AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00008
Edition Number	1
Date	18 October 2012

A Double-blind, Placebo-controlled, Randomised, Parallel-group, Phase II, Multi-centre Study to Assess the Efficacy, Safety and Tolerability of 4 Twice Daily Doses and 2 Once Daily Doses of AZD1981 Given as Tablets During 12 Weeks in Asthmatic Patients Treated with Inhaled Corticosteroids and Long-acting β_2-agonists

Study dates: First subject enrolled: 19 October 2010
Last subject last visit: 16 February 2012

Phase of development: Therapeutic exploratory (II)

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

Study centres

Patients were enrolled from 136 centres from the United States of America, Japan, Argentina, Brazil, Mexico, Romania, Russian Federation, Slovakia, Ukraine, and South Africa.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and outcome variables are presented in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate efficacy of AZD1981 compared with placebo in asthmatic patients treated with ICS and LABA.	**Primary efficacy variable** Pre-dose pre-bronchodilator FEV_1 measured at the clinic **Secondary efficacy variables:** **Efficacy at clinic visits** -Post-bronchodilator FEV_1 -Pre- and post-bronchodilator FVC -Time to severe asthma exacerbation -Time to treatment failure **PRO** -ACQ5 and AQLQ(S) **Recordings in eDiary** -Morning and evening PEF -Morning and evening FEV_1 -Daytime and nighttime asthma symptoms -Daytime and nighttime inhalations of bronchodilator reliever medication -Nights with awakenings due to asthma **Derived eDiary variables** -Total asthma symptoms score -Symptom-free days -Total reliever medication use -Reliever-free days -Awakening-free nights -Asthma-control days -Well-controlled asthma weeks -Uncontrolled asthma weeks	Efficacy
Secondary	**Secondary**	
To investigate the dose response relationship of AZD1981 in asthmatic patients treated with ICS and LABA	Compare data from dose levels and check for any dose responses. These responses were studied by using the results of the primary and secondary variables listed above.	Efficacy

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To compare once and twice daily administration of AZD1981 in asthmatic patients treated with ICS and LABA.	Compare the data of od and bid administrations. These responses were studied by using the results of the primary and secondary variables listed above.	Efficacy
Safety	**Safety**	
To investigate the safety and tolerability of AZD1981 in asthmatic patients treated with ICS and LABA.	-AEs (nature, incidence, severity) -Haematology -Clinical chemistry -Urinalysis -ECG -Vital signs and physical examination	Safety
Exploratory[a]	**Exploratory**	
To assess the extent of systemic exposure of AZD1981	Plasma concentration data analysed by HPLC-MS/MS method.	Pharmacokinetic

[a] Other exploratory variables are reported separately from the CSR.
ACQ5 Asthma control questionnaire 5-item; AE Adverse event; AQLQ(S) Standardised Asthma quality of life questionnaire; ECG Electrocardiogram; eDiary Electronic diary; FEV_1 Forced expiratory volume in 1 second; FVC Forced vital capacity; HPLC-MS/MS High performance liquid chromatography tandem mass spectrometry; ICS Inhaled corticosteroid; LABA Long-acting β_2-agonist; PEF Peak expiratory flow; PRO Patient-reported outcomes.

Study design

This was a Phase II, randomised, double-blind, parallel group, placebo-controlled, multi-centre study to assess the efficacy, safety, and tolerability of 4 doses of AZD1981 given twice daily (bid) and 2 doses of AZD1981 given once daily (od) in patients with asthma, treated with inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs). Patients who fulfilled all the inclusion criteria and none of the exclusion criteria at Visit 2 entered a 2-week run-in period, where they received treatment with SYMBICORT ® (budesonide/formoterol fumarate dihydrate) pressurised metered-dose inhaler (pMDI)[1] 80/4.5µg per actuation x 2 actuations bid. After the run-in period, patients who fulfilled the randomisation criteria (Visit 3) continued their maintenance treatment with SYMBICORT pMDI 80/4.5, and were randomised into the 12-week treatment period to receive AZD1981 or placebo. Study visits were scheduled after 2, 4, 8 and 12 weeks (±3 days; Visits 4 to 7) of treatment. A follow-up telephone contact was performed 1 week after completion of the treatment period (Visit 8). All patients used a short acting β_2-agonist as a reliever during the run in and the treatment period of the study.

