AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5069
Study Code	D3550C00014
Edition Number	1
Date	

A Phase II Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28-Day Oral Administration of AZD5069 Twice Daily in Patients with Bronchiectasis

Study dates:	First patient enrolled: 27 December 2010 Last patient last visit: 13 February 2012
Phase of development:	Therapeutic exploratory (II)
International Coordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective was to investigate the effect of AZD5069 on absolute neutrophil cell count in the sputum of bronchiectasis patients	Absolute neutrophil cell count in sputum	Efficacy
Secondary	**Secondary**	
To investigate the effect of AZD5069 on percentage neutrophil cell count in the sputum of bronchiectasis patients	Percentage neutrophil cell count in sputum 24-hour sputum weight Lung function tests Baseline Dyspnea Index (BDI)/ Transition Dyspnea Index (TDI)	Efficacy
To investigate the effect of AZD5069 on signs and symptoms of bronchiectasis (including effects on quality of life)	Bronkotest© diary card St George's Respiratory Questionnaire for COPD patients (SGRQ-C)	Patient-reported outcomes (PRO)
To investigate the plasma pharmacokinetics of AZD5069 in bronchiectasis patients	Determination of drug concentration	Pharmacokinetic (PK)
To investigate the effect of AZD5069 on other inflammatory markers in sputum	Tumor necrosis factor alpha (TNF-α), interleukin-8 (IL-8), IL-6, IL-1β, regulated on activation, normal T cell expressed and secreted (RANTES), monocyte chemoattractant protein (MCP-1), Growth-related oncogene-α (GRO-α)	Pharmacodynamic (PD)
To investigate the effect of AZD5069 on inflammatory markers in blood	Amyloid-A and high-sensitivity C-reactive protein (hsCRP) in serum; TNF-α, IL-8, IL-6, IL-1β and GRO-α in plasma	PD
To investigate the safety and tolerability of 28 day dosing with AZD5069 in bronchiectasis patients	Vital signs, physical examination, body temperature, 12 lead ECG, hematology, clinical chemistry, urinalysis, sputum quantitative microbiological analysis, adverse events (AEs)	Safety

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
To investigate the PK-PD relationship of AZD5069 in bronchiectasis patients	Calculation or derivation of the relationship between PK and PD variables Markers of mucus hyper-secretion Sputum bacterial count	Exploratory
To investigate how genetic variation of bronchiectasis patients may influence response to AZD5069	DNA	Exploratory

Study design

This was a randomized, double-blind, placebo-controlled, parallel group study in patients with bronchiectasis.

Target subject population and sample size

Patients (18 to 80 years, inclusive) with a clinical diagnosis of idiopathic or post infective bronchiectasis as diagnosed with a historical high resolution computerized tomography (HRCT) or bronchogram. (Note: per Amendment 2, 18 to 65 years of age for only Czech Republic.)

It was estimated that 25 patients in each treatment group would be required to detect a 50% decrease in neutrophils, using a 1-sided test with a 5% significance level and 80% power.

Planned: 30 patients each for AZD5069 and placebo groups (60 patients overall).

Analyzed: 26 patients, AZD5069; 26 patients, placebo (52 patients overall).

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product (IP): AZD5069, 80 mg twice a day (bd) orally.

Comparator: Placebo, bd orally.

Batch numbers

AZD5069: 10-002480AZ, 10-004820AZ

Placebo: 08-001091AZ

Duration of treatment

The duration of treatment was 4 weeks.

Statistical methods

The primary efficacy variable was the relative change from baseline (geometric mean of the values at visit 1a, 1b and 2) to end of treatment (geometric mean of the values at visit 3a, 3b and 4) for absolute neutrophil cell count in sputum.

To evaluate the effect on absolute neutrophil cell count in sputum of AZD5069 compared with placebo, an analysis of covariance (ANCOVA) has been fitted to the data with log (absolute neutrophil cell count in sputum at end of treatment) – log (absolute neutrophil cell count in sputum at baseline) as the response variable, log (absolute neutrophil cell count in sputum at baseline) has been included as a continuous covariate, treatment as a factor with 2 levels (placebo group as reference), inhaled corticosteroids as a factor, and *P. aeruginosa* infection as a factor.

This analysis was performed on the PD analysis set.

Subject population

Fifty-two patients were randomized in a 1:1 ratio between placebo (26 patients) and AZD5069 (26 patients). Twenty patients taking AZD5069 and 25 patients taking placebo completed treatment. All patients who completed treatment also completed the study. Six patients taking AZD5069 and 1 patient taking placebo discontinued the study. There were more females in the AZD5069 treatment group (61.5%, 16 patients) compared with the placebo group (46.2%, 12 patients). All patients were white. The treatment groups were generally balanced in terms of demographic and baseline characteristics (Table S2).

