# Supplemental Data

## Selection of study population

The patient population was selected without bias. The Investigators kept a record of the patient screening log and of patients who entered pre-study screening.

## Clinic visit methodologies

Visits 1a, 1b, 3a, and 3b were for spontaneous sputum collections at home prior to attending the study visit. Patients attended the clinic in the morning for visits 2, 3, and 4, but were instructed to start a 24-hour sputum collection on rising the day before the scheduled visits and to collect all sputum for the 24 hours until waking prior to the visit. On the day of the visit, patients were requested to collect all sputum produced spontaneously for 2 hours after waking into a separate sample pot. Patients were issued with a patient aid on how to collect sputum samples. Immediately after finishing collection of this sample, it was transported rapidly for sputum processing. If the spontaneous sputum sample was of limited volume, priority was given to cytospin production for cell counts over pharmacodynamic biomarker analysis. The 24-hour samples only had volume measured.

Spirometric lung function tests and sampling for blood pharmacodynamic biomarkers were performed at clinic visits 2 and 4. Patients were asked to withhold use of long-acting bronchodilators for 12 hours, short-acting β-agonists for 6 hours and ipratropium for 8 hours prior to lung function testing.

## Randomisation

Patients were assigned by the investigators to treatment groups using Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Routines for this were described in the IVRS/IWRS user manual that was provided to each site. Randomisation codes were only assigned to patients who were eligible for randomisation.

Randomisation was stratified for:

1) use of inhaled corticosteroids (yes/no) and

2) *P. aeruginosa* infection (past or current).

Patients were randomly allocated to AZD5069 80 mg bd or placebo in a 1:1 ratio. Patients who were withdrawn after randomisation were not replaced.

Individual treatment codes, indicating the treatment randomisation for each randomised patient, were available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this were described in the IVRS/IWRS user manual that was provided to each site. A copy of the randomisation scheme was also made available to the pharmacokineticist, to enable the analysis of samples from patients who received active treatment to be prioritized. This documentation was placed in a secure location until the end of the study. The treatment code was not to be broken except in medical emergencies when the appropriate management of the patient required knowledge of the treatment randomisation. The Investigator was to document and report the action to AstraZeneca or AstraZeneca's representative and study medical monitor, without revealing the treatment given to the patient to the AstraZeneca staff.

## Inclusion criteria:

For inclusion in the study patients fulfilled the following criteria:

1. Provision of informed consent prior to any study-specific procedures.

2. Male, or female of non-childbearing potential; ie, women who were permanently or surgically sterilised or post-menopausal.

Women were considered post-menopausal if they were:

(i) under 50 years of age and had been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range;

or

(ii) over 50 years old and had been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

Permanent sterilisation was defined as having undergone hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy; bilateral tubal occlusion on its own was not adequate.

3. Aged 18 to 80 years inclusive at screening (Visit 1).

4. Had a clinical diagnosis of idiopathic or post infective bronchiectasis as diagnosed with a historical HRCT or bronchogram.

5. Had been sputum producers with a history of chronic expectoration on most days of most weeks of the year. Patients should have had a history of spontaneously producing sputum on a daily basis and should have been able to provide at least 2 of the 3 required baseline sputum samples with an average of 3 mL or more.

6. Had been on a stable treatment regimen, as judged by the Investigator.

## Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Any clinically significant disease or disorder (e.g. cardiovascular, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either have put the patient at risk because of participation in the study, or may have influenced the absorption, distribution, metabolism and excretion of drugs.

2. Patients with known human immunodeficiency virus (HIV) or who belonged to a high-risk group for HIV infection.

3. Evidence of serum hepatitis or presence of hepatitis B surface antigen or hepatitis C antibodies.

4. Patients with other latent or chronic infections (e.g. recurrent sinusitis, urinary tract infection) or at risk of infection (surgery, trauma, significant infection within 90 days before Visit 2, history of skin abscesses or soft tissue infection within 90 days before Visit 2 or in the opinion of the Investigator patients in regular contact with active pulmonary tuberculosis).

5. An acute exacerbation (defined as an increase in respiratory symptoms requiring hospitalization and/or a course of oral glucocorticosteroids and/or antibiotics, either prescribed or self-administered); or acute respiratory infection (upper or lower) requiring oral steroids or antibiotics within 30 days prior to Visit 2.

6. A forced expiratory volume in the first second ($FEV_1$) of <30% of predicted normal at Visit 1.

7. Patients who had received live or live-attenuated vaccine in the 2 weeks prior to dosing (Visit 2).

8. Concomitant diagnosis of significant pulmonary disease other than bronchiectasis or chronic obstructive pulmonary disease (COPD), including symptomatic asthma and allergic bronchopulmonary aspergillosis.

9. Bronchiectasis associated with a generalised immunodeficiency, where manifestations other than bronchiectasis predominate.

10. Any clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, urinalysis, vital signs or 12-lead electrocardiogram (ECG) at baseline (Visit 1), which, in the opinion of the Investigator, may have either put the patient at risk because of participation in the study, or may have influenced the results of the study, or the patient's ability to participate in the study.

11. Patients who had a clinically significant illness within 4 weeks before Visit 2 as determined by the Investigator.

12. Blood donation of more than 500 mL during the previous 12 weeks before Visit 2 and more than 50 mL in the 2 weeks before Visit 2.

13. Known or suspected hypersensitivity to the investigational product or any excipients or a compound of the same class.

14. Current evidence of drug abuse or significant history of drug abuse as judged by the Investigator.

15. Current evidence of alcohol abuse or significant history of alcohol abuse as judged by the Investigator.

16. Participation (defined as administration of at least 1 dose of an investigational product) in another clinical study within 12 weeks preceding Visit 2.

