Drug substance(s):	AZD1981	**SYNOPSIS**	
Edition No.:	1		
Study code:	D9830C00003		
Date:	6 December 2007		

A 4 week randomised, double blind, placebo controlled, parallel group, phase II, PoP study to assess the efficacy and safety of AZD1981 in adult patients with asthma.

International co-ordinating investigator

[redacted]

Study centre(s)

21 centres in 5 countries enrolled patients into this study.

Publications

Not at the time of finalising this report.

Study dates		**Phase of development**
First subject enrolled	4 September 2006	Therapeutic exploratory (II)
Last subject completed	2 August 2007	

Objectives

The primary objective of the study was to compare the clinical efficacy of twice daily, orally administered AZD1981 with that of placebo over a 4-week treatment period in adults with persistent asthma.

A secondary objective of the study was to evaluate the safety and tolerability. Other secondary objectives were pharmacokinetics, exploratory pharmacodynamics, and pharmacogenetics of AZD1981 given at repeated oral doses.

Study design

The study was a randomised, double blind, parallel group, placebo controlled trial of AZD1981 in adults currently on inhaled glucocorticosteroid (iGCS) therapy (≤400 µg of any iGCS) with persistent asthma (GINA 2 to GINA 3). Eligible patients were enrolled to a 3-week run-in period during which their ordinary iGCS was withdrawn and a short-acting β_2-

agonist (SABA) was used as needed. After the run-in period, patients who fulfilled the randomisation criteria started a 4-week treatment period with either AZD1981 1000 mg bid or placebo together with a SABA, used as needed. Following the treatment period the patients returned to their usual asthma therapy as judged by the investigator. After 2 weeks the patient returned to the clinic for a follow up visit.

Target subject population and sample size

Men and women (post menopausal or surgically sterilised women), aged 18-60 years, diagnosed as having persistent asthma (GINA 2 to GINA 3) who were currently treated with any iGCS (≤ 400 µg daily), with documented history of asthma since at least 6 months, and a forced expiratory volume in 1 second (FEV_1) 65% to 110% of predicted normal were to be enrolled.

The sample size of 55 randomised patients per group was considered sufficient in order to detect clinically relevant effects on morning PEF.

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

During the run-in period patients were using Bricanyl® Turbuhaler® as-needed (0.5 mg/dose).

Patients were randomised to one of the following treatment groups:

- AZD1981 (1000 mg/dose, oral suspension to be taken morning and evening) as maintenance medication, plus Bricanyl Turbuhaler (0.5 mg/dose) as-needed.
- Placebo for AZD1981 (oral suspension to be taken morning and evening) as maintenance medication, plus Bricanyl Turbuhaler (0.5 mg/dose) as-needed.

The treatment group with AZD1981 is referred to as AZD1981, while the treatment group with placebo for AZD1981 is referred to as placebo.

Batch numbers were:
Bricanyl Turbuhaler [redacted] and [redacted]
AZD1981 [redacted] to [redacted]
Placebo for AZD1981 [redacted] to [redacted]

Duration of treatment

The run-in period was 3 weeks and the randomised treatment period 4 weeks, followed by a follow-up period of 2 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

The **primary outcome variable** was a change in **morning peak expiratory flow (mPEF)** from baseline (mean of the 10 last days of the run-in period) to the treatment period (mean of the 4-week treatment period).

The **secondary outcome variables** were evening PEF, asthma-symptom score, use of as-needed medication, nights with awakenings due to asthma symptoms, symptom-free days, as-needed-free days, asthma control days, FEV_1 pre- and post SABA, FVC pre SABA, patient reported outcomes as Asthma Control Questionnaire (ACQ), number of eosinophils in induced sputum (optional) and time to treatment failure.

Pharmacokinetic (PK)

Blood samples, a total of 2 samples per visit, were taken from all patients at Visits 4 and 5. Plasma concentration of AZD1981 was determined pre-dose ($C_{trough)}$ and 2 to 4 hours after dose ($C_{post\ dose}$).

In a subgroup of patients, extended PK sampling was performed. The following pharmacokinetic parameters were calculated from plasma concentration of AZD1981: AUC_{τ}, the AUC during one dosing interval at steady state; C_{max}, the observed maximum plasma concentration; C_{min}, the observed minimum plasma concentration; t_{max}, the time of the observed maximum plasma concentration and CL/F, the oral clearance.

