AstraZeneca

Clinical Study Report Synopsis

Drug Substance AZD8683

Study Code D1883C00002

Edition Number 1

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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 Multiple Ascending Inhaled Doses of AZD8683 in Healthy Volunteers and of Repeated Inhalation of One Dose Level of AZD8683 in Patients with Chronic Obstructive Pulmonary Disease (COPD), given Once Daily via Turbuhaler™

Study dates: First subject enrolled: 6 June 2012
Last subject last visit: 16 November 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
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD8683 following inhaled administration of multiple ascending doses in healthy volunteers and following repeated inhaled administration of 1 dose level of AZD8683 in patients with COPD, delivered once daily as dry powder via Turbuhaler™	Adverse events, vital signs (blood pressure and pulse rate), body temperature, ECGs, physical examinations, laboratory variables (clinical chemistry, haematology, and urinalysis), and spirometry to assess lung function (FEV_1 and FVC)
Secondary	Pharmaco-kinetic	To characterise the PK of AZD8683 following administration of a single and multiple ascending doses in healthy volunteers and following repeated inhaled administration of 1 dose level of AZD8683 in patients with COPD, delivered once daily as dry powder via Turbuhaler™	Following the single dose part of the study (Day 1) in healthy volunteers: C_{max}, t_{max}, $t_{1/2\lambda z}$, AUC, $AUC_{(0-24)}$, $AUC_{(0-72)}$, $AUC_{(0-t)}$, CL/F, V_z/F, MRT, CL_R, A_e, $Ae_{(0-t)}$, and f_e Following the single dose part of the study (Day 1) in COPD patients: C_{max}, t_{max}, and $AUC_{(0-24)}$ Following the multiple dose part of the study (Day 15) in healthy volunteers: C_{max}, t_{max}, C_{min}, $t_{1/2\lambda z}$, $AUC_{(0-\tau)}$, CL/F, $R_{acAUC(0-\tau)}$, R_{acCmax}, time dependency, CL_R, $A_{e(t1-t2)}$, $A_{e(0-\tau)}$, and $f_{e(0-\tau)}$ Following the multiple dose part of the study (Day 12) in COPD patients: C_{max}, C_{min}, t_{max}, $AUC_{(0-\tau)}$, C_{av}, CL/F, $R_{acAUC(0-\tau)}$, R_{acCmax}
	Pharmaco-dynamic	To investigate the PD effects of inhaled multiple ascending doses of AZD8683 in healthy volunteers and following repeated inhaled administration of 1 dose level of AZD8683 in patients with COPD, delivered once daily as dry powder via Turbuhaler™	FEV_1, FVC, SBP, pulse rate, QTcF, and heart rate: E_{av} and E_{max} DBP: E_{av} and E_{min}

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory[a]	Pharmaco-kinetic	To collect and store plasma and urine samples for possible exploratory analysis of metabolites of AZD8683 in healthy volunteers	-
	Pharmaco-genetic	To collect and store deoxyribonucleic acid (DNA), from healthy volunteers and from COPD patients, for possible future exploratory research into genes/genetic variation that may influence response (ie, safety, tolerability, PK, and PD) to AZD8683 (optional)	-
	Biomarker	To collect and analyse biological samples (eg, plasma) for circulating biomarkers from consenting healthy volunteers before the administration of the investigational product (optional)	-

Note: Turbuhaler is a trademark of the AstraZeneca group of companies.

[a] If performed, these results will be reported separately from this Clinical Study Report in a stand-alone report.

A_e: cumulative amount of AZD8683 excreted unchanged in urine; $A_{e(0-\tau)}$: A_e from zero (predose) to the end of the dosing interval; $A_{e(0-t)}$: A_e from zero (predose) to time t; $A_{e(t1-t2)}$: A_e in a collection interval; AUC: area under the plasma concentration-time curve; $AUC_{(0-24)}$: AUC from zero to 24 hours; $AUC_{(0-72)}$: AUC from zero to 72 hours; $AUC_{(0-\tau)}$: AUC during the dosing interval; $AUC_{(0-t)}$: AUC from zero to the time of the last measureable concentration; C_{av}: average plasma concentration; CL/F: apparent plasma clearance; CL_R: renal clearance; C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; E_{av}: average effect; ECG: electrocardiogram; E_{max}: maximum observed effect; E_{min}: minimum observed effect; f_e: fraction of dose excreted unchanged in urine; $f_{e(0-\tau)}$: f_e during the dosing interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MRT: mean residence time; PD: pharmacodynamic(s); PK: pharmacokinetic(s); $R_{ac,AUC(0-\tau)}$: accumulation ratio of $AUC_{(0-\tau)}$ (Days 15 or 12) compared to $AUC_{(0-24)}$ on Day 1; $R_{ac,Cmax}$: accumulation ratio of C_{max} (Days 15 or 12) compared to C_{max} on Day 1; SBP: systolic blood pressure; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to maximum plasma concentration; V_z/F: apparent volume of distribution during the terminal phase.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy male and female (of non-childbearing potential) volunteers and in chronic obstructive pulmonary disease (COPD) patients (1 dose level) conducted at a single centre. The study design allowed a gradual dose escalation with intensive safety monitoring to ensure the safety of the subjects.

