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Efficacy and safety of AZD1981, a CRTH2 receptor antagonist, in patients with moderate to severe COPD

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Summary
Objective: To evaluate the efficacy and tolerability of the selective CRTh2 (DP2) receptor antagonist AZD1981 compared with placebo in patients with moderate to severe COPD.
Methods: In this multicentre, randomised, double-blind, parallel-group, phase IIa study (ClinicalTrials.gov identifier: NCT00690482) patients with moderate to severe COPD received either AZD1981 1000 mg twice daily or matching placebo for 4 weeks. Inhaled terbutaline was used as-needed as reliever medication throughout. The co-primary endpoints were change from baseline to end of treatment in pre-bronchodilator forced expiratory volume in 1 s [FEV_1] and the Clinical COPD Questionnaire (CCQ). Additional endpoints included other lung function measures, 6-min walk test (6-MWT), COPD symptom score, reliever medication use and tolerability.
Results: 118 patients were randomised to treatment (AZD1981 $n = 61$; placebo $n = 57$); 83% of patients were male and the mean age was 63 years (range 43–83). There were no significant differences in the mean difference in change from baseline to end of treatment between AZD1981 and placebo for the co-primary endpoints of pre-bronchodilator FEV_1 (AZD1981 −placebo: −0.015, 95% CI: −0.10 to 0.070; $p = 0.72$) and CCQ total score (difference: 0.042, 95% CI: −0.21 to 0.30; $p = 0.75$). Similarly, no differences were observed between treatments for the other outcomes of lung function, COPD symptom score, 6-MWT, BODE index, and use of reliever medication. AZD1981 was well tolerated.

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Conclusion: There was no beneficial clinical effect of AZD1981, at a dose of 1000 mg twice daily for 4 weeks, in patients with moderate to severe COPD. AZD1981 was well tolerated and no safety concerns were identified.

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease characterised by airflow limitation that is not fully reversible, and often excessive mucus production and cough [1]. The airflow limitation characteristic of COPD is associated with an exaggerated inflammatory response of the lungs to noxious particles or gases including tobacco smoke [2,3]; the resulting damage includes disruption of the mucosal barrier and increased bronchiolitis and vasculitis.

Current first-line pharmacological therapies for COPD focus on the use of bronchodilators, with added inhaled corticosteroids in patients at risk of exacerbations. The oral phosphodiesterase IV (PDE4) inhibitor, roflumilast, can be used in patients with severe airflow limitation, frequent exacerbations and chronic bronchitis further to reduce the risk of exacerbations. These treatments provide some symptomatic relief but there are no current marketed therapies that have been shown to alter mucosal integrity, vascular or parenchymal changes or to alter inflammatory status in COPD patients. As such, there is no therapy available apart from smoking cessation that consistently modulates disease progression.

The chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) receptor (previously known as DP2) is highly expressed on human Th2 cells (but not Th1 cells), eosinophils, basophils and a subset of monocytes [4–6]; blocking the endogenous ligand (prostaglandin D_2) at this receptor inhibits chemotaxis in these cells [7]. Hence the CRTh2 receptor is a potential therapeutic target in allergic disorders of the respiratory tract. Several CRTh2 antagonists have progressed into clinical studies [8–10] and preliminary reports describe positive effects on reducing allergen-induced eosinophil count and circulating IgE levels in asthmatic patients [11].

Preclinical data have also shown that CRTh2 antagonism inhibited tobacco-smoke-induced inflammation and mucosal damage including mucus cell metaplasia and epithelial hyperplasia in a mouse model of inflammation [12,13]. CRTh2 receptor expression has been observed in COPD lung tissue, on mononuclear infiltrates and respiratory mucosal epithelial cells (see Methods and Results sections). Hence, inhibition of the CRTh2 receptor could also provide therapeutic benefits to patients with COPD via a new mechanism; the theoretical basis for this has been argued by Stebbins et al. [14]. Indeed, the dual thromboxane and CRTh2 receptor antagonist seratrodast has been reported to improve lung function in an 8-week study in a cohort of patients with chronic pulmonary emphysema [15].

AZD1981 is an oral, non-steroidal, CRTh2 receptor antagonist [16,17] that was well-tolerated in phase I trials and has been studied in asthma patients [18]. The aim of this phase IIa study was to evaluate the efficacy and tolerability of AZD1981 compared with placebo in patients with moderate to severe COPD.

