacodynamic profile reported separately. Treatment of patients with CF with acebilustat for 15 days resulted in apparent reductions in lung and systemic markers of inflammation without adversely affecting pulmonary infection status. For all inflammatory biomarkers examined in blood (CRP) and sputum (WBC, neutrophils, DNA, and elastase), acebilustat treatment showed a reduction compared with placebo. Reductions from baseline values were observed for sputum measures of WBC, neutrophils, DNA, and elastase. Additionally, dose-dependent trends either in mean values of reduction from baseline (sputum WBC and neutrophils) or in number of patients showing a reduction from baseline (sputum DNA and elastase) provide additional evidence for an anti-inflammatory effect in the lungs of patients with CF treated with once daily oral acebilustat for 15 days.

Although not statistically significant, the reduction in serum CRP in patients with CF treated with acebilustat when compared with baseline (-1.2 mg/L) or to placebo (-3.9 mg/L) suggests a potential systemic anti-inflammatory effect of acebilustat treatment in patients with CF. This is notable because serum CRP is strongly correlated with systemic inflammation status and risk for pulmonary exacerbations in CF.\(^{30–32}\) WBC and neutrophil counts in sputum provide an overall indication of lung inflammation status. Sputum DNA and elastase are important markers of neutrophilic inflammation in CF. Moreover, they are important active contributors to CF lung disease. Neutrophil-derived DNA is a significant contributor to mucus viscosity and airway obstruction.\(^{2,33}\) Elastase is a key mediator of lung tissue degradation, bacterial clearance deficiency and ion transport dysfunction that is highly correlated with lung disease and functional decline.\(^{3,5,6,8,10,11}\)

Recent reports have suggested that direct inhibition of LTA4H in mice may lead to increased inflammation. This effect is thought to result from decreased clearance of the proinflammatory tripeptide proline-glycine-proline, which is generated from breakdown of interstitial matrix proteins and eliminated via hydrolysis at the Pro-Gly bond by the aminopeptidase function of LTA4H.\(^{34}\) Although proline-glycine-proline levels in the lung were not measured in this study, it is worth noting that all acebilustat-treated patients in this study were colonized with hemophilus and most with pseudomonas, staphylococcus, and streptococcus as well. In spite of the prevalent pulmonary colonization status of the acebilustat-treated patients, there was a consistent decrease in all measures of inflammation, including decreases in sputum WBC and neutrophils with correlated decreases in inflammatory neutrophil products (DNA and elastase) and no signs of increased pulmonary infection or systemic inflammation (CRP). The reason for the difference in these outcomes remains to be determined, but could potentially be explained by differences in the level of inhibition of LTA4H aminopeptidase function in the lung, as well as differences between human CF disease and animal model systems. Whatever the source of the disparity in outcomes, the results of this study clearly demonstrate that acebilustat treatment does not seem to increase lung inflammation and, in contrast, provide strong evidence that

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**Table 1** Summary of treatment emergent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients starting treatment</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>No. of patients completing treatment</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>No. of patients with adverse event</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Total no. of adverse events</td>
<td>7</td>
<td>14</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>Adverse events of mild severity</td>
<td>5</td>
<td>8</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>Adverse events of moderate severity</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>1(^a)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Discontinued due to adverse event</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^{a}\)Occurred 29 days after last study treatment and discovered on extended follow-up for pregnancy testing.
Acebilustat reduces lung and systemic inflammation in patients with CF.

Previous attempts to intervene in LTB4 signaling and its consequent neutrophilic inflammation in CF have met with mixed outcomes. Konstan et al.\textsuperscript{35} and VanDevanter et al.\textsuperscript{36} showed that high-dose ibuprofen was able to reduce the decline of lung function over time and to improve survival in patients with CF. The likely mechanism of the high-dose ibuprofen therapeutic effect in patients with CF has been attributed to a secondary pharmacology of reducing LTB4 production based on nonclinical and clinical studies.\textsuperscript{37,38} In contrast, a large phase II clinical trial of the LTB4 receptor antagonist amelubant (BIIL-284) in patients with CF showed an increase in acute pulmonary exacerbations, leading to early termination of the study and discontinuation of the program.\textsuperscript{39} No cause for the increased pulmonary exacerbations could be attributed from the clinical studies of amelubant; however, in subsequent nonclinical studies, the increase in pulmonary exacerbations was attributed to increased infection with amelubant treatment.\textsuperscript{40} Whether this effect is unique to LTB4 receptor blockade or resulted from too great a level of pathway inhibition remains unknown, however, pharmacodynamic data suggest that the dosages and exposures of amelubant in the terminated phase II trial were in excess of that required for complete inhibition of BLT receptor signaling.\textsuperscript{41} Regardless of the origin of the increased pulmonary exacerbations observed in the phase II study, the experience with amelubant urges caution in development of anti-inflammatory treatments for CF. In contrast, the clinical experience with high-dose ibuprofen suggests that the effect seen with amelubant is not a general feature of intervention in LTB4 signaling.

