AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5423
Study Code	D2340C00002
Edition Number	1
Date	10 March 2011

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 Multiple Ascending Doses for 14 days in Healthy Male and Female Subjects

Study dates: First subject enrolled: 10 January 2010
Last subject last visit: 30 April 2010

Phase of development: Clinical pharmacology (I)

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)

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.

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 multiple ascending doses	AEs, laboratory safety tests, blood pressure, pulse, body temperature, ECG, lung function (FEV1 and FVC), physical examination.	Safety
Secondary	**Secondary**	
To characterise the multiple dose pharmacokinetics of AZD5423 and assess the time required to reach steady state and the degree of accumulation	C_{max}, t_{max}, $AUC_{(0\text{-}24h)}$, $t_{1/2\lambda z}$, CL/F, MRT, R_{ac} ($AUC_{(0\text{-}24h)}$ Day 14/ $AUC_{(0\text{-}24h)}$ Day 1), C_{av}	PK
To investigate pharmacodynamic effects of AZD5423 following administration of multiple ascending doses.	24 h plasma cortisol, 24 h urine cortisol, plasma cortisol after adrenocorticotropic hormone (ACTH)-stimulation, dehydroepiandrosterone sulphate ester (DHEAS), 4β-OH-cholesterol, osteocalcin and tartrate resistant acid phosphatase 5b (TRAP 5b)	PD
Exploratory	**Exploratory**[a]	
To investigate the presence and/or identity of drug metabolites of AZD5423 and, if appropriate, characterise their pharmacokinetics	Pharmacokinetic parameters may be investigated as required.	PK
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5423	DNA samples may be used to explore how genetic variation may affect the response to AZD5423.	PGx

a Outcomes of exploratory objectives are not reported in this clinical study report.

Study design

This was a phase I, single-centre, double-blind, randomised, placebo-controlled, parallel-group study to assess the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of inhaled AZD5423 after administration of multiple ascending doses in healthy male and female subjects. AZD5423/placebo was administered using the SPIRA nebuliser.

Target subject population and sample size

This study was to be conducted in healthy male and female subjects of non-childbearing potential. A total of 27 healthy subjects aged 18 to 45 years, weighing at least 50 kg and no more than 100 kg, with a body mass index between 18 and 30 kg/m^2 were to be randomised (9 subjects per cohort).

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 5 mg/g	AstraZeneca	09-008539AZ (Lot no. 10-000099AZ)
Placebo	Placebo solution for nebuliser	AstraZeneca	09-008542AZ (Lot no. 10-000081AZ)

The following lung deposited doses were given once daily for 14 days: 125 µg, 375 µg and 499 µg AZD5423 or matching placebo.

Duration of treatment

Once daily dosing for 14 days.

Statistical methods

The analyses of safety, tolerability, PK and PD data were summarised descriptively including tables, listings and graphs. Dose proportionality was analysed based on a graphical analysis of dose adjusted AUC and C_{max}. 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. For each PD parameter, the ratio of treatments over baseline were compared using a multiplicative analysis of covariance (ANCOVA) model with fixed factor treatment and the baseline value as a covariate.

Subject population

In total, 27 male subjects (24 white and 3 black) aged 20 to 39 years were randomised into the study at 1 study site, each received 14 once-daily administrations of AZD5423 or placebo during the planned treatment visit. It should be noted that although it was planned that both male and female subjects would be recruited no eligible female subjects were enrolled. 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

The predefined maximum exposure limits for $AUC_{(0-24h)}$ (73 h*nmol/L) and C_{max} (18.1 nmol/L) were not exceeded during once daily inhalation of 125, 375 and 499 µg for 14 days. The geometric mean C_{max} on Day 14 in Cohort 2 (375 µg) was 16.6 nmol/L, which was close to the predefined limit (18.1 nmol/L). The dose for Cohort 3 (499 µg) was therefore lower than a 3-fold escalation.

The PK of AZD5423 at steady state were characterised by rapid absorption from the lung (median t_{max} of 5 to 7 min), rapid distribution and multiphasic decline with an estimated geometric mean terminal plasma half-life of 51.3 to 95.1 h. Geometric mean CL/F ranged from 75.8 to 91.6 L/h and arithmetic mean MRT ranged from 23.1 to 38.1 h.

Following once daily inhalation of AZD5423, steady state was considered to have been reached after 6 doses in the 375 and 499 µg dose groups and after 7 doses in the 125 µg dose group. The plasma concentration profiles during once daily inhalation of AZD5423 were similar on Day 1 and 14 and median t_{max} was comparable. The accumulation was low as expected from single-dose data. Geometric mean R_{ac} ranged from 1.14 to 1.47.

There was no consistent deviation from dose proportional plasma exposure ($AUC_{(0-24h)}$ and C_{max}) of AZD5423 within the studied dose range of 125 to 499 µg on Day 1 or on Day 14. Furthermore, there was no consistent dose dependency seen for t_{max} on Day 1 and Day 14 or for $t_{½\lambda z}$, CL/F, MRT and R_{ac} on Day 14.

Summary of pharmacodynamic results

The active treatment/placebo ratio of $AUC_{(0-24h)}$ of plasma cortisol on Day 1 and Day 14 decreased with increasing dose. For the 375 and 499 µg dose groups, cortisol suppression based on $AUC_{(0-24h)}$ was statistically significant compared to placebo both on Day 1 (estimated decrease 30 and 40%, respectively) and Day 14 (estimated decrease 38 and 44%, respectively).

Cortisol suppression based on 24 h urine cortisol on Day 1 was statistically significant compared to placebo for the 499 µg dose group (estimated decrease 53%). On Day 14, there was no statistically significant decrease in 24 h urine cortisol compared to placebo for any of the dose groups.

All subjects except one (Subject E0001017 in the placebo group on Day 15) showed pre-ACTH plasma cortisol levels >150 nmol/L and all subjects had a maximum post ACTH plasma cortisol level above 400 nmol/L or an increase of 200 nmol/L. For two subjects in each of the 375 and 499 µg dose groups of AZD5423, ACTH stimulated maximum plasma cortisol levels at Day 15 were below 500 nmol/L, which is the cut off level most often used in ACTH tests. There was no statistically significant effect on ACTH stimulated plasma cortisol levels of AZD5423 compared to placebo following once daily inhalation of AZD5423 for 14 days.

There was no statistically significant change in serum DHEAS compared to placebo on Day 15.

There was no consistent change in 4β-OH-cholesterol compared to placebo on Day 14. For the 125 µg dose group, there was a statistically significant decrease compared to placebo (estimated decrease 23%), but no decrease was seen after the highest dose of 499 µg.

There was no consistent change in plasma osteocalcin compared to placebo on Day 15. For the 375 µg dose group, there was a statistically significant decrease in plasma osteocalcin compared to placebo (estimated decrease 13%), but no decrease was seen at the highest dose level of 499 µg.

There was no statistically significant change in plasma TRAP 5b compared to placebo on Day 15.

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 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 the highest dose given (499 µg, once daily, for 14 days).