Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00001
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A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Inhaled AZD5423 after Single Ascending Doses in Healthy Male Subjects

Study dates: First subject enrolled: 04 August 2009
Last subject last visit: 21 November 2009

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This was a single centre study at Quintiles Drug Research Centre at Guy's Hospital, 6 Newcomen Street, London, SE1 1YR, United Kingdom.

Publications

None at the time of writing this report.

Table S1 Objectives and criteria for evaluation

Objective	Outcome variables	Type
Primary		
To assess the safety and tolerability of AZD5423 following inhaled administration of single ascending doses and to estimate the maximum tolerated dose, if within the predefined exposure and dose limits, in healthy male subjects.	AEs, blood pressure, pulse, body temperature, ECGs, laboratory variables (haematology, clinical chemistry, urinalysis), lung function (FEV_1 and FVC) and physical examination.	Safety
Secondary		
To characterise the pharmacokinetics (PK) of AZD5423 and provisionally assess the dose proportionality of the PK following inhaled administration of single ascending doses of AZD5423 in healthy male subjects.	C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, $AUC_{(0-t)}$, AUC, CL/F, V_z/F and MRT	PK
To investigate the pharmacodynamic (PD) effect of inhaled single ascending doses of AZD5423 in healthy male subjects.	$AUC_{(0-24h)}$, $AUC_{(0-12h)}$ and $AUC_{(12-24h)}$ of plasma cortisol	PD

Study design

This was a Phase I, first time in human, randomised, double-blind, placebo-controlled, single ascending dose study in healthy male subjects conducted at a single centre. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects.

Target subject population and sample size

This study involved 59 healthy male subjects aged 19 to 43 years (mean 26 years), with a body mass index between 20 and 29 kg/m^2 and who weighed between 57 and 97 kg. It was planned that there would be 8 subjects in each treatment group.

Table S2 Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number
AZD5423	Nebuliser suspension for inhalation 5 mg/g	AstraZeneca	09-004875AZ
AZD5423	Nebuliser suspension for inhalation 0.05 mg/g	AstraZeneca	09-004876AZ
AZD5423	Nebuliser suspension for inhalation 0.5 mg/g	AstraZeneca	09-004868AZ
Placebo	Placebo solution for nebuliser	AstraZeneca	09-004877AZ

Single doses of AZD 5423/placebo were administered to subjects. Doses administered were 8.4 mcg, 50 mcg, 100 mcg, 208 mcg, 500 mcg, 998 mcg, 1248 mcg.

Duration of treatment

Single dose.

Statistical methods

The analyses of safety, tolerability, PK and PD data were summarized descriptively including tables, listings and graphs. Dose proportionality was analysed based on a graphical analysis of PK parameters and dose-adjusted AUC and C_{max} and by using the power model approach. Cortisol AUC ($AUC_{(0-24h)}$, $AUC_{(0-12h)}$ and $AUC_{(12-24h)}$) ratios of treatment over baseline were compared between treatments using a multiplicative analysis of covariance.

Subject population

Fifty-nine healthy male subjects were randomised into the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. All subjects randomised to treatment completed the study. The safety analysis included all randomised subjects. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

Following the highest dose, 1248 mcg, the predefined maximum exposure limit for C_{max} (18.1 nmol/L) was exceeded (geometric mean of 25.4 nmol/L), whereas AUC (geometric mean of 39.1 h*nmol/L) was still below the exposure limit (73 h*nmol/L). Absorption of AZD5423 from the lung was rapid and comparable between doses with a median t_{max} of 5 to 8 min. Due to the late terminal phase of the plasma concentration-time curve, the estimations of λ_z and associated parameters ($t_{1/2\lambda z}$, CL/F, V_z/F, AUC and MRT) were regarded as reliable for doses of 500 mcg and above. For the 500 to 1248 mcg dose groups, geometric means of

$t_{1/2\lambda z}$, CL/F and V_z/F ranged from 33.6 to 48.3 h, from 93.5 to 142 L/h and from 5410 to 7850 L, respectively, and arithmetic mean MRT ranged from 15.4 to 21.3 h.

Dose adjusted AUC and C_{max} varied over the studied dose range of 8.4 to 1248 mcg. The 208 to 998 mcg data indicated somewhat less than dose proportional plasma exposure of AZD5423. When including the 1248 mcg dose group, this trend was however broken. Based on a power model analysis of 208 to 1248 mcg data (95% CI of the slope included 1 both for AUC (0.76 to 1.23) and C_{max} (0.76 to 1.20)), dose proportional kinetics of AZD5423 cannot be excluded for this dose range. Taking the less reliable estimation of $t_{1/2\lambda z}$, CL/F, V_z/F and MRT at the lower doses into account, there was no consistent dose dependency seen for these variables.

Summary of pharmacodynamic results

The active treatment/placebo ratio of $AUC_{(0\text{-}24h)}$ of plasma cortisol decreased with increasing dose. For the 500 to 1248 mcg dose groups, cortisol supression based on $AUC_{(0\text{-}24h)}$ was statistically significant compared to baseline (estimated decrease 24 to 46%) and compared to placebo (estimated decrease 29 to 49%). Cortisol supression based on $AUC_{(0\text{-}12h)}$ was statistically significant compared to placebo for the 208 to 1248 mcg dose groups (estimated decrease 24 to 56%), whereas cortisol supression based on $AUC_{(12\text{-}24h)}$ was statistically significant compared to placebo only for the 998 and 1248 mcg dose groups (estimated decrease 35 and 42%, respectively).

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study.

A total of 16 adverse events (AEs) were reported by 11 subjects during this study (8 AEs reported by 6/43 subjects receiving AZD5423 and 8 AEs reported by 5/16 subjects receiving placebo). There was no apparent dose related trend in AEs. All of the AEs were of mild intensity.