Efficacy, safety and effect on biomarkers of AZD9668 in cystic fibrosis

J. Stuart Elborn, John Perrett, Kristina Forsman-Semb, Joanna Marks-Konczalik, Kulasiri Gunawardena, Neil Entwistle

1Respiratory Medicine Group, Centre for Infection and Immunity, Queen’s University, Belfast, UK; 2Soluble Biomarkers - Science & Validation, AstraZeneca, Loughborough, UK (JP, JM-K and KG former employees); 3Bioscience Department, AstraZeneca, Lund, Sweden (former employee)

Corresponding author:
J. Stuart Elborn
Respiratory Medicine Group
Health Sciences Building
Centre for Infection and Immunity
Queen’s University of Belfast
97, Lisburn Road
Belfast, BT9 7BC

Tel: +44 2890 632512
Fax: +44 2890 972671
E-mail: s.elborn@qub.ac.uk

Running title: AZD9668 in cystic fibrosis

ABSTRACT

Objective: To evaluate the safety and the effect on clinical outcomes and biomarkers of inflammation and tissue damage, of the neutrophil elastase (NE) inhibitor AZD9668, 60 mg twice daily orally for 4 weeks, in cystic fibrosis.
Methods: This was a randomised, double-blind, placebo-controlled study (NCT00757848). Primary outcome measures were sputum neutrophil count, lung function, 24-h sputum weight, BronkoTest® diary card data and health-related quality-of-life (revised cystic fibrosis quality-of-life questionnaire). Secondary endpoints included sputum NE activity, inflammatory biomarkers in sputum and blood, urine and plasma desmosine (an elastin degradation marker), AZD9668 levels and safety parameters (adverse events, routine haematology, biochemistry, electrocardiogram, sputum bacteriology)

Measurements and main results: 56 patients were randomised; 27 received AZD9668. There was no effect for AZD9668 on sputum neutrophil counts, NE activity, lung function or clinical outcomes, including quality-of-life. In the AZD9668 group, there was a trend towards reduction in sputum inflammatory biomarkers with statistically significant changes in interleukin-6 and RANTES and also in urinary desmosine. The pattern of adverse events was similar between groups.

Conclusions: Consistent reductions in sputum inflammatory biomarkers were seen in the AZD9668 group, and reduction in urinary desmosine suggests that AZD9668 impacts elastin cleavage by NE.

Keywords: Inflammatory lung disease, neutrophil elastase, tissue damage

Introduction

Bronchiectasis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) are inflammation and injury-driven respiratory conditions with significant unmet needs.

CF results from airway obstruction by dehydrated and thickened secretions and chronic endobronchial infections [1, 2]. Chronic infection is associated with an
exaggerated inflammatory response with high levels of the pro-inflammatory cytokine, interleukin-8 (IL-8), in the airways and neutrophil infiltration of the lungs [3, 4]. The presence of neutrophils in the airways, and the resulting high concentrations of neutrophil proteases, suggest that they are contributors in the pathogenesis of proteolytic lung destruction associated with CF [1, 3, 4]. Neutrophil elastase (NE) is a key proteolytic enzyme implicated in the pathogenesis and progression of neutrophil driven inflammatory lung diseases. It is pro-inflammatory [5, 6], stimulates mucus overproduction [7-9], impairs mucociliary clearance perpetuating the neutrophilic inflammation [1, 3], and directly causes lung-tissue damage [10, 11]. The use of NE inhibitors, such as α1-antitrypsin in patients with CF [4, 12], is therefore a logical approach to treating these conditions and offers the potential to address the current unmet medical needs.

AZD9668 is a oral inhibitor of human NE. Preclinical studies have shown that it reversibly inhibits NE activity, is highly potent and selective in biochemical and cellular assays, and shows efficacy in in vivo models of lung inflammation and degradation [13]. The favourable pharmacokinetic profile, allowing oral administration, and the decreased risk of toxicity due to its reversible interaction with the target enzyme suggest that AZD9668 represents a significant advance versus previous NE inhibitors, and it has shown good efficacy in preclinical models [13]. As such, AZD9668 was developed as a possible therapeutic agent for symptomatic treatment and disease modification in COPD, but which may also be of benefit in CF and other airway diseases characterised by neutrophilic inflammation.

