AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD8683 |
| Study Code | D1883C00006 |
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# A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Inhaled AZD8683 after Single Ascending Doses Administered via Turbuhaler™ in Healthy Volunteers

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| **Study dates:** | First subject enrolled: 24 October 2011 |
| | Last subject last visit: 12 May 2012 |
| **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 S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
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| **Priority** | **Type** | **Description** | **Description** |
| Primary | Safety | To assess the safety and tolerability of AZD8683 following inhaled administration via Turbuhaler™ of single ascending doses and to estimate the maximum tolerated dose, if within predefined exposure and dose limits, in healthy volunteers. | AEs, safety laboratory variables, physical examination, ECGs, vital signs, and spirometry |
| Secondary | PK[a] | To characterise the PK of AZD8683 and assess the dose proportionality of the PK following inhaled administration of single ascending doses of AZD8683 in healthy volunteers. | $C_{max}$, $t_{max}$, $t_{½\,\lambda z}$, AUC, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}24)}$, $AUC_{(0\text{-}48)}$, CL/F, $V_z$/F, mean residence time, $A_e$, $F_e$, and $CL_R$ |
| | PD | To investigate the PD of inhaled single ascending doses of AZD8683 in healthy volunteers. | $E_{av}$ and $E_{max}$ for $FEV_1$, FVC, systolic blood pressure, pulse rate, heart rate, and QTcF; $E_{av}$ and $E_{min}$ for diastolic blood pressure |
| Exploratory[b] | Pharmaco-genetic | 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 (optional). | Not applicable |
| | PK | To collect and store plasma and urine samples for possible exploratory analysis of metabolites of AZD8683. | Not applicable |
| | Biomarkers | To collect and analyse biological samples (eg, plasma) for circulating biomarkers from consenting healthy male volunteers before the administration of the investigational product (optional). | Not applicable |

[a] The delivered dose of AZD8683 was used for the calculation of CL/F, $F_e$, $CL_R$, and dose normalisation.
[b] Performed by AstraZeneca and reported separately from the clinical study report.

$\lambda_z$: terminal rate constant; $A_e$: amount excreted unchanged in urine; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0\text{-}t)}$: area under the plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0\text{-}24)}$: area under the plasma concentration-time curve from zero to 24 hours; $AUC_{(0\text{-}48)}$: area under the plasma concentration-time curve from zero to 48 hours;

CL/F: apparent plasma clearance: $CL_R$: renal clearance; $C_{max}$: maximum observed plasma concentration; DNA: deoxyribonucleic acid; $E_{av}$: average value over the first 4 hours; $E_{max}$: maximum value over the first 4 hours; $E_{min}$: minimum value over the first 4 hours; $F_e$: fraction of dose (%) excreted unchanged in urine; $FEV_1$: forced expiratory volume in 1 second; FVC: forced vital capacity; PD: pharmacodynamic(s); PK: pharmacokinetic(s); $t_{½\lambda z}$: terminal half-life; $t_{max}$: time to reach $C_{max}$; $V_z/F$: apparent volume of distribution during terminal phase

## Study design

This was a double-blind, randomised, placebo-controlled, parallel-group, single ascending dose study in healthy male volunteers.

The study was planned to consist of 4 cohorts (dose levels) with 8 healthy volunteers in each cohort. The randomisation scheme was produced using the global randomisation system (GRand). The 8 eligible healthy volunteers in each cohort were randomised to receive a single administration of the investigational product (6 healthy volunteers were to receive AZD8683 and 2 healthy volunteers were to receive placebo).

The study consisted of 3 visits. Screening took place at Visit 1 (-30 to -2 days), the investigational product was administered on Day 1 of Visit 2 (residential period from Day -1 to Day 3 with PK sampling on Days 4 and 6), and Visit 3 was the follow-up visit (7 to 13 days postdose).

## Target subject population and sample size

Up to 40 healthy male volunteers aged 18 to 45 years (inclusive) able to inhale from the Turbuhaler™ according to the instructions provided and able to perform spirometry, were to be included and randomised in the study.

Due to the exploratory nature of the study, the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds.

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

Each healthy volunteer received a single inhaled dose of AZD8683 or placebo via the Turbuhaler™ in the morning of Day 1.

The administered delivered doses were 200 µg (104 µg predicted lung deposited dose), 400 µg (208 µg predicted lung deposited dose), 600 µg (312 µg predicted lung deposited dose), and 950 µg (494 µg predicted lung deposited dose).

AZD8683 (50 and 250 µg/dose) and placebo batch number: 11-002197AZ.

## Duration of treatment

Single dose.

