AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9164
Study Code	D1882C00001
Edition Number	1
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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 AZD9164 after Single Ascending Doses in Healthy Male Subjects

Study Dates	First healthy subject enrolled: 6 February 2009 Last healthy subject completed: 29 April 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

This study was performed at one centre in Sweden

Publications

None at the time of writing this report

Objectives

Table 1 Primary and secondary objectives and variables

Objectives	Variables	Type
Primary		
To assess the safety and tolerability and to estimate the maximum tolerated dose (MTD) of AZD9164 following inhaled administration of single ascending doses in healthy male subjects.	• Adverse events • Laboratory variables: Clinical chemistry, Haematology, Urinalysis • Vital signs: Blood pressure, Pulse, Body temperature • ECG parameters: RR, PR, QT intervals, QRS duration	Safety
Secondary		
To characterise the pharmacokinetics (PK) of AZD9164 and to provisionally assess the dose proportionality of the PK following inhaled administration of single ascending doses of AZD9164 in healthy male subjects.	• AUC, C_{max}, t_{max}, $t_{½\lambda z}$, CL/F, CL_R, V_Z/F, MRT, Ae	PK
To investigate local and extrapulmonary effects of inhaled single ascending doses of AZD9164 in healthy male subjects.	• Lung function: FEV_1, FVC • Blood pressure, Pulse, Heart rate, QTcF	PD

PK Pharmacokinetics; PD Pharmacodynamics; AUC Area under plasma concentration time curve; C_{max} Maximum plasma concentration; t_{max} Time to maximum plasma concentration; $t_{½\lambda z}$ Terminal half life; CL/F Total apparent plasma clearance; CL_R Renal clearance; V_Z/F Apparent volume of distribution during terminal phase; MRT Mean residence time; Ae Amount excreted unchanged.
With regard to exploratory objectives, samples for possible future pharmacogenetic or metabolic investigation were collected - this has not been further addressed in the clinical study report

Study design

AZD9164 is a muscarinic antagonist intended to be developed for COPD treatment. This study was a double-blind, randomised, placebo-controlled, parallel-group study of inhaled AZD9164 after single ascending doses. Dose escalation was planned to continue until, either a non-tolerated dose was reached or the maximum allowed lung dose or the maximum allowed exposure was reached. After each dose cohort, a Safety Review Committee evaluated the safety, tolerability and the pharmacokinetics of AZD9164 and decided the next dose.

Target healthy subject population and sample size

The study population was selected according to the following main inclusion criteria: healthy male subjects aged 18 to 45 years; body mass index (BMI) between 19 and 30 kg/m^2 and body weight between 50 and 100 kg; non-smoker or ex-smoker who has stopped smoking (or using other nicotine products) for >6 months before study start; able to inhale from the Spira nebuliser according to given instructions. In each dose cohort 8 healthy subjects were randomised: 6 subjects received active treatment and 2 received placebo - each subject participated in one dose cohort only.

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

The subjects inhaled nebulised AZD9164 solution or placebo via a Spira Electro 2 dosimeter. All doses presented refer to lung deposited doses. The first cohort received 4 μg AZD9164 or placebo. The administered doses of AZD9164 for subsequent cohorts (20, 70, 250, 700, 1080, 1320, 1940 μg) were determined after review of data from the previous dose. All dose adjustments were based on pharmacokinetic data, since there were no safety concerns that required consideration. Investigational product: AZD9164, solution for nebulisation, 10 mg/g (AstraZeneca, Batch No. 09-000472AZ); Comparator: placebo / sodium chloride, solution for injection, 9 mg/mL (Fresenius Kabi, Batch No. BBL03)

Duration of treatment

This was a Single dose study.

Statistical methods

The analyses of safety and tolerability, pharmacokinetics (PK) and pharmacodynamic (PD) parameters were summarised descriptively including tables, listings and graphs. Dose-proportionality was checked by fitting a power model to PK data. Laboratory safety and PD data were compared between active treatment and placebo. Placebo subjects from different dose-levels were pooled for the comparison. Comparisons of peak and average effects were made for the change from baseline using analysis of variance models. All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

Subject population

A total of 65 male subjects were enrolled at 1 centre in Sweden. Of these, 64 were allocated to treatment at Visit 2. One enrolled subject was not randomised due to a Serious adverse event (appendicitis) during the screening period. All randomised subjects completed the study. In total 48 subjects received AZD9164 and 16 subjects received placebo.

All randomised subjects were included in the safety data set, and all subjects that received AZD9164 were included in the PK data set. The mean age was 26.5 years (range 19 to 45). With regard to baseline demographic data, only small differences between the treatment groups could be seen, with the exception of lung function in the 1320 µg group. This group had higher baseline FEV_1 and FVC than the other groups.

Summary of pharmacokinetic results

Inhaled AZD9164 showed a relatively fast absorption rate from the lung, as indicated by the median t_{max} of about 1 hour. The pharmacokinetics of inhaled AZD9164 was characterised by a multi-phasic plasma concentration-time profile with an estimated terminal half-life of 123 hours (range 80 to 204), as assessed at the three highest dose levels. Estimated mean MRT at dose levels between 70 and 1940 µg lung deposited dose was between 72 and 138 hours.

Systemic exposure, as determined by AUC, increased proportionally to dose, whereas C_{max} showed a dose-proportional increase above 250 µg, with a steeper than dose-proportional increase at lower dose levels.

Mean apparent plasma clearance was estimated at 23 L/h, and mean apparent volume of distribution during terminal phase estimated at 3300 L. The renal clearance was in the range of 0.17 to 0.30 L/h. The individual maximum fraction of AZD9164 excreted unchanged in urine was estimated to be less than 3.1% of the inhaled nominal dose.

Summary of pharmacodynamic results

A bronchodilating effect as measured by FEV_1 was observed, ie, a statistically significant increase from baseline in FEV_1 compared with placebo, of approximately 5%, could be seen at the four highest dose levels (700 to 1940 µg). In addition a statistically significant increase in heart rate (6.7 bpm) compared with placebo was detected at the highest dose level. No other pharmacodynamic treatment effects were observed.

Summary of safety results

The maximum tolerated dose could not be estimated, since there were no safety or tolerability concerns up to the highest dose given (1940 µg). Dose escalation was limited by the pre-determined exposure limit (plasma AUC of 158 nmol*h/L based on non-clinical data). There were no deaths, serious adverse events, discontinuations due to adverse events,

or other significant adverse events reported in this study. The reported adverse events (AEs) were few (37 in all), of mild intensity, and with no consistent pattern. No AEs of concern were identified after dosing. The most common AE was headache, both within the active treatment groups and placebo.

There were no patterns of any clinically significant abnormalities in blood pressure, pulse, body temperature, clinical laboratory data, haematology, urinalysis or ECG parameters. The evaluation of protocol-defined ECG parameters/intervals showed that all subjects had ECG-intervals within normal limits for the studied population.

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