As CF is an orphan disease, efficient and appropriate assessment of new therapies in the limited number of available patients is important. Frequently used outcome measures include clinical efficacy measures (such as survival, pulmonary
exacerbations, and hospitalisations), surrogate endpoints (such as forced expiratory volume in 1 second [FEV₁] at a given time point or the rate of decline in FEV₁), and biomarkers [2]. Given that proteolytic lung destruction is a key feature of CF, there is also a need for relevant, reproducible markers of injury/tissue degradation to enable assessment of the effectiveness of novel treatments.

The aim of this signal-searching study was to make a preliminary evaluation of the efficacy and safety of AZD9668, versus placebo, in patients with CF, and to examine its effect on biomarkers of inflammation and tissue damage.

**Methods**

**Study design**

This was a randomised, double-blind, placebo-controlled, parallel-group, Phase IIa study (NCT00757848). After a run-in period of up to 4 weeks, patients were randomised to 28 days of treatment with AZD9668 or matching placebo.

**Patients**

Male or female (post-menopausal or surgically sterile) patients, ≥16 years, with a clinical diagnosis of CF, a FEV₁ ≥40% predicted value, normal laboratory values, and normal renal function (glomerular filtration rate of >70 mL/min) were eligible. Exclusion criteria included any non-CF-related lung disease which could interfere with study assessments.

**Treatments**

Patients were randomised (1:1) via a computer-generated randomisation scheme, to AZD9668 60 mg twice daily (bid) or matching placebo. The dose selected was close to the maximum used in prior healthy volunteer studies with AZD9668 [14]. Standard
CF therapies were continued; oral corticosteroids and non-prophylactic antibiotics were not allowed during the study and for 8 and 4 weeks, respectively, prior to randomisation.

**Assessments**

Primary endpoints were: sputum absolute and percentage neutrophil counts; 24-h sputum weight; lung function; BronkoTest® diary card data; and quality-of-life (QoL) measured on the revised CF QoL questionnaire (CFQ-R) [15].

Secondary endpoints were: sputum NE activity; sputum inflammatory biomarkers; blood inflammatory biomarkers; urinary desmosine; safety; and AZD9668 concentration in plasma and induced sputum. Plasma desmosine was an exploratory outcome.

For sputum biomarkers, the average of the two baseline induced sputum samples obtained at baseline (Visits 1a and 2) was compared with the average of the two samples taken during the last week on treatment (Visit 3a and 4 – Figure 1). The average value of the two measurements was used to reduce the variance of the estimates of the biomarkers.

**Statistical analyses**

For neutrophil count and biomarker data, analysis of covariance (ANCOVA) was used to determine the ratio of AZD9668:placebo. Baseline data (log scale) and country were included as covariates. For other efficacy outcomes, ANCOVA was used to analyse differences in the change from baseline to Day 28 between AZD9668 and placebo, where treatment and country were fixed factors and baseline values were the covariate.
As this was an exploratory study, sample size was not based on obtaining power to
detect specific effects. Assuming a standard deviation of 1 for logged data, such that a
50% decrease in neutrophil numbers in the sputum would not be missed (80% power),
a sample size of 40 patients (20 per treatment group) was considered sufficient and a
2-sided P-value of <0.1, statistically significant. There was no adjustment for
multiplicity of tests.

**Ethical aspects**

The study protocol and amendments were approved by an independent ethics
committee and were in accordance with the Declaration of Helsinki and the
International Conference on Harmonisation/Good Clinical Practice. All patients
provided their informed consent.

Further methodological detail on exclusion criteria, prohibited treatments, sputum
sampling, biomarker analysis and assessment timelines can be found in the
Supplementary Material.