Methods

Expression of CRTh2 receptor in COPD lung

As a preliminary to the clinical trial, CRTh2 receptor expression was examined in a range of COPD human lung resections showing a wide range of cellular pathology changes from minimal to severe. In brief, immunohistochemistry was employed on formalin-fixed, paraffin-embedded sections from tissue obtained from lung volume reduction surgery ($n = 8$) and lobectomy ($n = 4$) procedures. A rabbit anti-human primary antibody (Cambridge Research Biochemicals) was used at a working concentration of 0.0108 mg/mL with a biotinylated swine anti-rabbit employed as secondary. Detection of signal was StepABC Complex/HRP (DAKO) with DAB chromogenic detection (DAKO).

Clinical trial design

This was a randomised, double-blind, placebo-controlled, parallel-group, phase IIa, 4-week study (Study code: D9831C00001; ClinicalTrials.gov identifier: NCT00690482) of the selective CRTh2 receptor antagonist AZD1981 in patients with moderate to severe COPD conducted at 22 centres across 5 European countries (Bulgaria, Denmark, Poland, Slovakia and Sweden).

Eligible patients were enrolled in a 2-week run-in period. After the run-in period, patients who fulfilled the randomisation criteria entered the 4-week treatment period with either AZD1981 1000 mg twice daily or matching placebo, in a 1:1 ratio.

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics. Approval was also obtained from the Institutional Review Boards/Independent Ethics Committees in the respective countries.

Patients

Male and female patients $\geq$40 years of age with a clinical diagnosis of moderate to severe COPD (GOLD stages II and III) [1]; post-bronchodilator FEV_1 of 30–80% of predicted normal, and post-bronchodilator FEV_1/forced vital capacity (FVC) $<$70%, symptoms for $>$12 months, current or ex-smokers with a smoking history of at least 10 pack-years, and use of inhaled short-acting β_2-agonists and/or anticholinergics as reliever during 1 year prior to the start of

the study were eligible for inclusion. Female patients had to be of non-childbearing potential.

For randomisation in the study at Visit 2 the patients also had to fulfil the following criteria: a score of $\geq$1 on the COPD symptom breathing score (5-point scale ranging from 0 [good] to 4 [bad]) on at least half of the days of the run-in period and a score of $\geq$2 on the COPD symptom sputum score (same 5-point scale as breathing score) on at least half of the days of the run-in period.

Patients receiving inhaled corticosteroid (ICS) therapy and/or stable doses of ipratropium/oxitropium prior to run-in were allowed to continue their pre-study medication throughout the study. However, long-acting β_2-agonists (LABAs) and long-acting anti-muscarinic agents (LAMAs) had to be discontinued prior to inclusion. Patients on combination ICS/LABA therapy were transferred to the corresponding ICS monotherapy. Inhaled short-acting β_2-agonist therapy (terbutaline) was provided as reliever medication to be used as-needed throughout the run-in and treatment period.

Treatments

Patients received either AZD1981 1000 mg orally (administered as four 250 mg tablets) or matching placebo twice daily, in the morning and the evening. Patients took the first dose of study medication at the clinic at baseline (Visit 2; on completion of the 2-week run-in period). Additional clinic visits took place at weeks 1, 2, 3 and 4 of the treatment period with a follow-up visit one week after the final on-treatment visit.

Objectives and endpoints

The primary objective of the study was to evaluate the efficacy of AZD1981 compared with placebo in patients with moderate to severe COPD; the secondary objective was to evaluate the tolerability of AZD1981 compared with placebo in this patient population.

The co-primary study endpoints were change from baseline to end of treatment in pre-bronchodilator FEV_1 and the Clinical COPD Questionnaire (CCQ) [19]. Additional efficacy endpoints were change from baseline to end of treatment in the lung function measures FVC, slow vital capacity (SVC), inspiratory capacity (IC), forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75\%}$), the 6-min walk test (6-MWT), COPD symptom score, morning and evening peak expiratory flow (PEF), BODE index and reliever medication use.

Safety was assessed throughout by reporting the nature, incidence and severity of adverse events (AEs). ECG, pulse, blood pressure and safety laboratory parameters (clinical chemistry, haematology and urinalysis) were also recorded at each clinic visit.

Statistical analysis

A sample size of 100 patients, 50 in each treatment group, was determined to have 80% power to detect a difference on FEV_1 of 0.125 L between the treatment groups, assuming a common standard deviation of 0.25 L, using a one-sided test with a significance level of 0.05.