The subjects were to be randomised to either AZD8683 or placebo in a 6:3 ratio. Up to 36 healthy volunteers in 4 cohorts and 1 cohort with 9 COPD patients were planned to be randomised in the study.

The COPD patients were dosed in a separate cohort after successful completion of 3 cohorts with healthy volunteers. This cohort was prematurely terminated as 2 of the COPD patients met the predefined stopping criteria of a decrease in forced expiratory volume in 1 second (FEV_1) of ≥30% within 1 hour after administration of the investigational product.

Target subject population and sample size

Healthy male and female volunteers aged 18 to 45 years and male and female COPD patients aged ≥40 years who provided written informed consent.

Patients randomised in the COPD cohort were to have a clinical diagnosis of COPD for more than 1 year at Visit 1, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and a FEV_1 between 40% and 80% (inclusive) of the predicted normal value (post-bronchodilator) and post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.

Up to 36 healthy volunteers in 4 cohorts and 1 cohort with 9 COPD patients were planned to be randomised in the study.

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

Table S2 Details of the investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD8683 Turbuhaler™	Dry powder for inhalation 50 µg/dose[a], 60 doses (fine particle dose 29.4 µg)	AstraZeneca	11-001036AZ
AZD8683 Turbuhaler™	Dry powder for inhalation 250 µg/dose[a], 60 doses (fine particle dose 151.6 µg)	AstraZeneca	11-001038AZ
Placebo	Dry powder for inhalation, 60 doses	AstraZeneca	11-001447AZ

[a] Strength per dose refers to the delivered dose from Turbuhaler™.

Duration of treatment

Healthy volunteers: Single dose on Day 1 and multiple doses from Days 4 to 15

COPD patients: Multiple doses from Days 1 to 12

Statistical methods

The statistical analysis was performed using SAS® Version 9.2 by Quintiles according to Standard Operation Procedures and Work Instructions.

All data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum). Only scheduled data were presented in the summary presentations. Categorical variables were summarised in frequency tables (frequency and proportion). Graphical presentations were used as appropriate.

Assessment of dose proportionality was accomplished graphically and by statistical analysis The time dependency of the PK was evaluated by comparing $AUC_{(0-\tau)}$ (Day 15) with AUC (Day 1). Attainment of the steady state was assessed graphically. The safety analysis set was used to assess safety and tolerability variables.

The PK analysis set included all subjects who received investigational product (AZD8683) and had evaluable PK data appropriate for the evaluation of interest. The PD analysis set included all randomised and treated subjects with sufficient data collected to compute the PD parameters. Data were presented by actual dose (not by cohort), and subjects who received placebo were pooled across cohorts for the purposes of summarising the safety and PD results. Due to the exploratory nature of the study the sample size was not based on formal statistical considerations.

Subject population

Screened: 106 subjects

Planned: 45 subjects (36 healthy volunteers and 9 COPD patients)

Randomised: 30 subjects (27 healthy volunteers and 3 COPD patients)

Analysed: 30 subjects (27 healthy volunteers and 3 COPD patients)

Completed: 26 subjects (25 healthy volunteers and 1 COPD patient)

The mean and median age varied between the healthy volunteer cohorts, the minimum age was 20 years and the maximum was 44 years. The median age for healthy volunteers on AZD8683 in Cohort 1 (100 µg AZD8683) was 36 years, in Cohort 2 (300 µg AZD8683) was 31 years, and in Cohort 3 (900 µg AZD8683) was 26 years. One female healthy volunteer was randomised to placebo, all other subjects were male; and the majority of subjects were white. The body mass index (BMI) ranged from 21.25 kg/m^2 to 29.83 kg/m^2 and the minimum weight was 63.6 kg, in accordance with the inclusion criteria.

The age for the 3 COPD patients ranged from 58 to 65 years. The BMI ranged from 24.38 kg/m^2 to 29.41 kg/m^2 and the minimum weight was 78.3 kg.

The mean screening FEV_1 values for healthy volunteers were: 4.07 L (100 µg AZD8683), 4.23 L (300 µg AZD8683), 4.19 L (900 µg AZD8683), and 4.09 L (placebo). The mean screening FEV_1 values for COPD patients were: 1.55 L (900 µg AZD8683) and 2.39 L (placebo).

