AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00004
Edition Number	1
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A double-blind, randomized, parallel group, multicentre Phase IIb, placebo-controlled 1 month dose response study of AZD1981 in asthma patients uncontrolled on inhaled steroids

Study Dates	First patient enrolled: 16 September 2008 Last patient completed: 13 July 2009
Phase of development	Therapeutic exploratory (II)

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

Study Centres

30 centres in 4 countries enrolled patients into this study.

Publications

None at the time of finalising this report.

Objectives

Table 1 Study objectives and variables

Priority	Objective	Outcome variables
Primary	To evaluate efficacy of AZD1981 compared with placebo in uncontrolled asthmatic patients on maintenance inhaled glucocorticosteroids	**Primary efficacy variable** -Morning PEF[a] (recorded in eDiary) **Secondary efficacy variables recorded at clinic visits** -FEV_1[b] -FVC[c] -ACQ[d] **Secondary efficacy variables recorded in eDiary** -Evening PEF -Asthma-symptoms score (day, night and total) -Use of reliever medication (day, night and total) -Nights with awakenings due to asthma symptoms -Symptom free days -Reliever free days -Asthma control days -Morning and evening FEV_1) (registered by electronic home spirometer
Secondary	To investigate the safety and tolerability of AZD1981	-AEs (nature, incidence, severity) -Hematology -Clinical chemistry -Urinalysis -ECG -Pulse and blood pressure
	To investigate the dose response relationship of AZD1981	
Exploratory	To investigate the CYP3A4 induction of AZD1981	Plasma levels of 4β-hydroxycholesterol
	To assess biomarkers over the study period [e]	Inflammatory mediators (eg IL-13, IL-10, IL-6, TNF)
	To collect optional genetic samples for possible future pooled analysis[e]	DNA from blood

a Peak expiratory flow
b Forced expiratory volume in 1 second
c Forced vital capacity
d Asthma control questionnaire
e Not reported in this CSR

Study design

This was a 1 month, randomized, double blind, placebo controlled, parallel group, multicentre study to asses the dose response of AZD1981 tablets in patients with moderate to severe asthma inadequately controlled on inhaled glucocorticosteroids (ICS). The investigated doses were 50, 400 and 1000 mg AZD1981 twice daily and placebo twice daily. Eligible patients entered a 2 week run-in period. Patients who fulfilled the randomisation criteria started treatment with either AZD1981 or placebo oral tablets twice daily. Patients that were on long acting β-2 agonists (LABA) prior to run in, either in a combination product with ICS or in separate devices, had to stop treatment with LABA and continue using ICS as monotherapy during the study. A short acting β-2 agonist (SABA) was provided/prescribed as reliever medication for use throughout the study. Patients were allowed to go back to their regular treatment after visit 5 (treatment stop). Study visits took place every second week during the treatment period. Two weeks after the completion of treatment, patients were contacted by telephone as a follow-up.

Target subject population and sample size

Men and post-menopausal or surgically sterilised women, aged 18 years or above, diagnosed as having moderate to severe asthma, who were currently treated with any ICS (≥500 μg daily), with documented history of asthma since at least 6 months, a pre-bronchodilatory FEV_1 of 40 to 85% of predicted and a post-bronchodilator reversibility of at least 12% in FEV_1 and at least 200 mL. Patients needed to use reliever medication on at least 4 of the last 7 days of the run-in period.

The sample size of at least 80 patients per treatment group was determined to have 80% power to detect a difference on morning PEF of 18 L/min between AZD1981 and placebo, assuming a common standard deviation of 45 L/min, using a one sided-test with a significance level of 0.05.

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

Patients were randomized to one of the following treatment groups:

- AZD1981 50 mg/dose, 1 AZD1981 50 mg tablet and 3 placebo tablets to be taken morning and evening
- AZD1981 400 mg/dose, 1 AZD1981 250 mg tablet and 3 AZD1981 50 mg tablets to be taken morning and evening
- AZD1981 1000 mg/dose, 4 AZD1981 250 mg tablets to be taken morning and evening

- Placebo for AZD1981, 4 placebo tablets

All patients were given a SABA, Bricanyl® Turbuhaler® 0.5 mg/ dose to be used as reliever medication throughout the study. Alternatively, any inhaled SABA eg, salbutamol, prescribed by the investigator, could be used as reliever medication.

Totally 5 batches of AZD1981 and 2 batches of placebo were used. The batch numbers used for each individual and treatment are described in Appendix 12.1.6 of the clinical study report.

Duration of treatment

The run-in period was 2 weeks, the treatment period was 4 weeks, and the follow-up period was 2 weeks.

Statistical methods

All hypothesis testing was done using two-sided alternative hypotheses, where p-values less than 10% were considered statistically significant on the two-sided tests (ie. 5% on one-sided).

Analysis of morning PEF and other eDiary variables

Daily mean values were calculated with imputation for missing data. The change, from run-in to treatment, in period means was analysed using an additive ANOVA model with treatment and country as factors and with the run-in period mean as covariate. Treatment differences were estimated from the model and confidence interval and p-values were calculated.

Analysis of variables measured at the clinic visits

The changes in FEV_1, FVC and overall ACQ were compared between treatments using an additive ANOVA model with treatment and country as factors and baseline measurement as covariate. The change was calculated as the difference between the last measurement during treatment and last baseline measurement. Confidence intervals and p-values were estimated from the model.