Pharmacodynamic

The following exploratory pharmacodynamic variables were to be assessed: biomarkers in induced sputum (optional), 11-dehydro thromboxane B_2/Leukotrine E_4 ratio in urinary samples, blood eosinophils, fractional exhaled nitric oxide (FE_{NO}) (where equipment was available).

Only blood eosinophils and exhaled nitric oxide have been analysed and are reported here.

Pharmacogenetics

Genetic samples were collected and stored for potential future research regarding genes, which may influence PK profile, drug disposition, efficacy, safety or tolerability of AZD1981. This research will form part of a possible future pooled analysis and is hence not reported as a part of this study.

Safety and tolerability

Safety evaluation was based on incidence, nature and severity of adverse events (AEs), pulse, blood pressure and safety laboratory variables.

Statistical methods

The primary outcome variable, a change in average mPEF, was analysed using an analysis of variance model (ANOVA), with treatment and country as factors and baseline measurements as covariate. The secondary outcome variables were analysed in the same way as primary variable.

Subject population

Of the 113 patients randomized into the study, 84% were male and 99% were Caucasian. The mean patient age was approximately 39 years. The patients enrolled in the study had a documented clinical history of asthma (with a median time since diagnosis of 13 years), average FEV_1 85% of the predicted normal value and all were on inhaled glucocorticosteroids before enrolment, with an average daily dose of 309 µg. The two treatment groups, AZD1981 (57 patients) and placebo (56 patients), were well balanced in demographic and baseline disease characteristics and comprised only patients with mild asthma. Nearly 87% of the 113 patients randomized to treatment completed the study. The number of discontinuations was similar between the treatment groups (12% in AZD1981 and 14% in placebo group), with most patients discontinuing due to adverse events. All randomized patients were analyzed for efficacy and safety.

Efficacy and pharmacokinetic results

The primary outcome variable, morning PEF, indicated a positive effect of AZD1981. While the average mPEF in placebo patients slowly decreased over the 4 weeks of study, it remained relatively unchanged in patients on AZD1981 1000 mg bid. Analysis of mean mPEF gave an estimated treatment difference of 9.5 L/min (SD = 29L/min). Taking into account the small size of this exploratory study, the treatment difference with the p-value of 8.6% in a two-sided test provides some evidence to claim an effect of AZD1981 on mPEF. Secondary outcome variables, which included eDiary and spirometry variables, time to treatment failure and ACQ variables, were numerically in a direction of improvement of lung function and asthma control, but differences were small; statistical analysis of secondary outcome variables provided no evidence of effect of AZD1981. Due to the limited number of patients undergoing sputum induction, the effect of AZD1981 on sputum eosinophils could not be statistically demonstrated, although individual data suggested a positive effect.

Treatment comparisons for some of the eDiary variables are summarized in Table S1.

Table S1 Treatment comparisons for some of eDiary variables

Variable	Mean Difference	95% C.I.	P-value
Morning PEF (L/min)	9.5	(-1.4, 20.5)	0.086
Use of as-needed medication; total daily no. of inhalations	-0.20	(-0.62, 0.22)	0.34
Asthma symptoms; total score (0-6)	-0.05	(-0.26, 0.16)	0.61

Overall, the pharmacokinetics of AZD1981 in asthmatic patients were as expected from the outcome upon single and repeat twice-daily oral administration to healthy subjects: an approximate steady state was reached within two weeks of treatment; mean values of peak plasma concentration and exposure during the dosage interval at steady state were compatible with the applied less restricted peridosing prandial conditions, ie, an outcome in-between that for dosing after fasting and that after a high-calorie and high-fat breakfast; there was an apparent drop in mean plasma exposure at steady state compared with single dose, thus confirming previous data indicating a exposure decline during regular dosing.

Safety results

The treatment with AZD1981 twice daily during 4 weeks was well tolerated. A total of 88 AEs were reported, whereof 46 in patients receiving AZD1981 and 42 in patients on placebo. The proportion of patients with AE was similar between active treatment (51%) and placebo group (46%). Asthma and nasopharyngitis were the most common AEs; asthma occurred at the same rate (9%) in both groups while nasopharyngitis was more common in placebo group. The majority of AEs were mild to moderate; the incidence of AEs of severe intensity was low and similar between the two treatment groups. No deaths were reported during this study. There were 2 SAEs and both of them were experienced by patients receiving placebo. More patients discontinued due to an AE in the placebo (13%) than in the AZD1981 group (9%). The most common adverse event leading to discontinuations was asthma. No consistent changes in safety laboratory variables, vital signs, ECG, or physical examination were observed.

Conclusion(s)

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Date of the report

6 December 2007