Clinical Study Report Synopsis

Drug Substance	AZD8683
Study Code	D1883C00001
Edition Number	1

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Inhaled AZD8683 after Single Ascending Doses in Healthy Male Subjects

Study Dates	First subject enrolled: 20 October 2009 Last subject completed: 14 January 2010
Phase of development	Clinical pharmacology (I)

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

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table 1 Primary and secondary objectives and variables

Objectives	Variables	Type
Primary		
To assess the safety and tolerability of AZD8683 following inhaled administration of single ascending doses and to estimate the maximum tolerated dose, if within predefined exposure and dose limits, in healthy male subjects.	• Adverse events • Laboratory variables: clinical chemistry, haematology, urinalysis • Vital signs: blood pressure, pulse, body temperature • ECG parameters	Safety
Secondary		
To characterise the pharmacokinetics of AZD8683 and assess the dose proportionality of the phamacokinetics following inhaled administration of single ascending doses of AZD8683 in healthy male subjects.	• C_{max}, t_{max}, λ_z, $t_{½}$, $AUC_{(0-t)}$, AUC, CL/F, V_Z/F, MRT, Ae, CL_R	PK
To investigate the pharmacodynamic effects of inhaled single ascending doses of AZD8683 in healthy male subjects.	• Lung function: FEV_1, FVC • Blood pressure, pulse, heart rate, QTcF	PD
Exploratory		
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD8683.		PGx
To collect plasma and urine samples for possible exploratory analysis of metabolites of AZD8683.		PK

AUC Area under plasma concentration time curve; C_{max} Maximum plasma concentration; t_{max} Time to maximum plasma concentration; λ_z Terminal rate constant; $t_{½}$ Terminal half life; CL/F Total apparent plasma clearance; CL_R Renal clearance; V_Z/F Apparent volume of distribution during terminal phase; MRT Mean residence time; Ae Amount excreted unchanged (% of dose); FEV_1 forced expiratory volume

(Continued)

Table 1 Primary and secondary objectives and variables

in 1 second; FVC forced vital capacity; QTcF QT interval corrected for heart rate using Fridericia's formula; PGx pharmacogenetic
With regard to exploratory objectives, samples for possible future pharmacogenetic investigation were collected - this has not been further addressed in the clinical study report

Study design

Phase I, randomised, double-blind, placebo-controlled, single centre study to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD8683 following single ascending dose administration to healthy male subjects. The study was designed to recruit up to 72 subjects in up to 9 separate cohorts. After each cohort, a Safety Review Committee evaluated the safety, tolerability and the pharmacokinetics of AZD8683 and decided the next dose (planned dose, increased or decreased dose, repeated dose or dose stopped). The actual dose escalation that was applied in the study is shown in Table 2 below.

Target healthy volunteer population and sample size

Up to 72 healthy male subjects aged 18-45 years inclusive were planned; 8 subjects per cohort (2 placebo and 6 active drug).

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

Single doses of AZD8683 (0.7 µg, 2.9 µg, 11.6 µg, 35 µg, 100 µg, 234 µg and 502 µg delivered dose) or placebo inhaled via Spira nebuliser.

AZD8683 was provided as a powder for oral solution/suspension for reconstitution (AZD8683 20 mg, batch no. 09-006688AZ and AZD8683 10 mg, batch no. 09-00687AZ). Placebo matching the AZD8683/vehicle for AZD8683 was composed of 0.5% Polysorbate 80 in 5% glucose solution pH 3.8, adjusted with phosphoric acid (batch no. 09-006756AZ).

Duration of treatment

Single dose.

Statistical methods

Safety and tolerability data, and PK and PD parameters were summarised descriptively including tables, listings and graphs. Laboratory safety and PD data were compared between active treatment and placebo. Placebo subjects from different dose-levels were pooled for

the comparison. Comparisons of peak and average effects were made for the change from baseline using analysis of variance models. All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

Subject population

A total of 52 healthy male subjects were randomised and received study treatment: 39 subjects received AZD8683 and 13 received placebo. The numbers of subjects exposed in each dose cohort are presented in Table 2. One subject in Cohort 4 (35 µg) discontinued the study after the treatment visit (lost to follow-up).

All 52 subjects allocated to treatment were male. Their average age was 33.6 years (range: 21 to 45) and their average body mass index (BMI) was 24.9 kg/m^2 (range: 19 to 30). The dose groups were generally well matched for demographic and other baseline characteristics.

Table 2 Summary of cohorts and dose escalation. Number of subjects who received AZD8683 and placebo via Spira nebuliser in each cohort

Cohort	Delivered dose (µg)	All n	AZD8683 n	Placebo n
1	0.7	8	6	2
2	2.9	8	6	2
3	11.6	8	6	2
4	35	8	6	2
5	100	8	6	2
6	234	8	6	2
7	502	4	3	1

Summary of pharmacokinetic results

Absorption of AZD8683 following inhalation dosing appeared to be rapid. The exposure to AZD8683 following single inhaled dosing as assessed by the C_{max} increased in an approximately proportional manner between 100 and 502 µg. The exposure as assessed by the AUC increased in a proportional manner between 234 and 502 µg, but in a greater than proportional manner between 100 and 234 µg.

Pharmacokinetic parameters could not be determined up to and including 35 µg; however the increase in exposure to AZD8683 between 35 and 100 µg appears to be in a considerably greater than proportional manner. At the two highest doses, the elimination half-life of AZD8683 was calculated to be approximately 41 h. The apparent volume of distribution of AZD8683 was very large and was calculated to be approximately 10700 L. The apparent

plasma clearance of AZD8683 was high and was calculated to be approximately 180 L/h. The amount of AZD8683 excreted unchanged in urine was low, at <1%.

Summary of pharmacodynamic results

There was no indication of an effect of AZD8683 on FEV_1 and FVC over the dose range studied. Only very minor systemic effects were seen - a small but statistically significant increase in peak pulse (5.6 bpm) and heart rate (4.2 bpm) was detected at the highest dose level (502 µg).

Summary of safety results

There were no deaths, SAEs, DAEs or AEs of severe intensity. In doses up to and including 234 µg (delivered dose) via nebulisation (Cohort 6), there was no indication of an increase in the frequency of AEs with increasing dose of AZD8683. However, at 502 µg (Cohort 7), inhalation of investigational product was accompanied by inspiratory difficulties during nebulisation and respiratory AEs. Dosing in Cohort 7 was therefore discontinued and no further dose escalation was performed in the study.

A total of 4 subject were dosed in Cohort 7: 3 received AZD8683 502 µg and 1 received placebo. All 4 subjects dosed in Cohort 7 experienced inspiratory resistance during inhalation; the reason for the inspiratory resistance is uncertain. AEs were reported by 2 subjects that received AZD8683 (9 events) and the subject on placebo (1 event). The majority of AEs reported at 502 µg were respiratory AEs, such as chest tightness and throat irritation.

Overall, there were no patterns of any clinically significant changes in vital signs, lung function, ECG or clinical laboratory parameters.