17. Patients who, in the opinion of the Investigator, should not participate in the study.

18. Previous exposure to AZD5069.

19. Scheduled inpatient surgery or hospitalisation during the study.

20. Pregnancy or breast-feeding during the study.

21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

22. Previous randomisation to treatment in the study.

23. Other acute infections requiring treatment in the 4 weeks prior to Visit 2.

24. Use of prohibited medications as detailed in Sections 5.4.5.2 and 5.4.5.3 of the CSP.

25. Patients who were receiving immunosuppressive medication such as oral or systemic corticosteroids.

26. Patients with active malignancy or who had had such a condition in the past 12 months.

27. Peripheral blood neutrophils below the laboratory normal reference range at Visit 1.

28. Serum creatinine above the upper limit of the reference range at screening (Visit 1).

29. Patients with active or latent tuberculosis, as judged by the Investigator.

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**Regulatory agencies**

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Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

United Kingdom: Medicines and Healthcare Products Regulatory Agency

## Table 1a. Descriptive statistics for absolute neutrophil cell count in sputum – PD analysis set

| | | Absolute neutrophil values ($10^6$/g) | | | | | | Ratio of end of treatment to baseline | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment group | Treatment period | n | Geo mean | CV (%) | Median | Min | Max | n | Ratio | CV (%) | Min | Max |
| Placebo | Baseline | 26 | 3.9 | 197.9 | 3.9 | 0.4 | 55.2 | | | | | |
| | End of treatment | 24 | 3.9 | 284.0 | 4.4 | 0.1 | 65.1 | 24 | 1.0 | 145.3 | 0.2 | 15.9 |
| AZD5069 80 mg | Baseline | 23 | 5.5 | 282.9 | 7.9 | 0.1 | 34.1 | | | | | |
| | End of treatment | 20 | 1.9 | 293.7 | 2.7 | 0.1 | 16.7 | 19 | 0.3 | 422.1 | 0.0 | 11.9 |

## Table 1b. Analysis of absolute sputum neutrophil cell counts - PD analysis set

| | | Baseline | | | End of treatment | | | Analysis of covariance | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Ratio of end of treatment to baseline | | | Ratio of AZD5069 80 mg to placebo | | | |
| Variable | Treatment group | n | Geo mean | CV (%) | n | Geo mean | CV (%) | n | Ratio | 90% CI | n | Ratio | 90% CI | p-value |
| Neutrophils ($10^6$/g) | Placebo | 24 | 3.7 | 213.3 | 24 | 3.9 | 284.0 | 24 | 1.0 | (0.7,1.5) | | | | |
| | AZD5069 80 mg | 19 | 7.2 | 165.9 | 19 | 2.1 | 279.9 | 19 | 0.3 | (0.2,0.5) | 43 | 0.31 | (0.2,0.6) | 0.004 |

## Table 2. Patients who had an adverse event leading to discontinuation of AZD5069 – safety analysis set

| Enrolment Number | Treatment | Blood Neutrophils ($10^9$/L) (Study Day) [a] | MedDRA [b] Preferred term | Start of AE (day)/ Duration of AE (days) [c] | Intensity | SAE | IC, PAI | Causality [d] | Outcome of AE |
|---|---|---|---|---|---|---|---|---|---|
| E1007002 | AZD5069 80 mg | 4.12 (-20)<br>2.22 (1)<br>2.34 (3)<br>1.66 (8)<br>3.28 (16)<br>3.03 (22) | Infective exacerbation of bronchiectasis | 10/ | Moderate | No | Yes, Yes | No | Recovering/resolving |
| E1003007 | AZD5069 80 mg | 10.97 (-21)<br>7.14 (1)<br>4.17 (3)<br>3.11 (8)<br>5.31 (15) | Chest discomfort | 4/9 | Moderate | No | Yes, No | No | Recovered/resolved |
| | | | Lower respiratory tract infection | 1/12 | Moderate | No | Yes, No | No | Recovered/resolved |
| E2000002 | AZD5069 80 mg | 6.46 (-14)<br>5.40 (1)<br>5.07 (3)<br>5.55 (21) | Blood pressure increased | 1/2 | Moderate | No | Yes, No | Yes | Recovered/resolved |
| | | | Headache | 1/2 | Moderate | No | Yes, No | Yes | Recovered/resolved |
| | | | Insomnia | 1/2 | Moderate | No | Yes, No | Yes | Recovered/resolved |
| | | | Non-cardiac chest pain | 1/2 | Moderate | No | Yes, No | Yes | Recovered/resolved |
| E1003002 | AZD5069 80 mg | 5.40 (-11)<br>7.02 (1)<br>3.39 (3)<br>3.07 (8)<br>3.99 (17)<br>10.68 (22) | Lower respiratory tract infection bacterial | 12/ | Severe | No | No, No | No | Not recovered/not resolved |
| E3000002 | AZD5069 80 mg | 5.10 (-20)<br>3.90 (1)<br>2.20 (3)<br>3.30 (13)<br>4.30 (28) | Infective exacerbation of bronchiectasis | 13/11 | Severe | Yes | No, No | No | Recovered/resolved |
| | | | Pneumonia | 13/16 | Moderate | No | No, No | No | Recovered/resolved |

AE = adverse event, IC = inhaled corticosteroid use, ND = not determined, PAI = *P. aeruginosa* infection (past or current).

[a] Onset day is given in relation to first dose.

[b] MedDRA version 14.1.

[c] Onset day is given in relation to first dose. A negative onset day indicates that the AE started before first dose.

[d] Causality as judged by the Investigator.