Efficacy data were analysed using an additive analysis of variance (ANOVA) model, with treatment and country as factors and baseline measurements as covariate. The outcome variable for diary card variables was the change from run-in period average to treatment period average. For other data the outcome variable was the change from last pre-dose value to last post-dose value.

All AE data were summarised for each treatment and analysed by means of descriptive statistics and qualitative analysis. All hypothesis testing was done using two-sided alternative hypotheses. p-Values <0.1 were considered statistically significant on two-sided tests (i.e. <0.05 on one-sided tests).

Results

Expression of CRTh2 receptor in COPD lung

Expression of the CRTh2 receptor was found on a range of both inflammatory and resident cell types in all lung specimens (Fig. 1). A prominent expression was seen on multifocal inflammatory infiltrates (notably mononuclear cell infiltrates) and on lymphoid tissue cells as well as on cells embedded within mucus plugs in the central airways. CRTh2 expression was noted on mononuclear cells both within the lung tissue and on cells adhering to the endothelial surface and trafficking through the vessel walls of the pulmonary vasculature.

An interesting, and consistent, finding was the observation of CRTh2 expression on mucosal epithelial cells. There was a range of epithelial phenotypes noted in this sample set — hypertrophic, hyperplasic, metaplastic and examples of both basal cell and squamous cell metaplasia. Not all cells of similar morphology expressed CRTh2 — there were many examples of cells showing marked expression adjacent to cells which showed little or no expression. CRTh2 expression was marked on hypertrophic and hyperplastic epithelium but was less intense, with a more diffuse pattern, on metaplastic cell types. With regards to the hypertrophic and hyperplastic phenotypes, expression of CRTh2 was markedly focal — showing a dense expression pattern at the apical surface of the epithelium. This pattern was less marked on the metaplastic forms, which may reflect either changes in receptor density on the cells or changes in cell morphology and volume as the epithelial cells move through the differentiation sequence.

Clinical trial findings

A total of 156 patients were enrolled in the study, of whom 118 were considered eligible for randomisation to treatment (AZD1981 $n = 61$; placebo $n = 57$). Of the 7 patients who discontinued during the study (AZD1981 $n = 4$; placebo $n = 3$), 3 were withdrawn because of adverse events, one because of incorrect enrolment, one because of non-allowed concomitant medication, one because of elevated liver enzyme levels and one withdrew consent (randomised to placebo) immediately after receiving the first dose (Fig. 2); since no data were collected on this patient, the patient was listed in the category "Not treated or no data on treatment" and excluded from the placebo