**Results**

**Patients**

The first patient was enrolled on 30 October, 2008, and the last patient completed the
study on 4 August, 2009. A total of 70 patients were enrolled in the study and 56 were
randomised to treatment: 29 received placebo and 27 received AZD9668 60 mg bid.
Of those patients randomised to treatment, 27 (93%) placebo patients and 24 (89%)
AZD9668 patients completed the study. The disposition of patients is shown in Figure
2.
All patients in the placebo group received at least one dose of study treatment and had post-dose efficacy data (safety and efficacy analysis sets, N=29). One patient in the AZD9668 group did not receive any study medication following randomisation and was excluded from the safety and efficacy analysis sets. A further patient in the AZD9668 group did not have post-dose efficacy data and was excluded from the efficacy analysis set. Therefore, for the AZD9668 group, the safety analysis set had 26 patients and the efficacy analysis set had 25.

Overall, the two treatment groups were well-matched for the majority of the demographic and patient characteristics (Table 1). There was only one female in the study. FEV₁ was lower, both at screening and randomisation, in the group receiving AZD9668.

**Primary outcome variables**

**Absolute and percent neutrophil counts**

At the end of treatment, the geometric mean absolute neutrophil count was lower in the placebo group (11.13 x 10⁶/g) than in the AZD9668 group (14.10 x 10⁶/g); however, the ratio between groups was not statistically significantly different, 0.97 (90% confidence interval [CI]: 0.69, 1.38; \( P = 0.891 \)) (Table 2a). Similarly, there was no statistically significant difference between AZD9668 and placebo for percentage neutrophil count at end of treatment - least squares mean difference 1.25% (90% CI: -2.53, 5.04; \( P = 0.581 \)) (Table 2b). Individual patient data for the changes from baseline in neutrophil counts are shown in Figure E1, Supplementary Material.
Sputum weight and lung function

Analysis of 24-h sputum weight, FEV$_1$, slow vital capacity (SVC), forced vital capacity (FVC), forced expiratory flow between 25% to 75% (FEF$_{25\%-75\%}$), and percentage predicted FEV$_1$ showed no statistically significant differences between groups (Table E1 and Figure E2 Supplementary Material) and there was no difference in lung function variables measured daily at home (BronkoTest® diary card data) (Table E1).

Signs and symptoms of CF

There were no statistically significant differences between the treatment groups for respiratory symptom scores or use of reliever medication (Table E1). During the study, antibiotics/steroids were used by up to 7 (24%) patients in the placebo group and 10 (40%) in the AZD9668 group. Concomitant medication use is summarised in the Supplementary Material. There were no statistically significant changes in individual CFQ-R categories with the exception of ‘emotion’ ($P < 0.05$) and ‘eat’ ($P < 0.1$), where deteriorations were recorded in the AZD9668 group (Table E1).

Secondary outcome variables

NE activity in sputum

Geometric mean baseline NE activity was higher in the AZD9668 than the placebo group. The ratios of NE activity at the end of treatment showed an increase (51%) in the placebo group and a decrease (5%) in the AZD9668 group. There was a 37% reduction in NE activity in the AZD9668 group versus the placebo group (ratio 0.63, [90% CI: 0.30, 1.31]), however, this was not statistically significant ($P = 0.292$)
(Table 3). Individual patient data for the changes from baseline in NE activity are shown in Figure E3, Supplementary Material.

**Inflammatory biomarkers**

Overall, there was a trend towards a reduction in all of the measured sputum inflammatory biomarkers except leukotriene B₄ (LTB₄) (i.e., tumour necrosis factor alpha [TNFα], IL-6, IL-8, IL-1β, RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted), monocyte chemoattractant protein-1 [MCP-1]) in the AZD9668 group and the changes were statistically significant for IL-6 ($P < 0.01$) and RANTES ($P \leq 0.1$) (Figure 3; Table E2 Supplementary Material). There were no statistically significant differences between the groups in changes in blood inflammatory biomarkers (data not shown).

