AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8683
Study Code	D1883C00004
Edition Number	1
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A double-blind, placebo-controlled, randomised, multi-centre, 3-way cross-over, single-dose phase II study to investigate the local and systemic effects of inhaled AZD8683 in patients with chronic obstructive pulmonary disease (COPD)

Study dates: First subject enrolled: 10 October 2010
Last subject last visit: 17 December 2010

Phase of development: Therapeutic exploratory (II)

International Co-ordinating 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 4 centres in Poland.

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 local and systemic effects of 2 different doses of inhaled AZD8683 compared to placebo in patients with COPD	For evaluation of local effect: - FEV_1 peak and trough (22-26 h average) effects (primary) - FEV_1 average effect (0-24 h) For evaluation of systemic effect (peak and average over first 4 h): - pulse and blood pressure - QTcF - Heart rate	PD
Secondary	**Secondary**	
To investigate the safety of single doses	AEs, clinical laboratory variables, physical examination, pulse and blood pressure, ECG, FEV_1, FVC	Safety
To investigate drug exposure of AZD8683	Plasma concentrations of AZD8683	PK

FEV_1, forced expiratory volume in the first second; QTcF, QT interval corrected for heart rate using Fridericia's formula; FVC, forced vital capacity

Study design

This was a double-blind, placebo-controlled, randomised, multi-centre, 3-way cross-over, single-dose, phase II study in patients with moderate to severe COPD. Eligible patients were randomly assigned using the Global Randomisation and blinding system to a treatment sequence which included 2 single doses of AZD8683 (50 and 200 μg delivered dose via Turbuhaler) and 1 single dose of placebo in a cross-over fashion.

Target subject population and sample size

Patients with COPD (men and/or post-menopausal or surgically sterile women), aged 40 years or above, with a post bronchodilator FEV_1 ≥40 to <80% of predicted normal, and a reversibility after ipratropium (Atrovent) of ≥12% increase in FEV_1 at 2 occasions.

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

Table S2 Details of investigational products

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD8683 Turbuhaler	Inhalation powder, 50 µg/ dose[a], 60 doses	AstraZeneca	D1000124	10-002491AZ
Placebo Turbuhaler	Inhalation powder, 60 doses	AstraZeneca	2154099/ 190005954	09-002533AZ

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

Duration of treatment

3 single dose administrations on 3 overnight visits to the clinic, separated by washout-periods of 7 to 14 days.

Statistical methods

All hypothesis testing was done using two-sided alternatives at a 5% significance level. Computed pharmacodynamic parameters based on FEV_1, FVC, pulse, blood pressure, heart rate and QTcF were compared between the 3 treatments using analysis of variance (ANOVA) technique. Additive models were used for measures of systemic effects, while FEV_1 and FVC were analysed using multiplicative models. Adverse events were analysed by descriptive statistics and qualitative analysis. Pharmacokinetic data were summarised using descriptive statistics.

Subject population

The randomised population consisted of 28 patients with moderate to severe COPD (mean FEV_1 63% of predicted normal and mean reversibility 26%), of whom 96% were previously receiving long-acting β_2-agonists and 61% inhaled corticosteroids. All were White, 68% were men, and the mean age was 63 years. Of the 28 randomised patients, 27 completed the study (1 patient was excluded after second treatment period). All 28 randomised patients were included in the analyses of all variables.

Summary of pharmacokinetic results

Inhaled AZD8683 showed a fast absorption rate from the lung, as indicated by a median t_{max} of 15 min. Increase in mean exposure was approximately dose proportional.

Summary of pharmacodynamic results

AZD8683 200 µg was shown to be effective regarding bronchodilation as measured by FEV_1 peak (E_{max}), trough (E_{22-26}) and average (E_{av}) (Figure 1 and Table S3), and FVC (E_{max}, E_{22-26} and E_{av}). AZD8683 50 µg was shown to be effective only on FEV_1 E_{av}. Onset of bronchodilation was first evident after 2 hours for AZD8683 200 µg.

Based on the evaluations of pulse, blood pressure, QTcF and heart rate (average and peak effects) over the first 4 hours after administration, there was no evidence of systemically mediated effects, with the exception of a decrease in maximum systolic blood pressure after the 200 µg dose.

