AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00005
Edition Number	1
Date	12 June 2009

A phase I, randomised, double-blind, placebo-controlled, parallel-group, single-centre study to investigate the safety, tolerability and pharmacokinetics of single and multiple ascending doses of AZD3199 given once daily as inhaled formulation via Turbuhaler to Japanese healthy men

Study dates: First healthy volunteer enrolled: 31 October 2008
Last healthy volunteer completed: 06 February 2009

Phase of development: Clinical Pharmacology (1)

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

Publications

There were no publications at the time of writing this report.

Objectives

The primary objective of the study was to investigate the safety and tolerability of single and multiple once daily ascending doses of AZD3199 delivered as dry powder via the Turbuhaler inhaler (TURBUHALER® is a trademark of the AstraZeneca group of companies) in healthy male Japanese subjects by assessment of:

- Incidence and nature of adverse events (AEs).
- Clinically significant abnormalities in electrocardiogram (ECG) parameters, blood pressure (BP), pulse rate, lung function parameters, body temperature and laboratory variables (clinical chemistry, haematology and urinalysis).

The secondary objectives of the study were:

- To investigate the pharmacokinetics (PK) of single and multiple ascending doses of AZD3199 by assessment of the degree of accumulation, dose proportionality and time linearity in healthy Japanese subjects.
- To investigate β_2-adrenoreceptor mediated effects of single and multiple ascending doses of AZD3199 by assessment of potassium and lactate concentrations, tremor and palpitations, heart rate, QTc, pulse rate, blood pressure and forced expiratory volume in 1 second (FEV_1).

The exploratory objectives of the study were:

- To obtain material for possible exploratory analysis of metabolites of AZD3199 in urine and plasma.
- The PK analysis of urine samples. This will only be performed as an exploratory objective if plasma data indicates there is a need.

The exploratory data do not form part of the clinical study report (CSR).

Study design

This was a Phase I randomised, double-blind, parallel-group, placebo-controlled, single centre study to assess the safety, tolerability and pharmacokinetics of AZD3199 following single and multiple ascending dose administration to healthy male Japanese subjects.

Target healthy volunteer population and sample size

In total, 27 healthy, non-smoking, Japanese male subjects aged 20 to 45 years were enrolled and analysed in the study. Nine subjects participated in each cohort and received either AZD3199 or placebo, randomised 6:3.

Investigational product, dosage, mode of administration and batch numbers

Single and multiple inhaled doses of AZD3199 were administered via Turbuhaler. In total, three different dose levels of AZD3199 were administered to three different cohorts of subjects. The planned delivered doses were 240 µg, 720 µg and 2160 µg.

Although no significant safety concerns were observed following review of the data, the SRC agreed for Cohort 3 to be dosed at a lower dose (1680 µg) than the planned dose (2160 µg) to match the dose escalation scheme in the global MAD study. The actual delivered doses were 240 µg (4 actuations x 60 µg/actuation), 720 µg (3 actuations x 240 µg/actuation) and 1680 µg (7 actuations x 240 µg/actuation).

Batch numbers: 08-000075AZ/KE12 (AZD3199 Turbuhaler: Dry powder for inhalation, 60 µg/dose, 60 doses); 08-000076AZ/KE21 (AZD3199 Turbuhaler: Dry powder for inhalation, 240 µg/dose, 60 doses).

Comparator, dosage and mode of administration

Placebo was provided as dry powder for oral inhalation, administered via Turbuhaler.

Batch number: 08-000080AZ/IK29 (Placebo Turbuhaler: Dry powder for inhalation, 60 doses).

Duration of treatment

Each subject received a single dose of AZD3199 or placebo on Day 1. The first dose of inhaled AZD3199 at each dose level was monitored for 48 h before the next dose was given. Repeated dosing was then commenced on Day 3 with AZD3199 or placebo once daily for 12 days until Day 14.

Criteria for evaluation - pharmacokinetics (main variables)

Maximum plasma drug concentration (C_{max}), time to maximum plasma drug concentration (t_{max}), area under the plasma drug concentration time curve (AUC), terminal half-life of drug in plasma ($t_{½}$), apparent plasma clearance following oral drug administration (CL/F), mean residence time (MRT), apparent terminal volume of distribution (V_z/F), observed accumulation ratio (R_{ac}).

Criteria for evaluation - pharmacodynamics (main variables)

Tremor, palpitations, potassium and lactate concentration, heart rate and QTc, blood pressure and pulse rate, FEV_1.

Criteria for evaluation – safety and tolerability (main variables)

Incidence and nature of AEs and clinically significant abnormalities in ECG parameters, BP, pulse rate, lung function, body temperature and laboratory variables (clinical chemistry, haematology and urinalysis).