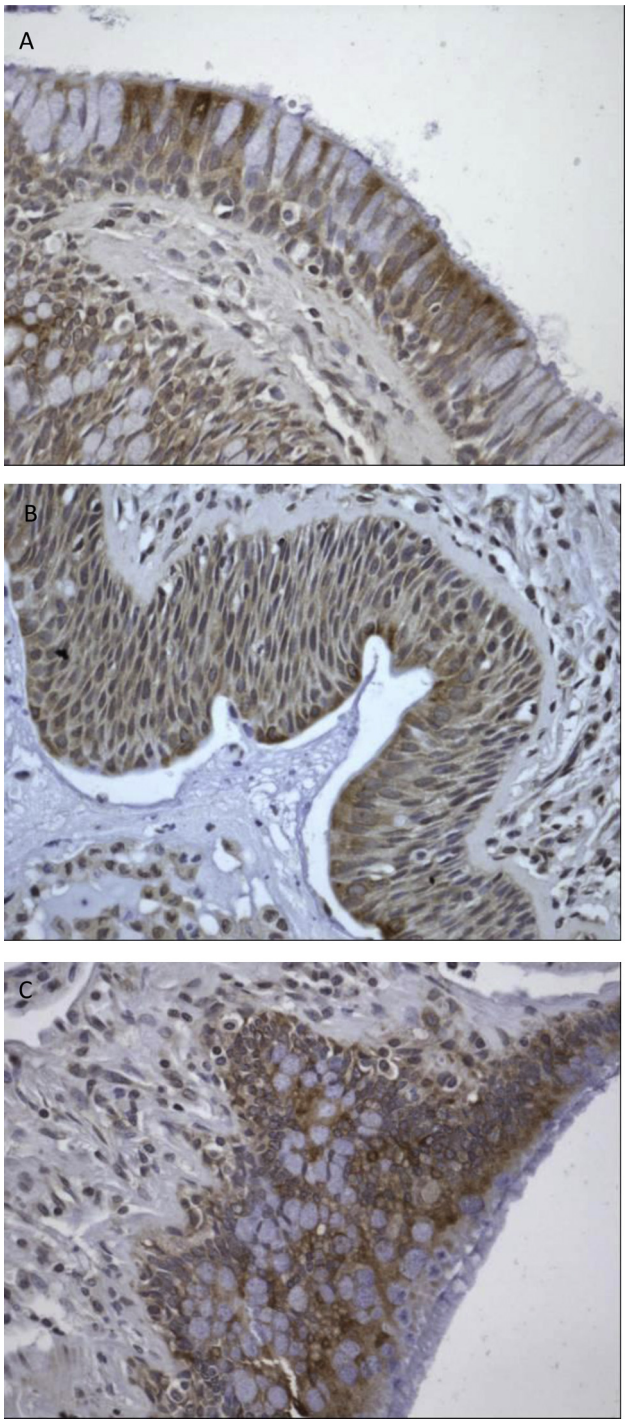

Figure 1 Three typical lung fields (×20) showing expression of CRTh2 receptor in airway mucosa. (A) shows a mainly hyperplastic epithelium with prominent Goblet cell hypertrophy. Note receptor expression on epithelium with denser expression at the apical surface. (B) shows a metaplastic epithelium with a squamous phenotype and diffuse CRTh2 expression. Note positive inflammatory cells within the connective tissue zone and within the lumen mucus deposit. (C) shows a mixed phenotype epithelium with intra-epithelial leucocytes. There is punctate expression of CRTh2 within the epithelium and connective tissue zone.

group dataset. Of the 117 patients allocated to treatment, 97 (83%) were male and 20 (17%) were female; all patients were Caucasians aged between 43 and 83 years (mean age 63.3 years). The median time since diagnosis of COPD was 6 years and the median number of pack years of smoking was 36. The treatment groups were comparable at baseline with respect to demographic characteristics except that the AZD1981 group had a higher mean inhaled corticosteroid dose at entry and a slightly lower FEV_1 (Table 1).

Efficacy

AZD1981 at a dose of 1000 mg twice daily for 4 weeks did not have any effect on the co-primary study endpoints of change from baseline in pre-bronchodilator FEV_1 and CCQ (total score and individual symptom, function and mental scores) compared with placebo (Fig. 3A and B). There were no statistically significant differences in the mean change from baseline to end of treatment between AZD1981 and placebo for FEV_1 (difference: −0.015, 95% CI: −0.10 to 0.070; $p = 0.72$), CCQ total score (difference: 0.042, 95% CI: −0.21 to 0.30; $p = 0.75$), CCQ symptom score (difference: 0.020, 95% CI: −0.28 to 0.32; $p = 0.90$), CCQ function score (difference: 0.064, 95% CI: −0.22 to 0.35; $p = 0.66$) and CCQ mental score (difference: −0.005, 95% CI: −0.37 to 0.36; $p = 0.98$).

Similarly, no differences were observed between treatments on the other clinically measured spirometric variables of FVC (difference: 0.028, 95% CI: −0.14 to 0.20; $p = 0.75$), SVC (difference: −0.025, 95% CI: −0.21 to 0.16; $p = 0.79$), IC (difference: 0.063, 95% CI: −0.10 to 0.23; $p = 0.45$) and FEF_{25-75} (difference: −0.12, 95% CI: −0.24 to 0.003; $p = 0.056$) (Fig. 4).

Following 4 weeks of treatment, no differences were observed between treatment arms for PEF, COPD symptom score, use of reliever medication, 6-MWT and BODE score after 4 weeks of treatment (Table 2).

Tolerability

A total of 20 patients (33%) in the AZD1981 group experienced an AE compared with 18 patients (32%) in the placebo group. The majority of adverse events were mild in intensity and no AEs of severe intensity were reported. The most frequently reported adverse events were nasopharyngitis (in total: 9 patients [8%]) and COPD (8 patients [7%]); twice as many patients in the AZD1981 group reported nasopharyngitis as those receiving placebo (Table 3).

One patient (receiving placebo) experienced a serious AE of COPD exacerbation resulting in hospitalisation. There were 4 discontinuations due to AEs during the treatment period: 3 of these were in patients receiving AZD1981 (2 cases of a COPD exacerbation and 1 elevation of liver enzymes) and 1 was a patient receiving placebo (a COPD exacerbation). There were no deaths during the study.