Target patient population and sample size

Male or female (either surgically sterilised or post-menopausal or using a highly effective barrier method of birth control) patients, aged 18 years or above, with at least 6 months

[1] SYMBICORT® is a trademark of the AstraZeneca group of companies.

documented history of asthma, who had currently been treated with combination of ICS (low to medium dose) and LABA, and had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 40% to 85% of predicted normal (PN), were enrolled in this study. In addition, the patients were required to be non-smokers or ex-smokers, and atopic, as shown by a Phadiatop test™. The patients were required to have an asthma control questionnaire 5-item (ACQ5) score of at least 1.5 in order to be randomised to the study.

A total of 1120 patients, distributed in 7 different treatment groups, were planned to be included in the study. With 160 patients per group, and assuming a standard deviation for the change from baseline in FEV_1 of 420 mL (average of 2 measurements), this study had 80% power to demonstrate an effect for a true group difference of 117 mL if the test was 1-sided at the 5% level. The corresponding difference for a 2-sided test was 131 mL. For ACQ5, the standard deviation was assumed to be 0.7 units, and the group difference therefore would be 0.20 units for a 1-sided test at the 5% level and 0.22 units for a 2-sided test. If AZD1981 had clinically meaningful effects on ACQ5 (set to be 0.5 units), this study would be able to provide robust dose-response information on ACQ5, whereas FEV_1 was mainly powered to demonstrate that there was an effect (comparison to placebo). The estimated standard deviation used for FEV_1 was a conservative guess, because there was no available data on ICS and LABA as background medication.

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

AstraZeneca supplied AZD1981 and matching placebo tablets, packaged in blisters and inserted in child-resistant wallets, to the investigational sites. Patients had to take 4 tablets in the morning and 4 tablets in the evening, swallowed whole with a glass of water. The dose groups were: AZD1981 400 mg bid, 200 mg od, 100 mg bid, 80 mg od, 40 mg bid, 10 mg bid and placebo. A total of 7 batches of AZD1981 100 mg tablets, 4 batches of AZD1981 20 mg tablets, 2 batches of AZD1981 10 mg tablets and 8 batches of matching placebo tablets for AZD1981 were used in this study. Individual batch numbers and further information are included in the clinical study report.

Duration of treatment

The study included a 2-week run-in period followed by a 12-week treatment period.

Statistical methods

The primary efficacy variable in this study was the change from baseline in pre-dose, pre-bronchodilator FEV_1 averaged over the treatment period. This was analysed using an analysis of covariance (ANCOVA) model, including the fixed factors of treatment and country and the covariate of baseline pre-dose FEV_1. All other variables were secondary. All hypothesis testing were conducted using 2-sided tests. The p-values were rounded to 4 decimal places; all p-values ≤ 0.05 after rounding were considered statistically significant. In this dose-response study, a number of analyses were performed. In order to establish the lowest effective dose of AZD1981, the bid dosing regimens were compared to placebo, starting with the highest dose (400 mg bid) and testing doses in decreasing order. In order to

deal with multiplicity issues related to the primary objective of the study, a step-down procedure was used when making comparisons of doses of AZD1981 with placebo for the primary variable pre-dose, pre-bronchodilator FEV_1 measured at the clinic.

Subject population

In total 1144 (54.9%) of the 2082 enrolled patients, were randomised to 7 treatment groups. Of these, 4 patients (2 patients each in the AZD1981 200 mg od group and AZD1981 100 mg bid group) did not receive the study treatment and therefore were excluded from safety and efficacy analyses. Of the 1140 (99.7%) patients who received the study treatment, 1034 (90.4%) patients completed the study and 106 (9.3%) patients discontinued from the study. After unblinding of the study data, a Good Clinical Practice (GCP) violation was identified at centre 4323 in Japan. Hence all the 3 randomised patients (1 patient in the AZD1981 40 mg bid group and 2 patients in the placebo group) from this centre were excluded from the efficacy analyses. For reasons of transparency, safety analyses are therefore reported for 2 safety analyses sets; one including and one excluding data from the 3 Japanese patients affected by the GCP violation. A total of 561 (49.2%) patients were female and 580 (50.8%) were male. Mean age of the patients was 45.9 years and the majority of patients (72.2%) were white. The median time since diagnosis of asthma was 15 years; majority (87.4%) of patients were non-smokers and others (12.6%) were former smokers. Mean pre-bronchodilator FEV_1% PN at randomisation was 68.74 %; mean total daily dose of ICS was similar across the treatment groups with mean dose of 407.30 µg. The treatment groups were well balanced with respect to the demographic characteristics; however, the proportion of males versus females seen in this study was higher compared to that seen in the general asthma population. Baseline disease characteristics were reflective of the study entry criteria, and were consistent with a predominantly Global Initiative for Asthma (GINA) III/IV population.