Summary of pharmacokinetic results

In healthy volunteers, AZD8683 plasma concentration profiles were characterised by rapid absorption followed by multi-phasic decline with rapid distribution phase and a slower terminal phase. The predefined exposure stopping criteria were not met for C_{max} (16.7 nmol/L) or AUC (46.7 nmol*h/L) in any of the subjects after the single and multiple inhaled doses of 100, 300 or 900 µg AZD8683. Exposure parameters increased approximately proportional to dose. The maximum AZD8683 plasma concentration occurred consistently at a median time of 5 minutes following single and multiple dosing, and was independent of the dose. After multiple dosing on Day 15, where the terminal phase was well defined, geometric mean elimination half life ($t_{1/2\lambda z}$) ranged from 98.2 to 107 hours. Based on visual observation, steady state had been achieved following 12 consecutive daily inhaled doses of AZD8683. Geometric mean AUC accumulation ratios ranged from 1.70- to 3.19-fold AZD8683 following multiple doses. No time-dependent PK of AZD8683 was observed in the dose range of 100 to 300 µg. On average, <1.06% of the dose was excreted as unchanged drug in urine cumulatively over 0 to 72 hours postdose on Day 1. On Day 15, < 1.30% of the dose was excreted unchanged in urine cumulatively over 0 to 24 hours postdose.

The 2 COPD patients AZD8683 exposure values (AUC and C_{max}) after a single dose of AZD8683, were lower than the geometric mean exposure for healthy volunteers receiving the same dose of 900 µg.

Summary of pharmacodynamic results

Single doses of AZD8683 at the delivered doses of 300 and 900 µg healthy volunteers provided an increase in FEV_1 E_{av} (6.15 and 6.04%, respectively) and E_{max} (8.43% and 5.75 %, respectively) compared to placebo over the first 4 hours postdose. Multiple doses of AZD8683 at the delivered doses of 300 µg healthy volunteers provided an increase in FEV_1 E_{av} and E_{max} (6.01% and 7.72%, respectively) compared to placebo over the first 4 hours postdose. Following single or multiple doses in healthy volunteers there were no substantial differences observed in FVC (E_{av} and E_{max}) compared to placebo over the first 4 hours postdose.

There were no substantial differences observed in systemically-mediated effects (pulse, heart rate, systolic and diastolic blood pressure, and QTcF) relative to placebo over the first 4 hours postdose following single or multiple doses in healthy volunteers.

PD data were available for only 2 COPD patients following single dose of 900 µg on Day 1 with no PD data on Day 15; this was due to stopping the investigational product administration after 2 COPD patients met the stopping criteria for a decrease in FEV_1 (see safety results).

Summary of safety results

No deaths or serious adverse events (SAEs) were reported.

The investigational product administration was discontinued for 2 healthy volunteers due to adverse events (AEs): 1 healthy volunteer in Cohort 1 due to abnormal liver function test (Subject E0001017; placebo) and 1 healthy volunteer in Cohort 3 due to oropharyngeal pain and tonsillitis (Subject E0001058; 900 µg AZD8683).

At least 1 AE was reported for 4 healthy volunteers (66.7%) on 100 µg AZD8683, 2 healthy volunteers (33.3%) on 300 µg AZD8683, and 5 healthy volunteers (83.3%) on 900 µg AZD8683. At least 1 AE considered related to the investigational product by the Investigator was reported for 4 healthy volunteers (66.7%) on 100 µg AZD8683, no healthy volunteers on 300 µg AZD8683, and 5 healthy volunteers (83.3%) on 900 µg AZD8683.

For healthy volunteers, the proportion of subjects with AEs was similar between the dose levels and treatments (AZD8683 versus placebo) and no clear drug-effect was observed with regards to any of the AEs.

The investigational product administration was discontinued for 2 COPD patients, 1 due to cough and productive cough (Subject E0001101; 900 µg AZD8683) and 1 due to chest discomfort and cough (Subject E0001103; 900 µg AZD8683) in association with a fall in FEV_1 meeting the discontinuation criterion.

At least 1 AE was reported for both COPD patients (100.0%) on 900 µg AZD8683 and were considered to be related to the investigational product by the Investigator.

An alanine aminotransferase (ALT) value of >3.0 times the upper limit of normal (ULN) was reported for Subject E0001017 (Cohort 1; placebo) on Day 3. This was reported as an AE and the investigational product administration was discontinued for this healthy volunteer.

Subjects E0001101 and E0001103 (both were COPD patients) had clinically significant decreases in FEV_1 postdose which met the stopping criterion for the study. Subject E0001101 had a FEV_1 reduction from predose of 30.4% within 1 hour of the investigational product administration on Day 1. Subject E0001103 had a FEV_1 reduction from predose of 46% within 1 hour of the investigational product administration on Day 2. After this initial decline, these values returned to approximately the predose values at 2 and 4 hours postdose.

No safety concerns were identified from the laboratory, vital signs, electrocardiogram (ECG), or physical examination assessments.