AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8683
Study Code	D1883C00007
Edition Number	1
EudraCT Number	2012-002900-42

A Randomised, Double-Blind, Placebo- and Active-Controlled, Multi-Centre, 6-Way Cross-Over, Single-Dose Phase IIa Study to Investigate the Bronchodilatory and Systemic Effects of 4 Different Doses of Inhaled AZD8683 in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study dates: First patient enrolled: 19 October 2012
Last patient last visit: 3 December 2012

Phase of development: Therapeutic exploratory (IIa)

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.

Reason for synopsis-format Clinical Study Report - Early termination of the study

The D1883C00007 study was prematurely terminated on 3 December 2012 due to findings in another AZD8683 study (Study D1883C00002), a Phase I multiple ascending dose (MAD) study in healthy volunteers and chronic obstructive pulmonary disease (COPD) patients. The MAD study was terminated early on 9 November 2012 due to a transient drop in forced expiratory volume in the first second (FEV_1) within 1 hour after AZD8683 administration in 2 COPD patients, fulfilling the pre-specified-stopping criterion. The D1883C00007 study was placed on hold from 9 November 2012 till it was terminated on 3 December 2012.

Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables of the study.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PD	To investigate the bronchodilatory effects of 4 different single doses of inhaled AZD8683 compared with placebo, with respect to peak and trough FEV_1, in patients with COPD	Change from baseline in: Peak FEV_1 (0-24h) Trough FEV_1 (22-26h)
Secondary	PD	To investigate dose-response within the tested dose range for AZD8683 with respect to peak, trough, and average FEV_1	Peak FEV_1 (0-24h) as change from baseline Trough FEV_1 (22-26h) as change from baseline Average FEV_1 (0-24h)
	PD	To investigate the bronchodilatory effects of 4 different single doses of inhaled AZD8683 compared with an active comparator, Spiriva®[1] (tiotropium bromide), with respect to peak, trough, and average FEV_1	Peak FEV_1 (0-24h) as change from baseline Trough FEV_1 (22-26h) as change from baseline Average FEV_1 (0-24h)

[1] Spiriva® (tiotropium bromide) is a registered trademark of Boehringer Ingelheim.

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
	PD	To investigate the systemic effects with respect to HR, QTcF, SBP, and DBP of 4 different single doses of inhaled AZD8683	Individual maximum change from pre-dose to 0-24 hours post-dose in: HR QTcF SBP DBP
	Safety	To investigate the safety and tolerability of single doses of inhaled AZD8683	AEs, safety laboratory variables, physical examination, vital signs, ECG variables, and lung function (FEV_1 and FVC)
	PK	To investigate AZD8683 plasma exposure after single doses of inhaled AZD8683	Plasma concentration of AZD8683 pre-dose, 0-24 hours post-dose
Exploratory	PD	To investigate the onset of action of AZD8683 within the tested dose range	Change in FEV_1 from baseline to 15, 30, 60, 120, and 240 min post-dose
	PD	To investigate the bronchodilatory effects of 4 different single doses of inhaled AZD8683 compared with placebo, with respect to peak FEV_1 (0-4h)	Change from baseline to peak FEV_1 (0-4h)
	PD	To investigate the effects of 4 different single doses of inhaled AZD8683 compared with placebo, with respect to peak, trough, and average FVC	Change from baseline in: Peak FVC Trough FVC Average FVC
	PK	To explore the AZD8683 PK after single doses of inhaled AZD8683. This population PK analysis was not to form a part of the CSR	Not applicable

Table S1 Objectives and outcome variables

Objective Priority	Type	Description	Outcome Variable Description
	PGx	To collect and store DNA for possible future exploratory research into genes/genetic variation that may influence response (ie, safety, tolerability, PK, and/or PD) to AZD8683. This was not to form a part of the CSR	Not applicable

AE Adverse event; COPD Chronic obstructive pulmonary disease; CSR Clinical study report; DBP Diastolic blood pressure; DNA Deoxyribonucleic acid; ECG Electrocardiogram; FEV_1 Forced expiratory volume in the first second; FVC Forced vital capacity; h hours; HR Heart rate; PD Pharmacodynamics; PGx Pharmacogenetics; PK Pharmacokinetics; QTcF QT interval corrected for heart rate using Fredericia's formula; SBP Systolic blood pressure.

