Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00003
Edition Number	1
Date	14 June 2012

A phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Inhaled AZD5423 after Administration of Single and Multiple Ascending Doses in Healthy Male Japanese Subjects

Study dates: First subject enrolled: 22 June 2011
Last subject last visit: 14 October 2011

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 study was conducted at one centre in Japan.

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 safety and tolerability of AZD5423 following administration of single and multiple ascending doses in healthy male Japanese subjects.	Adverse events, laboratory variables, physical examination, ECG, vital signs including lung function	Safety
Secondary	**Secondary**	
To characterise the single and multiple dose pharmacokinetics of AZD5423, and assess the dose proportionality, the time required to reach steady state and the degree of accumulation.	Day 1: $AUC_{0\text{-}inf}$, V_z/F Days 1 and 17: C_{max}, t_{max}, $AUC_{0\text{-}24}$, $t_{½\lambda z}$, CL/F, MRT. Day 17: R_{ac} [$AUC_{0\text{-}24}$ Day 17/$AUC_{0\text{-}24}$ Day 1], time dependency ($AUC_{0\text{-}24}$ Day 17/$AUC_{0\text{-}inf}$ Day 1), average plasma concentration during a dosing interval following last dose (C_{av}[$AUC_{0\text{-}24}$/24 h]).	PK
To investigate the pharmacodynamic effects of AZD5423 following administration of single and multiple ascending doses.	24-hours plasma cortisol AUC, plasma cortisol pre and post ACTH stimulation, DHEAS, osteocalcin and 24 hours urine cortisol	PD
Exploratory	**Exploratory**	
To investigate the presence and/or identity of drug metabolites of AZD5423 and, if appropriate, characterise their PK.	Blood and urine samples for drug metabolites analyses	PK*
To collect and store DNA for future possible exploratory research into genes/genetic variation that may influence response (ie, pharmacokinetics, safety, tolerability and efficacy) to AZD5423.	An optional blood sample for DNA extraction	PGx*

*: Results from the exploratory objectives are not presented in this CSR.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled study with single and repeated ascending dose levels of inhaled AZD5423 conducted in healthy Japanese male subjects at a single centre. AZD5423/placebo was administered using the I-neb® (PHILIPS RESPIRONICS, US).

Originally, 4 cohorts of 10 subjects each were planned to be dosed. However, upon analysis of the plasma exposure limits following completion of dosing in cohort 3, the C_{max} on Day 1 was found to be over the exposure limit (18.1 nmol/L) defined in the stopping criteria for dose escalation in the clinical study protocol, although the geometric mean C_{max} on Day 17 (11.1 nmol/L) was still below the exposure limit. Therefore the 4th cohort was not initiated. Thus 3 cohorts of 10 subjects each were dosed; in each cohort 7 subjects were randomised to AZD5423 and 3 subjects to placebo.

Target subject population and sample size

Japanese healthy male subjects aged 20-45 years.

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

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD5423	Nebuliser suspension 0.27 mg/g	AstraZeneca	D1000343	10-005195AZ
AZD5423	Nebuliser suspension 0.54 mg/g	AstraZeneca	D1000344	10-005196AZ
AZD5423	Nebuliser suspension 1.6 mg/g	AstraZeneca	D1100064	11-000923AZ
				11-000923AZ-2*
AZD5423	Nebuliser suspension 2.2 mg/g	AstraZeneca	D1100061	11-000925AZ*
AZD5423	Nebuliser suspension 2.7 mg/g	AstraZeneca	D1100062	11-000927AZ*
Placebo	Placebo solution for nebuliser	AstraZeneca	D1100059	11-000913AZ

Lung deposited doses were predicted based on droplet size distribution measured *in vitro* and on assumptions on breathing pattern and anatomy of the subjects.
Lung deposited doses of 50, 100, 300 and 500 µg were predicted to result from dose delivery of 70, 140, 420 and 700 µg from the device (I-neb®), which in turn was accomplished by filling the device with suspensions of 0.27, 0.54, 1.6 and 2.7 mg AZD5423 per gram of formulation, respectively.
*: The IPs of the following batch numbers (11-000923AZ-2, 11-000925AZ, and 11-000927AZ) were not used.

The starting predicted lung deposited dose of AZD5423 for this study was 50 µg. Subsequent predicted lung deposited dose levels were 100 and 300 µg.

Duration of treatment

For the 1st cohort, subjects received a single administration. For the 2nd and 3rd cohort, subjects received a single administration followed by 14-day repeated once daily administration with washout period of 72 hours.

Statistical methods

The analyses of safety, tolerability, pharmacokinetic and pharmacodynamic data were summarised descriptively using tables, listings and graphs.

Statistical analysis of PD data followed a closed test procedure, by first testing the placebo difference for the highest dose level, and then, only if statistically significant, testing differences at the next highest dose level etc. For each PD parameter, treatments were compared using an analysis of variance (ANOVA) model with fixed factor treatment and the baseline value as a covariate.

Subject population

In total, 30 Japanese healthy male subjects aged 22 to 44 years were randomised into the study at 1 study site. All subjects randomised to treatment completed the study. The safety analysis included all randomised subjects and there were no protocol deviations that led to exclusion of data from the PK or PD analyses. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of pharmacokinetic results

At the predicted lung deposited dose, 300 µg via I-neb®, C_{max} exceeded the pre-defined exposure limits on Day 1 but not on Day 17.

There was no apparent deviation from dose proportional plasma exposure ($AUC_{(0\text{-}24h)}$ and C_{max}) of inhaled AZD5423 via I-neb® within the studied predicted lung deposited dose-range of 50 to 300 µg on Day 1 or 100 to 300 µg on Day 17 (after 14 days of once daily inhalation).

Steady-state plasma concentrations were attained after approximately 6 days of repeated once daily inhalation of AZD5423 assessed by visual inspection of trough plasma concentration vs. time curve shape in doses 100 and 300 µg.

The accumulation of AZD5423 in plasma up to steady-state was low.

There was no indication of time dependent pharmacokinetics of AZD5423 as assessed by $AUC_{(0\text{-}24h)\ Day17}$ / $AUC_{(0\text{-}inf.)\ Day\ 1}$.

Summary of pharmacodynamic results

Predicted lung deposited dose 300 µg AZD5423 via I-neb® suppressed plasma cortisol $AUC_{(0\text{-}24h)}$ statistically significantly more than placebo after 14 days of once daily inhalation (estimated decrease 22% [95% CI: 7%-35%]).

Predicted lung deposited dose 300 µg of AZD5423 via I-neb® suppressed 24 h urine cortisol statistically significantly more than placebo after 14 days of once daily inhalation (estimated decrease 48% [95% CI: 21%-66%]).

All subjects treated with AZD5423 and placebo were classified as adequate responders to ACTH stimulation after 14 days of once daily inhalation.

There was no statistically significant effect on serum DHEAS compared to placebo after 14 days of once daily inhalation.

There was a statistically significant decrease in plasma osteocalcin compared to placebo for the AZD5423 300 µg dose group after 14 days of once daily inhalation (estimated decrease 9% [95% CI: 1%-18%]).

Summary of safety results

There were no deaths, serious adverse events or adverse events that led to discontinuation of investigational product during this study.

There were few adverse events; all were of mild in intensity.

There were no clinically relevant patterns in laboratory safety test results, ECG, vital sign or spirometry measurements during the study.

No safety or tolerability concerns were identified in this study up to and including once daily inhalation of 300 µg predicted lung deposited doses of AZD5423 via I-neb® for 14 days.