**Desmosine**

Desmosine at baseline and changes from baseline are shown in Figure 4a. Statistically significant reductions in both free and total urinary desmosine occurred in the AZD9668 group; free and total urine desmosine (normalised for creatinine) were reduced by 30% ($P < 0.01$) and 31% ($P < 0.05$), respectively (Table 3; Figure 4b). Plasma desmosine was also reduced by 16% in the AZD9668 group compared with placebo but this reduction was not statistically significant ($P = 0.146$).

**Safety**

Overall, 14 (48%) patients reported treatment-emergent adverse events (AEs) in the placebo group compared with 12 (46%) in the AZD9668 group (Table E3...
Supplementary Material): in total there were 54 and 32 AEs reported in the placebo and AZD9668 groups, respectively.

Two patients, both in the placebo group, reported serious AEs (pulmonary exacerbation and pneumonia) and two patients in the placebo group discontinued treatment due to an AE (non-cardiac chest pain and pneumonia). There were no deaths or other significant AEs (Table E3 Supplementary Material).

In general, the AE profile (by preferred term) was similar between the treatment groups. The most commonly reported AE was headache, which was reported by a greater number of patients in the AZD9668 group than in the placebo group (Table E3 Supplementary Material).

There were no clinically significant differences between groups in sputum bacteriology, haematology or clinical chemistry parameters, vital signs, electrocardiogram, or physical examinations. One patient in the AZD9668 group showed a rise in creatinine phosphokinase, alanine transaminase, aspartate transaminase, and lactic dehydrogenase peaking on Days 7 and 28 of treatment. Heavy exercise was temporally associated with the initial increase; however, insufficient information was available to explain the second increase at Day 28, meaning that a relationship to study drug cannot be excluded.

**AZD9668 in sputum and plasma**

Concentrations of AZD9668 measured in plasma and sputum supernatant samples confirmed that the AZD9668 levels were comparable to a previous study in patients with bronchiectasis [16].
Discussion

Treatment with AZD9668 60 mg bid over 28 days had no effect on symptoms, lung function, sputum neutrophil count, sputum weight, or sputum NE activity, in patients with CF, compared with placebo. However, with the exception of LTB₄, AZD9668 treatment did result in a consistent pattern of reduction in sputum inflammatory biomarkers, which was statistically significant for IL-6 and RANTES. AZD9668 treatment also significantly decreased free and total urine desmosine, biomarkers of elastin degradation. There was also a reduction in plasma desmosine in the AZD9668 group, although the difference versus placebo was not significant. AZD9668 was generally well tolerated throughout.

Given the proteolytic activity of sputum in CF disease, there is significant interest in identifying biomarkers that indicate the extent of airway inflammation and lung tissue damage in CF. A biomarker of structural injury may enable earlier intervention and the ability to monitor lung tissue changes during the course of the disease. Desmosine, a cross-linking amino acid present in elastin is released during matrix degradation and can be detected in sputum, blood, and urine of COPD patients [17-20] and has been considered as a potential biomarker of lung tissue injury. Our study demonstrated consistent reductions in urinary and plasma desmosine in response to AZD9668 treatment and is one of few studies where a therapeutic agent has shown a positive effect on desmosine levels, suggesting AZD9668 may have disease-modifying potential in neutrophil-driven disease states. (A related NE inhibitor, ZD0892, also reduced desmosine levels in lavage fluid in a guinea pig model of smoke-induced emphysema [11]). Another CF patient study measured desmosine in the sputum of patients hospitalised for treatment of a pulmonary exacerbation and found that sputum
desmosine levels decreased significantly during the first week of hospitalisation ($P = 0.04$) [21]. Desmosine levels were also positively correlated with decreases in plasma C-reactive protein ($P = 0.03$), sputum IL-8 ($P < 0.01$), and sputum NE protein ($P < 0.01$). In a study of 39 patients with CF, Downey and colleagues showed an inverse correlation between urinary desmosine levels and survival where analysis of data taken from patients one year after the start of the study showed significantly higher levels of urinary desmosine in non-survivors compared with survivors ($P < 0.0001$) [22]. There is also evidence that the urinary excretion of desmosine is increased in smokers and in COPD patients [20, 23, 24]. A recent study from the Swedish Twin Registry evaluated the relationship between desmosine and lung function [25]. This study found that, urinary desmosine was significantly and inversely correlated with FEV$_1$, FVC and the diffusion capacity for carbon monoxide, and positively correlated with residual volume (RV) and RV/total lung capacity, and that the correlations were markedly stronger in subjects with COPD.