Study design

This was a randomised, double-blind, double-dummy, placebo- and active-controlled, multi-centre, 6-way cross-over, single-dose Phase IIa study to investigate the bronchodilatory and systemic effects of 4 different doses of inhaled AZD8683 in patients with COPD.

Eligible patients were randomised to receive single doses of 6 different treatments: AZD8683 at the doses 50 µg, 150 µg, 300 µg, and 900 µg, placebo, and Spiriva® 18 µg. Randomisation was done in balanced blocks across the study using Williams' design to control the sequences of the treatments. Randomisation codes were assigned strictly sequentially as patients became eligible for randomisation.

Target subject population and sample size

The target population included male and female patients with COPD, aged ≥40 years, and post-bronchodilator FEV_1 ≥30% to <80% of predicted normal and post-bronchodilator FEV_1/Forced Vital Capacity (FVC) <70%.

Approximately 36 patients were planned to be randomised.

Investigational product and comparators: Dosage, mode of administration, and batch numbers

The details of the investigational products (IP) and other study treatments are given in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength[a], and route of administration	Manufacturer	Batch number
AZD8683 Turbuhaler®	Inhalation powder 50 µg/dose	AstraZeneca	12-000405AZ
	100 µg/dose	AstraZeneca	11-003543AZ
	300 µg/dose	AstraZeneca	11-003555AZ
Placebo for AZD8683 Turbuhaler®	Inhalation powder	AstraZeneca	12-002394AZ
Spiriva® (tiotropium bromide)	Inhalation powder (hard capsule), 18 µg	Boehringer Ingelheim	12-002577AZ
Placebo for Spiriva®	Inhalation powder (hard capsule)	Fisher Clinical Service	11-003489AZ

[a] Strength per dose was referred to AZD8683 delivered dose from the inhalers. One gram of AZD8683 was equivalent to 1.173 g of AZD8683 bromide.

The following 6 delivered doses were planned to be inhaled in random order at 6 separate visits:

- AZD8683 50 µg (1x50 µg) administered via Turbuhaler®
- AZD8683 150 µg (1x100 µg and 1x50 µg) administered via Turbuhaler®
- AZD8683 300 µg (1x300 µg) administered via Turbuhaler®
- AZD8683 900 µg (3x300 µg) administered via Turbuhaler®
- Spiriva® 18 µg (1x18 µg) administered via HandiHaler®
- Placebo administered via Turbuhaler® and HandiHaler®.

To maintain blinding, patients inhaled from 3 Turbuhalers® and 1 HandiHaler® inhaler at each visit; 1 inhalation from each of the 3 Turbuhalers®, and 2 inhalations from the HandiHaler® (5 inhalations in total during each visit).

Duration of treatment

The study duration planned for each patient was 13 to 22 weeks. The treatment period (6 single doses of IP) was to span across 10 to 15 weeks and included 6 visits to the clinic.

Each treatment visit was to be separated by a wash-out period 2 to 3 weeks. A follow-up visit was planned 2 to 3 weeks after the last dose of the IP.

Statistical methods

No formal statistical analysis was conducted due to the early termination of the study. Data for the enrolled patients are presented in the listings.

Subject population

The first and last patients were enrolled on 19 October 2012 and 7 November 2012, respectively; the last patient completed the study on 3 December 2012. A total of 14 patients were enrolled, of which 3 patients were randomised to treatment.

The 3 randomised patients were withdrawn from the study after the first treatment visit as AstraZeneca decided to terminate this study.

Summary of pharmacodynamics and pharmacokinetic results

The primary variable of this study was pharmacodynamics. However, due to early termination of the study, no formal analysis could be conducted and the results are presented as listings.

Summary of safety results

There were 3 patients who were exposed to single doses of the IP. Each patient received any 1 of the following: AZD8683 50 µg, AZD8683 900 µg, and placebo.

A total of 3 adverse events (AEs) were reported by the patient who received a single dose of AZD8683 900 µg. The AEs included mild and moderate cough and moderate dyspnoea. The mild cough and moderate dyspnoea were causally related to the IP, as judged by the investigator. However, the moderate cough was not causally related to the IP, as judged by the investigator. No other patient reported an AE.