There were no marked changes in haematology, clinical chemistry and urinalysis parameters. There were no clinically relevant differences between the treatment groups in safety laboratory variables, ECG, vital signs or physical examination.

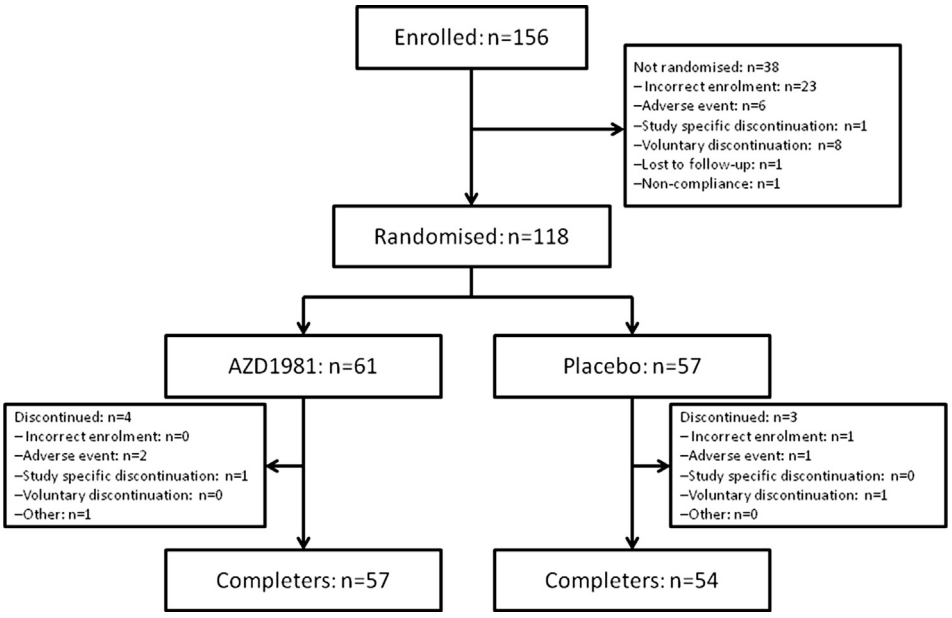

Figure 2 Patient flow through the study.

Discussion

This study was the first to examine the expression of CRTh2 receptors in COPD lung, and the pulmonary effects of the oral CRTh2 antagonist AZD1981 in patients with COPD. The primary objective of the study was to explore the efficacy of 4 weeks' treatment with AZD1981 in patients with COPD and the secondary objectives were to assess its safety and tolerability. There was no indication of a beneficial clinical effect of AZD1981 in patients with moderate to severe COPD given at a dose of 1000 mg twice daily for 4 weeks.

The rationale for testing the CRTh2 antagonist AZD1981 on patients with COPD stems from preclinical data showing that the CRTh2 antagonist inhibited tobacco-smoke-induced inflammation and mucosal damage, including mucus cell metaplasia and epithelial hyperplasia, in a mouse model [12,13]. This, combined with the finding of CRTh2 receptor expression in COPD lung tissue, on

Table 1 Patients' baseline demographics and disease characteristics (n = 117).

Characteristic	AZD1981 (n = 61)	Placebo (n = 56)
Gender, n (%)		
Male	49 (80)	48 (86)
Female	12 (20)	8 (14)
Mean age, years (range)	64.1 (47–78)	62.4 (43–83)
Mean body mass index, kg/m^2 (range)	24.8 (18–31)	24.9 (17–30)
Smoking status, n (%)		
Previous	27 (44)	27 (48)
Occasional	2 (3)	2 (4)
Habitual	32 (52)	27 (48)
Mean pack-years (range)	35 (12–99)	36 (10–81)
ICS at entry, n (%)		
Yes	47 (77)	38 (68)
No	14 (23)	18 (32)
Mean daily dose, μg (range)	680.4 (320–1600)	545.3 (200–1600)
Lung function parameters (mean)		
FEV_1 post-bronchodilator, L (range)	1.55 (0.7–2.7)	1.66 (0.8–2.8)
FEV_1 pre-bronchodilator, L (range)	1.42 (0.5–2.7)	1.58 (0.7–2.7)
FEV_1, post-bronchodilator, % predicted normal (range)	53.1 (31–79)	55.3 (31–100)
FVC, L (range)	3.08 (1.3–6.5)	3.11 (1.8–4.9)
FEV_1/FVC ratio, % (range)	50.9 (34–70)	53.4 (31–70)
Mean no. of reliever inhalations/day, n (range)	3.6 (0–12)	3.1 (0–9)