Summary of efficacy results

Improvements in mean change from baseline pre-dose, pre-bronchodilator FEV_1 value over the treatment period was seen across all treatment groups, with values ranging from 0.14 L for placebo (95% CI: 0.08 to 0.19) to 0.20 L for AZD1981 40 mg bid (95% CI: 0.15 to 0.26). The results of the highest dose comparison (AZD1981 400 mg bid vs. placebo) for pre-dose, pre-bronchodilator FEV_1 was not significant (LSmean difference: 0.02, 95% CI: -0.06 to 0.10, p-value: 0.5802) (Table S2). Therefore nothing could be inferred from the subsequent hypothesis testing of the lower doses. Nominal p-values were reported for all remaining treatment comparisons. No dose-response relationship was observed across the active treatment groups.

Improvement in mean change from baseline post-bronchodilator FEV_1, pre- and post-bronchodilator forced vital capacity (FVC) measurements over the treatment period was seen in all treatment groups. None of the AZD1981 doses showed any significant treatment difference for improvement in post-bronchodilator FEV_1 and pre- and post-bronchodilator FVC measurements compared to placebo. The number of patients with ≥1 severe asthma exacerbation and treatment failures was low across the treatment groups.

Table S2 ANCOVA Summary of Treatment Comparisons for Pre-dose, Pre-bronchodilator FEV_1 (L) by time point (Full Analysis Set)

			Difference between groups		
Time Point	**Comparison**	**n**	**LSmean (SE)**	**95% CI**	**p-Value**
Trt Avg, Main	400 mg bid vs Placebo	160 vs 154	0.02 (0.04)	(-0.06, 0.10)	0.5802
	100 mg bid vs Placebo	162 vs 154	0.05 (0.04)	(-0.03, 0.13)	0.1903
	40 mg bid vs Placebo	158 vs 154	0.07 (0.04)	(-0.01, 0.14)	0.0963
	10 mg bid vs Placebo	157 vs 154	0.01 (0.04)	(-0.06, 0.09)	0.7090
	200 mg od vs Placebo	156 vs 154	0.06 (0.04)	(-0.02, 0.13)	0.1592
	80 mg od vs Placebo	159 vs 154	0.02 (0.04)	(-0.06, 0.09)	0.6638
	200 mg od vs 100 mg bid	156 vs 162	0.00 (0.04)	(-0.07, 0.08)	0.9104
	80 mg od vs 40 mg bid	159 vs 158	-0.05 (0.04)	(-0.13, 0.03)	0.2149

400 mg bid, 200 mg od, 100 mg bid, 80 mg od, 40 mg bid and 10 mg bid are AZD1981 dose groups.
Analysis of covariance (ANCOVA) model included treatment and country as the fixed factors and baseline pre-dose FEV_1 as covariate.
'Trt Avg, Main' is defined as the average derived using all available data during randomised treatment that occurred on or prior to date of first treatment failure. All available data during the randomised treatment period was included for patients who did not experience treatment failure.
CI Confidence interval; FEV_1 Forced expiratory volume in 1 second; SE: Standard error.

Improvements in mean change from baseline ACQ5 measurements over the treatment period average were seen in all treatment groups, with values ranging from -0.78 for placebo (95% CI: -0.91 to -0.66) to -0.98 for AZD1981 40 mg bid (95% CI: -1.10 to -0.86). Numerical differences in the number of patients who had well-controlled asthma (ACQ5≤0.75) at the end of treatment were seen between the AZD1981 treatment group and placebo. Improvements in mean change from baseline overall asthma quality of life questionnaire (AQLQ) scores over the treatment period were seen in all treatment groups. No dose-response relationships were observed across the treatment groups for overall ACQ5 and AQLQ scores.

There were small numerical improvements in morning peak expiratory flow (PEF) measurements over the treatment period, observed at the bid doses of AZD1981 greater than or equal to 40 mg bid. No significant improvements were seen across the treatment groups in evening PEF measurements over the treatment period. Numerical improvements in the morning FEV_1 measurements over the treatment period were observed at bid doses of AZD1981 greater than or equal to 40 mg bid. There were generally no improvements seen across the treatment groups in evening FEV_1 measurements over the treatment period. Improvements in mean total asthma symptom scores, symptom-free days, total reliever use, and reliever-free days were noted over the treatment period were observed across all treatment groups. However there were no notable treatment differences between the AZD1981 treatment groups and placebo. Improvements in the percentage of awakening-free nights and asthma-control days were observed across all doses of AZD1981. There was no difference

between active treatment and placebo in the mean number of well-controlled and uncontrolled weeks.