The current study also showed that AZD9668 treatment resulted in a consistent pattern of reduction in sputum inflammatory biomarkers. No treatment effect was observed for plasma inflammatory biomarkers. The results for the plasma inflammatory biomarkers are consistent with the assessments in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study which reported weak associations between neutrophil measurements in sputum and blood and systemic biomarkers [26]. Biomarker analysis in studies of NE inhibitors is also challenging because appropriate biomarkers for inhibition of NE associated with a clinically meaningful anti-inflammatory effect, are currently unknown.

The lack of effect of AZD9668 on neutrophil counts, NE activity and lung function measures observed in the current study could be for various reasons. Our study was a
short, signal-searching, proof-of-principle study, carried out in a small number of patients, and was associated with large inter-individual variation resulting in large CIs. The study duration was most likely too short and not powered to investigate disease-modifying effects of AZD9668. Longer study durations are often needed before an impact on lung function and endpoints such as QoL can be detected. Previous analyses in patients with bronchiectasis have demonstrated the presence of AZD9668 in plasma and sputum supernatants at expected concentrations [16] and the measured concentrations of AZD9668 in plasma and sputum in our study confirmed exposure at pharmacologically relevant levels, predicted to inhibit NE. However, one possibility that needs to be considered is that higher concentrations of AZD9668 would be required to reach a sufficient level of NE inactivation in the airways. Other possibilities are that AZD9668 may not be reaching its site of action or being inactivated at its site of action. It is known that inactivation of endogenous inhibitors of NE, such as α1-antitrypsin, can occur due to oxidants present in lung tissue [27, 28], although it is unclear if a small molecule drug is susceptible to similar inactivation processes in patients.

Another possible reason for the lack of an effect could be related to its target specificity. AZD9668 has been shown to selectively target NE [13], however, airway inflammation and proteolytic activity is driven by a number of different mechanisms and several other neutrophilic proteases. For example, high levels of cathepsin G and proteinase 3 have been identified in bronchoalveolar lavage fluid of CF patients [29, 30]. In addition, the neutrophil metalloproteases, collagenase (MMP-8) and gelatinase (MMP-9), released under inflammatory conditions, have also been detected in high concentrations in the bronchoalveolar lavage fluid from CF patients [31, 32]. As AZD9668 demonstrates in vivo anti-inflammatory effects [13], it is possible that it
could affect NE-independent anti-inflammatory pathways leading to a reduction in inflammatory biomarkers as well as a reduction in the levels of desmosine.

A further explanation is that NE damages extracellular matrix in the process of transmigration. It is generally assumed that the high concentrations of NE result in proteolytic damage to matrix proteins. However, as elastase is released during neutrophil migration from the circulation into the airway, it is possible that due to increased priming they release more NE or that the increased number of neutrophils results in more NE. It is therefore possible that AZD9668 is more active in the extracellular matrix than in the airway where concentrations of NE are very much greater. This could account for the reduction in desmosine concentrations in the absence of much change in neutrophil numbers or NE activity in the airway.

Alternatively, the complex biology of the sputum matrix could have played a role in the high inter-patient variability of the sputum NE assay. This variability, together with a small sample size, could in part explain the trend towards reduced NE activity but lack of statistical significance.