Abbreviations: FEV_1, forced expiratory volume in 1 min; FVC, forced vital capacity; ICS, inhaled corticosteroid.

mononuclear infiltrates and mucosal epithelial cells and the fact that the dual thromboxane and CRTh2 receptor antagonist seratrodast improved lung function in an 8-week study in patients with chronic pulmonary emphysema [15] suggested that inhibition of CRTh2 receptors might provide therapeutic benefits to patients with COPD.

There are a number of possible reasons for the negative finding in this study. There are differences in CRTh2 expression patterns between mouse and human so mouse models may not be wholly predictive of effects in man [14]. The time course for any clinical effect of a CRTh2 antagonist in patients with COPD is far from clear. It is equally unclear on what aspect of the disease the first signs of a beneficial effect could be found. This study was undertaken with the constraint that it could be no longer than 4 weeks because the necessary toxicological studies to support

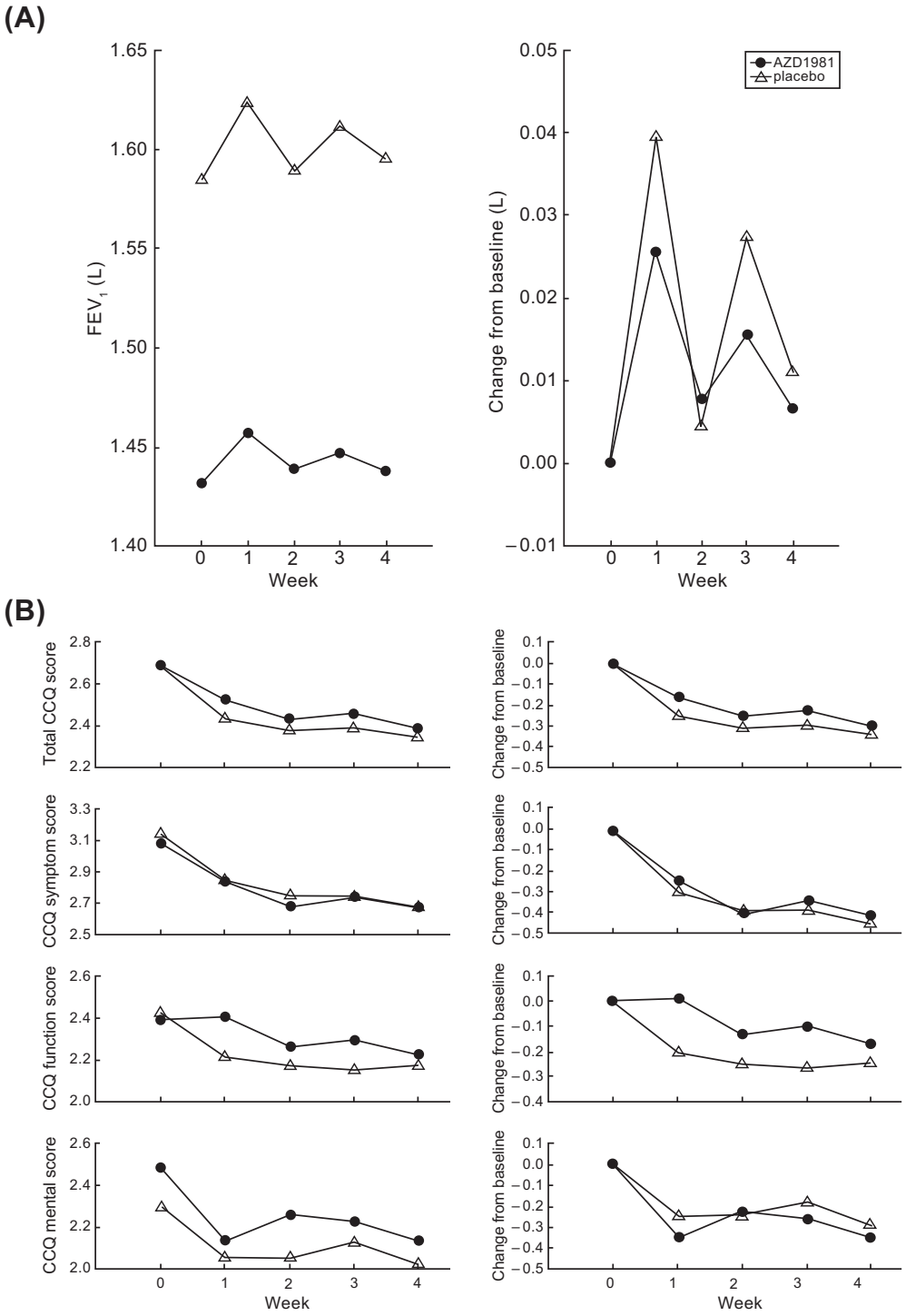

Figure 3 (A) Pre-bronchodilator FEV_1 and change from baseline pre-bronchodilator FEV_1 and (B) CCQ and change from baseline CCQ in patients with moderate to severe COPD receiving either AZD1981 at a dose of 1000 mg twice daily or placebo for 4 weeks.