Acebilustat was safe and well tolerated in this study. Adverse events were generally characterized as mild to moderate in severity and were characterized by the investigators as unlikely or not related to the study drug. In addition to the clinical safety assessments, circulating neutrophil counts and sputum microbiology were monitored during the course of the study. No treatment-related changes were observed in these measures. For circulating neutrophils, there was no difference from placebo or change from baseline for the acebilustat-treated patients with CF. Conversely, the lack of a trend toward increase in circulating neutrophil counts after 15 days of acebilustat treatment suggests that acebilustat is unlikely to increase circulating neutrophils, as was observed for amelubant after 28 days of treatment.\textsuperscript{39} Sputum microbiology did not show any longitudinal pattern of increase in total bacterial load, individual genera, or total genera in acebilustat-treated patients with CF. There was also no increase in total bacterial load compared with placebo, and no dose-dependent change from baseline was observed. Together, these results provide further evidence that treatment with 50 mg or 100 mg acebilustat is not generally immunosuppressive and is not likely to increase susceptibility to pulmonary infection in patients with CF.

In spite of the encouraging reductions in markers of lung inflammation observed in patients with CF in this study, no change was observed for spirometry measures or lung clearance index with 15 days of acebilustat treatment. Because clearance of preexisting neutrophilic material is slow in patients with CF due to thickened mucus, stifled ciliary beat, and dysfunctional lung clearance is exacerbated by neutrophilic DNA, sputum DNA and elastase values can be expected to change more slowly than neutrophil counts.\textsuperscript{2,42} It is therefore likely that the trends toward reduction in these important disease effectors observed in this study will continue to accrue over time with continued treatment. Consequently, an even slower change in clinical outcomes, such as FEV1, is reasonably anticipated with treatments that primarily act by reducing lung inflammation in CF. This effect is in contrast to that observed for treatments that improve CF transmembrane conductance regulator function, such as oral ivacaftor, treatments that actively degrade preexisting DNA, such as inhaled dornase alpha, or treatments that reduce bacterial infection, such as inhaled aztreonam, which act in a matter of days to weeks.\textsuperscript{43–45}

However, the lack of effect on lung function measures in trials of short duration, even in the presence of effects on inflammatory biomarkers, is consistent with prior experience for anti-inflammatory treatments in CF.\textsuperscript{46,47} Conversely, even though high-dose ibuprofen has demonstrated meaningful improvements in clinical outcomes in trials of long duration, it exhibited minimal effects on inflammatory biomarkers in the short term.\textsuperscript{48} Taken together, these findings indicate that a longer treatment period is required to observe a change in clinical outcomes for anti-inflammatory treatments in CF.

In conclusion, treatment of patients with CF with 50 mg or 100 mg oral acebilustat once daily for 15 days was safe and well tolerated. Although no improvements in lung function were observed in this study, acebilustat treatment showed promising signs of reduced lung and systemic inflammation without signs of increased lung infection or systemic immunosuppression. The results of this study support further development of acebilustat as a new once daily oral anti-inflammatory for treatment of CF. A phase II study assessing clinical outcomes in patients with CF after 48 weeks of acebilustat treatment is currently in progress.\textsuperscript{49}

**Acknowledgments.** The authors wish to thank Frank Accurso and Mary Jo “Hobie” Harrington, Children’s Hospital Colorado, for their advice on and conduct of the sputum DNA and elastase measures. We also wish to thank Vanessa Brown, Queens University Belfast, for her conduct of the sputum bacterial cultures and cell counts. Additional thanks are given to Rabin Tiouravaniam, Emory University, for his advice and assistance on the sputum processing protocol and kit preparation. Special thanks to Lopa Bhatt and Tam Van for valuable assistance with the manuscript.


**Conflict Of Interest.** R.G., S.A., and E.B.S. are employees of Celtaxsys, Inc. D.B. and G.M. were consultants for Celtaxsys. J.S.E. was a consultant for Vertex, Novartis, Raptor, and Celtaxsys during the conduct of this study. A.H. received advisory board fees from Vertex, received grant support from Vertex and the Danish Markedmodlingsfonden Fund.
was a consultant for Boehringer Ingelheim, Chiesi Ltd and Celfaxys, and has a collaboration agreement with Innovision Aps.