Safety and other data

Laboratory safety data was mainly analysed in terms of descriptive statistics and were graphically illustrated over time. Data was individually listed and graphically illustrated, presented as descriptive statistics and mean value plots by treatment and assessment time. In addition the change from baseline to end of treatment was analysed statistically with confidence intervals and p-values. AEs were summarised for each treatment and analysed in terms of descriptive statistics and qualitative analysis.

Subject population

A total of 510 patients were enrolled at 30 centres in 4 countries: Argentina, Brazil, Costa Rica and Poland. Of these 368 were allocated to treatment at visit 3. Of these 255 (69%) were male and 337 (92%) were white, and 265 (72%) were atopic. The mean patient age was 43.9 years and the median time with asthma was 12 years. The mean FEV_1 of predicted normal was 67.5%, the mean pre-bronchodilator FEV_1 was 2.29 L, the mean reversibility was 26.4% and all were on ICS before enrolment, with an average daily dose of 723 µg.

The 4 treatment groups, 50 mg (95 patients), 400 mg (90 patients) 1000 mg (92 patients) and placebo (91 patients) were well balanced in demographic and baseline disease characteristics. Of the randomized patients 95% completed the study. The number of discontinuations were similar between the treatment groups (3% for 50 mg, 3% for 400 mg, 7% for 1000 mg and 7% for placebo). All randomized patients were analysed for efficacy and safety.

Summary of efficacy results

The study did not show an effect on the primary variable, morning PEF. The mean value curves of morning PEF in the AZD1981 groups remained relatively unchanged while the placebo group indicated a slow decline after the first 2 weeks in the treatment period. Analysis of mean morning PEF gave an estimated treatment difference vs placebo of 8.5 to 12 L/min (SD 57 L/min), but the differences were not statistically significant for any of the AZD1981 groups.

For the secondary outcome variables measured at the clinic, improvements were found in all 3 AZD1981 groups for the ACQ5 score where the estimated difference vs placebo ranged from 0.26 to 0.30. In FEV_1, the estimated difference vs placebo was 180 mL for the 400 mg group. For FVC no differences were detected. Also, as measured in the eDiary there was an effect (one-sided test) in evening PEF and evening FEV_1 in the 1000 mg group compared to placebo.

Table 2 Treatment comparisons for some secondary efficacy variables

Variable	Treatment	Mean difference	95% CI	P-value
FEV_1 (L)	50 mg vs placebo	0.10	(-0.042, 0.25)	0.17
	400 mg vs placebo	0.18	(0.036, 0.33)	0.015
	1000 mg vs placebo	0.095	(-0.050, 0.24)	0.20
ACQ5	50 mg vs placebo	-0.28	(-0.51, -0.047)	0.019
	400 mg vs placebo	-0.28	(-0.51, -0.042)	0.021
	1000 mg vs placebo	-0.30	(-0.53, -0.060)	0.014

Atopic vs non-atopic patients

Approximately 72% of the patients in the study were atopic (= Phadiatop test positive), and a stronger signal for treatment effects occur in the atopic patient population. When comparing the atopic with the non-atopic population, the ACQ5 score is improved only in the atopic population (decrease in scores of 0.38 to 0.42). In the atopic population FEV_1 showed differences of 180 and 170 mL, respectively, compared to placebo for the 400 and 1000 mg groups. In the non-atopic population, FEV_1 increased numerically in the 400 mg group vs placebo, but this difference was not statistically significant.

Table 3 Treatment comparisons for FEV_1 and ACQ5 in atopic and non-atopic patients.[a]

Variable	Treatment	Mean difference	95% CI	P-value
FEV_1 (L)				
-non atopic patients	50 mg vs. placebo	0.035	(-0.25, 0.32)	0.81
	400 mg vs. placebo	0.21	(-0.089, 0.51)	0.17
	1000 mg vs. placebo	-0.039	(-0.31, 0.23)	0.78
-atopic patients	50 mg vs. placebo	0.13	(-0.043, 0.30)	0.14
	400 mg vs. placebo	0.18	(0.014, 0.35)	0.034
	1000 mg vs. placebo	0.17	(-0.006, 0.34)	0.059
ACQ5				
-non-atopic patients	50 mg vs. placebo	0.095	(-0.36, 0.55)	0.68
	400 mg vs. placebo	0.10	(-0.38, 0.58)	0.67
	1000 mg vs. placebo	-0.031	(-0.47, 0.40)	0.89
-atopic patients	50 mg vs. placebo	-0.42	(-0.69, -0.15)	0.003
	400 mg vs. placebo	-0.40	(-0.67, -0.13)	0.004
	1000 mg vs. placebo	-0.38	(-0.67, -0.096)	0.009

a Change from last measurement pre dose to last measurement post dose

Summary of pharmacodynamic results

AZD1981 increased the plasma concentration levels of 4β-hydroxycholesterol (exploratory variable) with 37% in the 400 mg group and 57% in the 1000 mg group compared to placebo. In the 50 mg group the increase was a mere 5% compared to placebo and the difference was not statistically significant.

Summary of safety results

AZD1981 given twice daily for 4 weeks was well tolerated and no safety concerns were identified. A total of 141 AEs were reported. The proportion of AEs were similar between treatment groups, with gastritis, headache and asthma being the most common AEs. Gastritis occurred in slightly higher frequency in the 1000 mg group. The majority of the AEs were of mild to moderate intensity and the incidence of severe AEs was low and similar between the treatment groups.

No deaths were reported in this study. There were 3 SAEs, 1 during run-in, 1 in the 1000 mg group and 1 in the placebo group. The most common adverse event leading to discontinuations was gastritis, again with a slightly higher frequency in the 1000 mg

group. No consistent changes in safety laboratory variables, vital signs ECG or physical examination were observed.