Statistical methods

The analyses of safety, tolerability and PK were summarised descriptively including tables, listings and graphs, as appropriate. Pharmacodynamic data were reduced to PD parameters such as the average and the peak effects, and these parameters were compared between active treatments and placebo using analysis of variance (ANOVA) technique. A closed test procedure, by descending dose order, was used when comparing AZD3199 and placebo regarding PD.

Subject population

A total of 27 healthy male Japanese subjects were randomised in the study, which included 18 subjects who received AZD3199 (ie, 6 subjects in each AZD3199 dose group [240 µg, 720 µg, and 1680 µg], and 9 subjects who received placebo.

All subjects except one completed the study. The subject was discontinued as he was lost to follow-up.

There were no protocol deviations identified in this study.

Demography and baseline characteristics were in line with the healthy population that was intended to be included in the study. Japanese subjects in all dose groups were comparable in terms of demographics.

Summary of pharmacokinetic results

The pharmacokinetics of AZD3199 in Japanese healthy men showed that the systemic exposure increased proportionally to the nominal dose increments of 240 and 1680 µg, but overall dose proportionality was not confirmed because the exposure of mid dose (720 µg) was relatively higher. However, assessment of dose-proportionality should not be over-interpreted as sample size was small and variability was high. Irrespective, this should not cause a safety concern for further administration of AZD3199 to Japanese subjects, as a less than dose proportional increase rather than a potentiation of exposure at the last dose increment constituted the deviation from linearity. Two alternative approaches were applied to calculate R_{ac}, the measure of time linearity ($AUC_{(0\text{-}24),\ \text{repeat dosing}}$ divided by $AUC_{(0\text{-}\text{inf}),\ \text{single dosing}}$). Thus, the extrapolated part of AUC after single dose was either assessed using the individual estimate of $t_{½}$ or the joint global mean estimate after the last dose (116 h). The mean estimate of R_{ac} ranged from 1.18 to 1.39 using the individual estimate of $t_{½}$ and 0.78 to 0.92 using the joint longer estimate of $t_{½}$. A slight underestimation of single dose AUC (the denominator in the R_{ac} ratio), because the use of a too short $t_{½}$ could likely explain tendency of a value >1 with the former approach. On the other hand, two alternative (or joint) explanations could explain why mean R_{ac} tended to be <1 with the latter approach: 1)

overestimation of single dose AUC, because the terminal phase of elimination was not reached at 48 h (too high plasma concentration at the time from which extrapolation with the long $t_{½}$ was performed); 2) underestimation of AUC during the dosage interval at steady state (the numerator in the R_{ac} ratio), because full steady state had not been attained. The results were overall compatible with time linear pharmacokinetics - a R_{ac} close to 1. The accumulation ratio with respect to AUC during the dosage interval, $R_{ac\ (0\text{-}24)}$, was estimated to less than 2-fold. Mean C_{max} increased moderately whereas the trough values were increased up to 5-fold during the 24 h dosage interval after the last as compared with the first dose. Using the mean $t_{½}$ of 116 h and presuming time linear pharmacokinetics as rationalised above, extrapolation beyond the studied 12 day dosing period suggests that the maximum increase of the trough concentration – a slow steady-state attaining pharmacokinetic parameter - would be 6-fold at the most. In other words, 80% of the steady state trough level should have been reached after in the present study, whereas C_{max} and AUC - two parameters likely to attain steady state more rapidly - should have been even closer.

Summary of pharmacodynamic results

Pharmacodynamic evaluation aimed at investigating β_2-adrenoreceptor stimulating effects such as decreases in serum potassium and diastolic BP, and increases in lactate concentration, heart rate, QTc, pulse and systolic BP. In addition the local effect of AZD3199 on lung function was investigated. Overall, systemic effects were seen on serum potassium, heart rate/pulse and QTc B, particularly after 1680 µg AZD3199, and more marked after repeated dosing compared to single dose. Effects on serum potassium, heart rate/pulse rate and QTc B of AZD3199 were not considered to be of safety concern. No consistent effects were seen on FEV_1.

Summary of safety results

In terms of safety, AZD3199 was well tolerated during single and multiple doses. The incidence of AEs was low (29 treatment-emergent AEs overall) with the most frequent AE being dysgeusia (7 AEs overall). Of the 14 AEs the Investigator considered causally related, 10 AEs occurred in subjects dosed with AZD3199 (ie, dysgeusia, tremor, cough, and throat tightness) and 4 AEs occurred in subjects dosed with placebo (ie, headache, tremor, dysgeusia, and chest discomfort). There were no deaths, SAEs, DAEs, or OAEs.

The clinical laboratory evaluations showed some slight elevations in ALT and AST in some healthy volunteers towards the end of the multiple dose phase (ie, Days 10-14). These increases were seen in the placebo and AZD3199 dose groups and similar findings have also been demonstrated in previous SAD/MAD studies.

Overall, there were no clinically relevant changes in laboratory variables, vital signs, ECG, or lung function that posed any safety concerns for single and multiple dosing of AZD3199 in healthy Japanese men.