Our results suggest that AZD9668 is safe and well tolerated in patients with CF and has a consistent impact on sputum biomarkers of inflammation, though little effect on NE activity or lung function. These data are similar to those from other studies investigating inhibitors of NE. One pilot study, investigating the safety and efficacy of inhaled recombinant human \( \alpha_1 \)-antitrypsin (an endogenous inhibitor of NE) as a treatment for CF, found that nebulised recombinant \( \alpha_1 \)-antitrypsin was safe and well tolerated, but had a limited effect on absolute sputum NE levels, NE activity, and other markers of inflammation [12]. Another Phase II trial in CF suggested no effect of \( \alpha_1 \)-antitrypsin on pulmonary function (FEV\(_1\)) but did result in an increase in \( \alpha_1 \)-antitrypsin levels and decreases in free NE activity, neutrophil numbers,
Pseudomonas aeruginosa colony forming units, IL-8 and TNFα levels, and intact immunoglobulin G. [4]

The results of the current study are suggestive of an effect of AZD9668 in inflammatory respiratory diseases with a neutrophil-driven component such as CF. Studies of longer duration including more patients are needed to further investigate the impact of AZD9668 on neutrophil numbers, NE activity and lung function, and to confirm the effectiveness of NE inhibition as a therapeutic approach. In addition, these results point to the potential usefulness of desmosine as a biomarker of lung tissue degradation.

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Principal Investigators

Tacjana Pressler: Rigshospitalet, Denmark
Matthias Griese: Ludwig Maximilian University, Germany
Rainald Fischer: Munich University Hospital, Germany
Hans-Eberhard Heuer: Othmarschen Park Children and Youth Medical Practice, Germany
Hubert Wirtz: Leipzig University Hospital, Germany
Burkhard Bewig: Schleswig-Holstein University Hospital, Germany
Henryk Mazurek: Institute of Tuberculosis and Lung Diseases, Poland
Elena Amelina: Roszdrav Pulmonology Research Institute, Russia
Ferenc Karpati: Karolinska University Hospital, Sweden

Lena Mared: Lund University Hospital, Sweden

Annika Hollsing: Uppsala University Hospital, Sweden

Anders Lindblad: Gothenburg Children’s Hospital, Sweden

Marita Gilljam: Sahlgrenska University Hospital, Sweden

Stuart Elborn: Belfast City Hospital, United Kingdom

Martin Walshaw: Liverpool Heart and Chest Hospital, United Kingdom.

References


FIGURE LEGENDS

Figure 1. Flow chart of study design

Figure 2. Patient disposition
Figure 3. Ratios (and 90% confidence interval) for AZD9668 to placebo for the inflammatory biomarkers in induced sputum

Figure 4. A) Individual patient data for urinary desmosine, B) Ratio (and 90% confidence interval) for AZD9668 to placebo for urinary and plasma desmosine
A)

Placebo

AZ09668

Total urinary desmosine (nmol/mmol)

Baseline | Treatment period | End of treatment

Total urinary desmosine (nmol/mmol)

Baseline | Treatment period | End of treatment

B)

Improvement

Deterioration

Free desmosine (urine) normalised for creatine

Total desmosine (urine) normalised for creatine

Desmosine (plasma)

*P = 0.44; **P = 0.002 vs placebo
### Table 1. Demographic and key baseline characteristics (efficacy analysis set)

<table>
<thead>
<tr>
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<th>Treatment Group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=29)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>27 (8.5)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
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<tr>
<td>White</td>
<td>29 (100)</td>
</tr>
<tr>
<td>BMI, Kg/m², median (range)</td>
<td>22.2 (3.2)</td>
</tr>
<tr>
<td>Nicotine use, n (%)*</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>24 (83)</td>
</tr>
<tr>
<td>Current</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Former</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Number of pack years, mean (SD)</td>
<td>6 (5.4)</td>
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<tr>
<td>% predicted FEV₁, mean (SD)</td>
<td>78.4 (23.7)</td>
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<tr>
<td>Cystic fibrosis duration, years, mean (SD)*</td>
<td>19.8 (10.4)</td>
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<tr>
<td>Pancreatic insufficiency, n (%)*</td>
<td>26 (90)</td>
</tr>
<tr>
<td>Cystic fibrosis-related diabetes mellitus, n (%)*</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