Summary of pharmacokinetic results

The mean plasma concentrations for AZD1981 dosing regimens (bid and od) increased in a dose proportional manner. Trough plasma concentrations of AZD1981 were lower for the od regimens compared with the bid regimens at the same total daily dose. There was a high variability noted in the trough plasma concentrations.

Summary of safety results

Median duration of exposure was 84.0 days for AZD1981 and 85.0 days for placebo. The average exposure time was similar between the AZD1981 treatment groups. Table S3 summarises adverse events (AEs) in each category reported during the study. There were no deaths or other significant AEs reported in this study. Percentage of patients who experienced at least 1 AE was similar between the total AZD1981 treatment groups (29.0%) and placebo (30.1%). Infection and infestations was the most commonly reported system organ class on both AZD1981 and placebo, but the percentage was higher in the placebo group (17.2% versus 15.6%). Nasopharyngitis was the most commonly reported AE on both total AZD1981 (4.6%) and placebo (3.7%). Incidence of skin-related AEs reported on AZD1981, eg, pruritus (0.6%), urticaria (0.3%), atopic dermatitis (0.2%), rash (0.2%), dermatitis (0.1%) and contact dermatitis (0.1%) were too small to draw any conclusion. There was no notable trend of individual AEs or differences across treatment groups. The majority of AEs were of mild (19.3% and 18.4% on AZD1981 and placebo, respectively) or moderate (9.3% and 10.4% on AZD1981 and placebo, respectively) intensity. A total of 50 patients (44 [4.5%] on AZD1981 and 6 [3.7%] on placebo) reported causally related AEs. None of them were graded as SAEs. Majority of the causally related AEs were of mild or moderate intensity. A total of 6 patients (5 [0.5%] on AZD1981 and 1 [0.6%] on placebo) reported 8 SAEs during the treatment period. None of these SAEs were suspected to be causally related to the study drug by the investigator. A total of 24 patients (20 [2.0% on AZD1981 and 4 [2.5%] on placebo) discontinued from the study due to an AE (DAE), and the total number of DAEs was 31. All the DAEs, except the severe leukopenia reported by patient E0703004 (AZD1981 40 mg bid group), were of mild or moderate intensity.

A small percentage of patients treated with AZD1981 had alanine aminotransferase and aspartate aminotransferase values exceeding 3, 5, 10 and 20xULN with the highest incidence in the AZD1981 400 mg bid group. The majority of transaminase abnormalities identified in the active treatment groups occurred after 50 days of exposure to study treatment and consistently returned to baseline after AZD1981 was stopped. For other haematology, clinical chemistry including serum testosterone and TSH, and urinalysis assessments, there were no clinically important changes in mean values over time, individual subjects over time and individual clinically important changes. No clinically meaningful changes across treatment groups were observed for vital signs, physical examination, or ECG findings.

Table S3 Number (%) of patients who had at least 1 AE in any category during treatment (Safety analysis set I)

	Number (%) of patients[a]							
AE category	**400 mg bid (N=164)**	**200 mg od (N=159)**	**100 mg bid (N=164)**	**80 mg od (N=164)**	**40 mg bid (N=163)**	**10 mg bid (N=163)**	**Total AZD1981 (N=977)**	**Placebo (N=163)**
Any AE	46 (28.0)	46 (28.9)	46 (28.0)	40 (24.4)	49 (30.1)	56 (34.4)	283 (29.0)	49 (30.1)
Any SAE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	0 (0.0)	1 (0.6)	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)	5 (0.5)	1 (0.6)
Any AE leading to discontinuation of treatment	3 (1.8)	2 (1.3)	5 (3.0)	4 (2.4)	4 (2.5)	2 (1.2)	20 (2.0)	4 (2.5)
Any other significant AE[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs (OAEs).

400 mg bid, 200 mg od, 100 mg bid, 80 mg od, 40 mg bid and 10 mg bid are AZD1981 dose groups.

During treatment is defined as the onset date ≥the first day of randomised treatment and ≤the last day of randomised treatment+1 day.

The 1 SAE in the placebo group was removed from the safety analysis set II due to the GCP violation.

AE Adverse event; SAE Serious adverse event

There was no significant difference in safety results between safety analysis set I, which included all patients, and safety analysis set II, which excluded the 3 patients affected by the GCP violation.