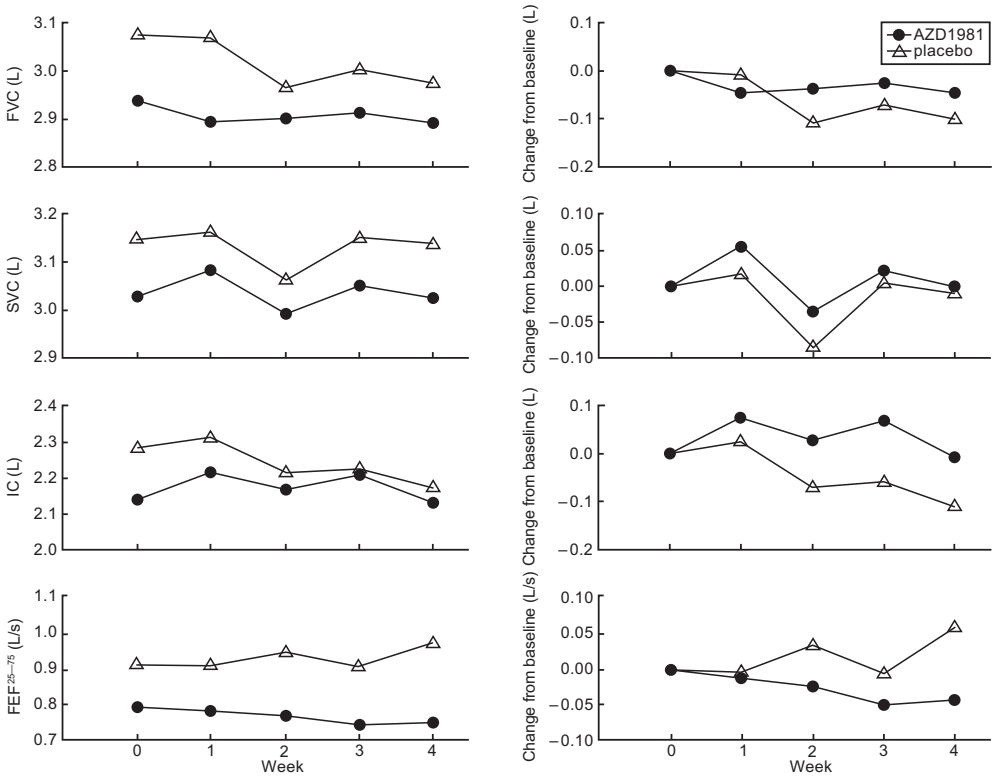

Figure 4 Forced vital capacity (FVC), slow vital capacity (SVC), inspiratory capacity (IC) and FEV_1 between 25% and 75% of the FVC (FEF_{25-75}), and change from baseline in these spirometric outcomes, in patients with moderate to severe COPD receiving either AZD1981 at a dose of 1000 mg twice daily or placebo for 4 weeks.

studies of longer duration had not been reported. The study was, therefore, designed both as a signal searching study, to find out if any clinical effects of AZD1981 in COPD patients can be detected after only 4 weeks of treatment, and as a safety and tolerability study, to facilitate the step from short-term healthy volunteer studies to longer studies in COPD patients from a safety and tolerability perspective. In terms of efficacy, two co-primary efficacy endpoints were chosen, FEV_1 as measure of lung function and CCQ as measure of health status, in order to provide a level of

Table 2 Treatment effect of AZD1981 on lung function and other outcome measures in patients with moderate to severe COPD (change from baseline to last assessment).