*Nicotine use, cystic fibrosis duration, pancreatic insufficiency and diabetes mellitus data are for the safety analysis set (n=26) for patients in the AZD9668 group.
Table 2. Effect of AZD9668 versus placebo on A) absolute neutrophil counts, and B) differential neutrophil counts (up to Day 28) (efficacy analysis set)

A)

<table>
<thead>
<tr>
<th></th>
<th>Gmean at Baseline (CV [%])</th>
<th>Gmean at End of Treatment (CV [%])</th>
<th>Ratio of AZD9668 to Placebo at End of Treatment (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=28)</td>
<td>AZD9668 60 mg bid (n=24)</td>
<td>Placebo (n=28)</td>
</tr>
<tr>
<td>Sputum neutrophils (10⁶/g)</td>
<td>9.00 (228)</td>
<td>13.95 (106)</td>
<td>11.13 (178)</td>
</tr>
</tbody>
</table>

Abbreviations: ANCOVA, analysis of covariance; bid, twice daily; CI, confidence interval; CV, coefficient of variation; Gmean, geometric mean.

B)

<table>
<thead>
<tr>
<th></th>
<th>Mean at Baseline (SD)</th>
<th>Mean at End of Treatment (SD)</th>
<th>Difference Between AZD9668 and Placebo (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=28)</td>
<td>AZD9668 60 mg bid (n=24)</td>
<td>Placebo (n=28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum neutrophils (%)</td>
<td>86.28 (22.28)</td>
<td>95.41 (5.67)</td>
<td>90.19 (16.63)</td>
</tr>
</tbody>
</table>

Abbreviations: ANCOVA, analysis of covariance; bid, twice daily; CI, confidence interval; LSM, least squares mean; SD, standard deviation; SEM, standard error of the mean.
Table 3. Effect of AZD9668 versus placebo on neutrophil elastase activity and desmosine levels at end of treatment (up to Day 28) (safety analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Gmean at Baseline (CV [%])</th>
<th>Gmean at End of Treatment (CV [%])</th>
<th>Ratio of AZD9668 to Placebo at End of Treatment (ANCOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=29)</td>
<td>AZD9668 60 mg bid (n=26)</td>
<td>Placebo (n=29)</td>
</tr>
<tr>
<td>Neutrophil elastase activity (µmol/L AMC/h)*</td>
<td>55.72 (4275)</td>
<td>154.7 (400)</td>
<td>106.7 (746)</td>
</tr>
<tr>
<td>Free desmosine (urine)† (nmol/mmol)</td>
<td>1.75 (53.62)</td>
<td>1.56 (38.83)</td>
<td>2.22 (51.23)</td>
</tr>
<tr>
<td>Total desmosine (urine)‡ (nmol/mmol)</td>
<td>2.56 (64.41)</td>
<td>2.56 (53.01)</td>
<td>2.67 (104.3)</td>
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<tr>
<td>Desmosine (plasma)§ (pmol/L)</td>
<td>85.70 (60.47)</td>
<td>75.08 (59.62)</td>
<td>92.86 (70.90)</td>
</tr>
</tbody>
</table>

Abbreviations: ANCOVA; analysis of covariance; bid, twice daily; CI, confidence interval; CV, coefficient of variation; Gmean, geometric mean.
*Number of patients in the placebo group = 21, and in the AZD9668 group = 17.

†Free desmosine adjusted for creatinine. Number of patients in the placebo group = 25, and in the AZD9668 group = 21.

‡Total desmosine adjusted for creatinine. Number of patients in the placebo group = 27, and in the AZD9668 group = 22.

§Number of patients in the placebo group = 27, and in the AZD9668 group = 23.