AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00021
Edition Number	1
Date	20 May 2011

An open, phase I study in male adolescents with asthma, aged 12 to 17 years, to assess pharmacokinetics of orally administered AZD1981 tablets 100 mg twice daily for 6½ days

Study dates: First patient enrolled: 14 October 2010
Last patient last visit: 2 February 2011

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

The study was conducted at 1 centre

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**	
To investigate the pharmacokinetics of orally administered AZD1981 in male adolescents with asthma.	AUC_{τ}, $C_{ss,max}$, $C_{ss,trough}$, and CL/F	PK
	Secondary	
	$Ae_{\tau,ss}$, $fe_{\tau,ss}$, and CL_R	
Secondary	**Secondary**	
To evaluate the tolerability and safety of AZD1981	Incidence and severity of AEs, clinical laboratory variables, vital signs, physical examination, and ECG	Safety
To evaluate efficacy of AZD1981	ACQ5 and FEV_1 (changes since pre-dose; measured at the clinic)	Efficacy
Exploratory[a]	**Exploratory**	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to AZD1981 or susceptibility to asthma.	DNA/genotype	PGx

ACQ5: Asthma Control Questionnaire (5 items); **AE**: Adverse Event; **$Ae_{\tau,ss}$**: Amount of administered dose excreted in urine during a dosage interval (τ) at steady state; **AUC_{τ}**: Area under the plasma concentration-time curve during a dosing interval (τ) at steady state; **CL/F**: Apparent plasma clearance; **CL_R**: Renal clearance; **$C_{ss,max}$**: Maximum plasma concentration during a dosing interval at steady state; **$C_{ss,trough}$**: Minimum plasma concentration during a dosing interval at steady state (sampled just before the next dose during repeated dose-administration); **ECG**: Electrocardiogram; **$fe_{\tau,ss}$**: Fraction of administered dose excreted in urine during a dosage interval (τ) at steady state; **FEV_1**: Forced expiratory volume in one second; **PGx**: Pharmacogenectics; **PK**: Pharmacokinetics.

[a] Optional part of the study. To be reported separately from the Clinical Study Report.

Study design

This was an open-label, repeated-dose, phase-I study designed to assess the pharmacokinetics (at steady-state conditions), safety, and tolerability of orally administered AZD1981 when given to male adolescents (12 to 17 years) with asthma. Lung function and symptoms were measured pre-dose and at the last day of treatment.

Target subject population and sample size

The target population was male adolescents with asthma, aged 12 to 17 years inclusive.

The aim was to include 21 patients to achieve 18 evaluable patients, but no formal statistical power calculation was performed. Age distribution was considered: At least 5 patients from each of the following 3 age groups were to be included: 12 to 13 years (incl.), 14 to 15 years (incl.), and 16 to 17 years (incl.).

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

All patients received (oral administration) 1x 100 mg AZD1981 as film-coated tablets (manufactured by AstraZeneca; batch number 10-003598AZ) twice daily.

No comparator was used.

Duration of treatment

AZD1981 (twice daily) was to be given over 6½ consecutive days, with a time window of –1 day and +2 days. However, because the clinic visits were on same day every week, the actual treatment period was 7½ days for all patients. The duration of each patient's participation in the study was about 5 weeks. The study comprised 6 visits: Visits 1 and 2: screening (Visit 2 within 21 days of Visit 3); Visit 3: start of treatment; Visit 4: telephone contact in conjunction with the last evening dose to capture time of morning and evening dosing on Day 6; Visit 5: last day of treatment; Visit 6: follow-up (7 to 10 days after last dose).

Statistical methods

No formal statistical hypothesis testing was performed in this study. There was no analysis performed regarding efficacy.

The safety analysis set consists of all patients who had taken at least one dose of AZD1981 and for whom post-dose data are available (full-analysis set). The PK analysis set consists of all patients who received AZD1981 and who have evaluable PK data. All generated data were included in the statistical analysis. No patient was excluded from the analysis due to protocol deviations.

Subject population

In total, 23 male adolescents with asthma were enrolled, and 22 were allocated to treatment.

Median time since diagnosis of asthma was 12.3 years. All patients except one were prescribed other asthma medication at study entry; 16 patients were using inhaled glucocorticosteroids. Besides asthma, allergy, eczema, and rhinitis were common conditions amongst the patients in the studied population. No patient took any disallowed medication during the study.

The mean age of the population was 14.3 years. There was a relatively even spread over the age span of interest with 9, 8 and 5 patients, respectively in the 3 pre-specified age groups: 12 to 13 years, 14 to 15 years, and 16 to 17 years.

All 22 patients completed the study. All patients took 15 doses of AZD1981; the mean exposure time was 7½ days.

The number of patients, in total and in each of the 3 age groups, as well as their demography and baseline characteristics were in line with the population that was intended to be included in the study.

Summary of efficacy results

No analysis has been performed on the lung function (FEV_1) and ACQ5 data.

Summary of pharmacokinetic results

Geometric mean plasma C_{max} and AUC following oral administration of 100 mg twice daily via tablets during 7½ days to male adolescents were 4157 nmol/L and 16248 h•nmol/L, respectively. Geometric mean renal clearance of AZD1981 was 4.7 L/h.

There was no indication of a correlation between plasma- and urine-derived pharmacokinetic variables and body weight/ age.

Summary of safety results

No safety or tolerability concerns were identified in this study. There were no deaths, no Serious Adverse Events, no discontinuations of investigational product (IP) due to adverse Event (AE), and no other significant AEs in the study.

Eight patients (36%) reported in total 12 AEs. No event was of severe intensity and none was judged by the Investigator to be causally related to the IP. All but 2 AEs were mild; 2 patients reported each a moderate AE: *syncope* and *fatigue* (preferred-term level), respectively. Most events were reported in the SOC (system organ class) “Respiratory, Thoracic and Mediastinal” (4 AEs), and in the SOC “Infections and Infestations” (2 AEs).

There were no clinically relevant changes in clinical laboratory, vital signs, ECG, or physical examination.