Variable	Estimated mean difference[a]	95% confidence interval	*p*-Value (treatment effect)
COPD symptoms[b]			
Breathing	−0.082	−0.239 to 0.075	0.305
Cough	−0.111	−0.286 to 0.063	0.208
Sputum	0.003	−0.176 to 0.181	0.974
Sleeping	−0.067	−0.232 to 0.099	0.427
Use of reliever medication			
Total daily reliever use	−0.048	−0.695 to 0.599	0.883
Day-time reliever use	0.024	−0.401 to 0.448	0.651
Night-time reliever use	−0.073	−0.394 to 0.247	0.912
6-min walk test, m	−2.7	−20 to 15	0.76
BODE index score	0.11	−0.28 to 0.50	0.57
PEF, L/min			
Morning	−2.76	−10.1 to 4.61	0.460
Evening	−8.47	−16.3 to −0.585	0.035

Abbreviation: PEF, peak expiratory flow.
[a] ANOVA estimated difference AZD1981 versus placebo (original values).
[b] Symptoms rated on a 5-point scale (0: good through to 4: bad).

Table 3 The most frequently reported adverse events (reported in at least 3% of patients).

Adverse event, *n* (%)	AZD1981 ($n = 61$)	Placebo ($n = 56$)
Nasopharyngitis	6 (10)	3 (5)
COPD	4 (7)	4 (7)
Urinary tract infection	1 (2)	2 (4)
Cough	2 (3)	1 (2)

confidence when interpreting the study. Also, since the mode of action of a CRTh2 antagonist in COPD is different from those of current COPD therapies, the study was designed to address the effect of AZD1981 with a variety of background medication. Enrolled patients who were on ICS and/or ipratropium/oxitropium maintenance therapy were allowed to continue on their pre-study regimen throughout the study while LAMAs and LABAs were discontinued and patients using an ICS/LABA combination inhaler were transferred to the corresponding ICS monotherapy. Overall, this resulted in about 70% of patients in the study receiving ICS and 40% were receiving anticholinergics, and while the discontinuation of LAMAs and LABAs was intended to allow improvement in lung function to be detected, this high level of maintenance therapy may have diminished the ability to detect an independent effect from AZD1981.

In a separate phase II study evaluating histological and cellularity effects of AZD1981 given for 4 weeks in patients with COPD, AZD1981 reduced the percentage of eosinophils in induced sputum compared with placebo; however, no evidence of clinical efficacy of AZD1981 over the 4-week treatment period was observed and effects on airway histology were not seen [20]. The reduction in the percentage of eosinophils in induced sputum is consistent with the mechanism of action of this drug class and has been seen with another CRTh2 antagonist in preventing allergen-induced eosinophilic inflammation in patients with mild asthma [11]. Whether AZD1981 would have an effect on eosinophilic inflammation and potentially in preventing eosinophilic-driven COPD exacerbations remains to be determined.

The study did not indicate any tolerability or safety issues with AZD1981 that would cause concern for longer-term studies. In terms of safety, there were no serious AEs with AZD1981 and nothing noteworthy in the pattern or the frequency of AEs.

In conclusion, while the results of this 4-week study did not demonstrate a beneficial clinical effect for AZD1981 1000 mg twice daily, longer-term studies might reveal benefits in terms of COPD exacerbations in certain patients, or in slowing the rate of decline in lung function. AZD1981 was well tolerated and no safety concerns were identified.

Conflicts of interest

The study was funded by AstraZeneca R&D, Molndal, Sweden. The study sponsor had input into the design, collection and analysis of the data. The study sponsor had no involvement in the interpretation of the data, the writing of the manuscript or the decision to submit to Respiratory Medicine.

NS was in full-time employment with AstraZeneca R&D, Charnwood, UK during the design and initiation of this study.

MF was in full-time employment with AstraZeneca R&D, Charnwood, UK during the design and initiation of this study.

JV has received honoraria from various pharmaceutical companies, including AstraZeneca, for consulting and presenting. JV's wife has been an employee of AstraZeneca.

The authors have been involved in all stages of the study, including the design, implementation, data collection, analysis and interpretation. The authors have also been involved and provided input throughout the preparation of the manuscript; they have had full access to all data and the content of this manuscript represents the authors' interpretation of the data. It was the authors' decision to submit the manuscript to Respiratory Medicine.

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