Figure 1 Mean value curves of change from baseline in FEV_1

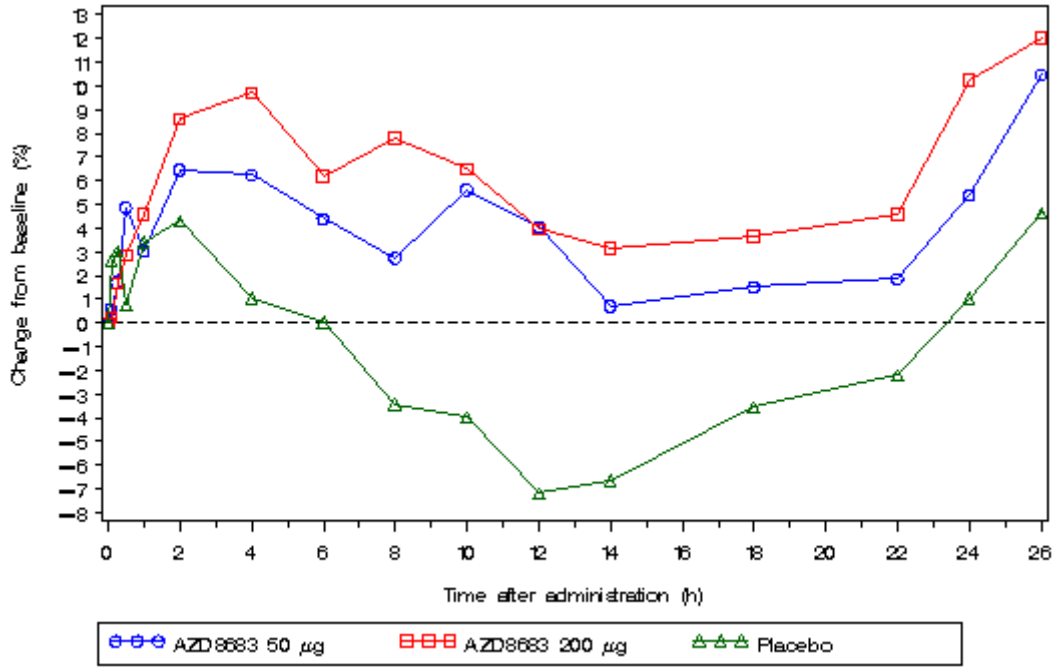

Table S3 Treatment estimates and pairwise contrasts for FEV_1 parameters

Parameter	Treatment	Baseline ratio	Treatment contrasts	Ratio	95% CI	P-value
E_{max}	AZD8683 50 µg	1.159	AZD8683 50 vs Placebo	1.04	(1.00, 1.07)	0.060
	AZD8683 200 µg	1.185	AZD8683 200 vs Placebo	1.06	(1.02, 1.10)	0.002
	Placebo	1.119	AZD8683 200 vs AZD8683 50	1.02	(0.99, 1.06)	0.223
E_{22-26}	AZD8683 50 µg	1.051	AZD8683 50 vs Placebo	1.03	(0.99, 1.09)	0.169
	AZD8683 200 µg	1.097	AZD8683 200 vs Placebo	1.08	(1.03, 1.13)	0.003
	Placebo	1.016	AZD8683 200 vs AZD8683 50	1.04	(0.99, 1.09)	0.087
E_{av}	AZD8683 50 µg	1.032	AZD8683 50 vs Placebo	1.05	(1.01, 1.09)	0.007
	AZD8683 200 µg	1.060	AZD8683 200 vs Placebo	1.08	(1.04, 1.12)	<0.001
	Placebo	0.982	AZD8683 200 vs AZD8683 50	1.03	(0.99, 1.06)	0.134

Summary of safety results

There was no evidence of any safety concerns. No deaths, serious adverse events or AEs leading to discontinuation of investigational product were reported. There were few adverse events, none of severe intensity, and no notable differences between treatments with regard to adverse events (Table S4). There were no indications of any safety concern based on clinical laboratory parameters, vital signs, lung function and ECG monitoring.

Table S4 Number (%) of patients who had at least 1 AE by preferred term

	Number (%) of patients[a]			
	AZD8683 50 µg (N=28)	**AZD8683 200 µg (N=28)**	**Placebo (N=27)**	**TOTAL (N=28)**
Preferred Term				
Patients with any AE	2 (7.1)	3 (10.7)	4 (14.8)	7 (25.0)
Dry Mouth	1 (3.6)	1 (3.6)	1 (3.7)	2 (7.1)
Supraventricular Extrasystoles	1 (3.6)	0 (0.0)	1 (3.7)	2 (7.1)
Bundle Branch Block Right	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.6)
Dyspnoea	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.6)
Electrocardiogram QT Prolonged	1 (3.6)	0 (0.0)	0 (0.0)	1 (3.6)
Electrocardiogram T Wave Inversion	1 (3.6)	0 (0.0)	1 (3.7)	1 (3.6)
Haemoglobin Urine Present	0 (0.0)	1 (3.6)	0 (0.0)	1 (3.6)
Parotid Gland Enlargement	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.6)
Right Atrial Dilatation	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.6)
Syncope	0 (0.0)	1 (3.6)	0 (0.0)	1 (3.6)
Ventricular Extrasystoles	0 (0.0)	0 (0.0)	1 (3.7)	1 (3.6)

[a] Patients with multiple events are counted only once.