Table S2 Demographic characteristics

Demographic characteristic	Number (%) of patients		
	Placebo (N=26)	**AZD5069 80 mg (N=26)**	**Total (N=52)**
Age (years)			
Mean	65	66	65
SD	8.8	6.6	7.7
Sex n (%)			
Female	12 (46.2%)	16 (61.5%)	28 (53.8%)
Male	14 (53.8%)	10 (38.5%)	24 (46.2%)
Duration of bronchiectasis (years) [a]			
Mean	13	22	17.5
SD	21.8	22.9	22.64
Median	4	8	6
Min	0	0	0
Max	68	63	68

Table S2 Demographic characteristics

Demographic characteristic	Number (%) of patients		
	Placebo (N=26)	AZD5069 80 mg (N=26)	Total (N=52)
Type of bronchiectasis			
Purulent sputum (*Pseudomonas*)	4 (15.4%)	6 (23.1%)	10 (19.2%)
Purulent sputum (non-*Pseudomonas*)	16 (61.5%)	17 (65.4%)	33 (63.5%)
Mucoid sputum	5 (19.2%)	3 (11.5%)	8 (15.4%)
Lung function (FEV_1 on Day 1) (L)			
Mean	1.88	1.52	
SD	0.959	0.535	
Median	1.78	1.42	
Min	0.80	0.78	
Max	5.39	2.75	
Nicotine use			
Never	14 (53.8%)	12 (46.2%)	26 (50.0%)
Former	10 (38.5%)	10 (38.5%)	20 (38.5%)
Current	2 (7.7%)	4 (15.4%)	6 (11.5%)

[a] Duration of bronchiectasis is calculated as the date of screening minus the date bronchiectasis first appeared.

Summary of efficacy results

The primary objective of the study was to investigate the effect of AZD5069 on absolute neutrophil cell count in the sputum of bronchiectasis patients. The data show that there was a statistically significant reduction in absolute neutrophil cell count (69%) in the sputum of patients taking AZD5069 when compared with placebo (p=0.004). The results for the same analysis excluding early withdrawals had similar results. The mean percentage sputum neutrophil counts were similar for patients in both treatment groups at baseline but were more greatly reduced over time in the AZD5069 group.

There were no clinically relevant effects on 24-hour sputum weights, clinic lung function tests, TDI, symptom scores derived from Bronkotest diary card or SGRQ-C for AZD5069 compared with placebo.

Summary of pharmacokinetic results

The AZD5069 plasma concentrations in bronchiectasis patients were in the same range as those previously observed in patients with COPD (D3550C00002/CIRRUS study).

Summary of pharmacodynamic results

The analysis of inflammatory markers in sputum showed statistically significant increase differences between the treatment groups for levels of IL-6 and GRO-α with patients on AZD5069 having greater changes from baseline. Likewise for inflammatory markers in serum, there were statistically significant differences between the treatment groups for levels of GRO-α, IL-1β, and IL-8, with patients on AZD5069 having greater changes from baseline.

No other changes were observed in the inflammatory marker analysis. Notably, there were no significant concomitant increases in CRP.

Summary of safety results

A higher proportion of patients taking AZD5069 reported an AE. Twenty-three patients taking AZD5069 and 16 patients taking placebo had at least 1 AE. In patients taking AZD5069, 1 reported a SAE (infective exacerbation of bronchiectasis) and 5 patients reported an AE that led to discontinuation of study drug (2 patients with infective exacerbation of bronchiectasis, 2 patients with lower respiratory tract infection, and 1 patient with blood pressure increased, headache, insomnia, and non-cardiac chest pain). No patients taking placebo reported a SAE or discontinued study drug due to an AE. There were no deaths or other significant AEs in either treatment group.

The most commonly reported AEs were infections and infestations (9 patients) and respiratory, thoracic, and mediastinal disorders (9 patients) by patients taking AZD5069 and were reported in a similar number of patients taking placebo (8 patients, infections and infestations; 5 patients, respiratory, thoracic, and mediastinal disorders). Cough was the most frequently reported AE by patients taking AZD5069 (6 patients) and was reported by 1 patient taking placebo, followed by headache (5 patients and 3 patients, respectively), rhinorrhea (4 patients and 1 patient, respectively), and diarrhea (3 patients and no patient, respectively). Infective exacerbation of bronchiectasis, non-cardiac chest pain, and dyspepsia were reported by the same number of patients taking AZD5069 and placebo (2 patients per treatment group per AE). Nasopharyngitis was reported in more patients taking placebo (5 patients) than AZD5069 (3 patients).

Patients taking AZD5069 had reduced blood neutrophils during treatment; however, no patients discontinued the study due to low neutrophils. Other laboratory values for hematology and clinical chemistry were unremarkable. Vital signs, ECGs, and physical examination findings did not raise any safety concerns.

Conclusions