## Statistical methods

The analysis of data was based on the different subsets according to the purpose of the analysis, ie, for safety, PK, and PD, respectively. The analyses of safety, tolerability, PK, and PD were summarised descriptively including table, listings, and graphs, as appropriate. Data were presented by actual delivered dose (not by cohort) and healthy volunteers who received placebo were pooled across cohorts for the purpose of summarising the results. Baseline for the PD and safety variables was the last valid value before investigational product administration.

Dose proportionality was analysed using a power model approach using the logarithm of the PK parameters AUC, $AUC_{(0-t)}$, and $C_{max}$ as the dependent variable and the logarithm of the dose as the independent variable. Point estimates with a 2-sided 90% confidence interval (CI) of slope parameter for each of the variables AUC, $AUC_{(0-t)}$, and $C_{max}$ were calculated.

For each PD parameter (average value over the first 4 hours [$E_{av}$], maximum value over the first 4 hours [$E_{max}$], or minimum value over the first 4 hours [$E_{min}$]), treatments were compared using an analysis of covariance model with fixed factor treatment and the baseline value as a covariate. The dependent variable was the difference between parameter and baseline (or for lung function parameters, the ratio between parameter and baseline). For forced expiratory volume in 1 second ($FEV_1$) and forced vital capacity (FCV) multiplicative models were used, for other variables additive models were used. Point estimates for each treatment as well as point estimates, p-values and 95% CI for the ratios or differences versus placebo were calculated.

## Subject population

For Cohort 1 (200 µg delivered dose) only 7 healthy volunteers could be recruited and were randomised.

The first 4 healthy volunteers in Cohort 2 (400 µg) were incorrectly provided with empty training inhalers that did not contain any investigational product. No investigational product was administered to these healthy volunteers. Due to this error, the study was suspended and the 4 healthy volunteers were withdrawn from the study. The data for these 4 healthy volunteers were not included in the demographic and safety listings. Therefore no data are available to report for these healthy volunteers. When the study was restarted, the dose level originally intended for Cohort 2 (400 µg) was instead administered to Cohort 3 consisting of 8 new healthy volunteers.

A total of 35 healthy male volunteers were enrolled and randomised, of which 4 healthy volunteers were incorrectly dosed with empty training inhalers and 31 healthy volunteers received investigational product and completed the study:

- 200 µg AZD8683 delivered dose: 6 healthy volunteers
- 400 µg AZD8683 delivered dose: 6 healthy volunteers

- 600 µg AZD8683 delivered dose: 6 healthy volunteers
- 950 µg AZD8683 delivered dose: 6 healthy volunteers
- Placebo: 7 healthy volunteers

Overall, the cohorts were comparable with regards to demographic characteristics.

**Summary of pharmacokinetic results**

Following a single inhaled delivered dose (200, 400, 600, and 950 µg) AZD8683 appeared rapidly in plasma with a median $t_{max}$ range of 3 to 7 minutes. Following $C_{max}$ the plasma concentration profile was characterised by a rapid distribution phase, followed by a terminal elimination phase with a geometric mean $t_{½\,\lambda z}$ range of 58 to 72 hours across dose groups. The highest geometric mean $C_{max}$ was 6.15 nmol/L (observed at 600 µg) and the highest geometric mean AUC was 16.6 nmol*h/L (950 µg). The geometric mean apparent oral clearance was 89.9 to 123 L/h and apparent volume of distribution was 7630 to 12700 L, respectively. Less than 1% of the AZD8683 delivered dose was excreted unchanged in urine cumulatively over 48 hours across the dose range tested.

There was no consistent deviation from dose-proportional PK across the dose range tested in this study.

**Summary of pharmacodynamic results**

There were 7 PD markers assessed in this study. At the highest dose of AZD8683 administered via Turbuhaler™ (950 µg delivered dose) a statistically significant increase in $FEV_1$ $E_{av}$ and $E_{max}$ (6.3% and 5.1%, respectively) was observed compared to placebo. The FVC ($E_{av}$ and $E_{max}$) was not different from placebo. There were no consistent effects on systolic blood pressure or diastolic blood pressure within the dose range tested. There were no consistent effects on heart rate and pulse within the dose range tested. There were no consistent effects on QTcF within the dose range tested.

**Summary of safety results**

There were no serious adverse events (SAEs), severe AEs, or discontinuations of the investigational product due to an AE reported in the study. A total of 5 AEs were reported by 4 healthy volunteers after the investigational product administration. No AEs were reported for the 200 and 950 µg delivered dose levels. By Preferred Term, no AE was reported by more than 1 healthy volunteer. All the AEs were considered to be mild in severity by the investigator and resolved by the end of the study. No respiratory-related AEs were reported.

No clinically relevant safety findings were reported for the safety laboratory assessments, vital signs, ECG assessments, physical examinations, or spirometry assessments. The maximum tolerated dose could not be determined in this study as the highest allowed dose, according to the clinical study protocol, was reached.