AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00002
Edition Number	1
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A phase I, randomised, double-blind, placebo-controlled, parallel-group, single-centre study to investigate the safety, tolerability and pharmacokinetics of multiple ascending doses of AZD3199 (a β_2-agonist) given once daily as inhaled formulation via Turbuhaler to healthy men

Study Dates	First healthy volunteer enrolled: 11 August 2008 Last healthy volunteer completed: 4 November 2008
Phase of development	Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the safety and tolerability of multiple once daily ascending doses of AZD3199 delivered as dry powder via the Turbuhaler inhaler by assessment of incidence and nature of adverse events (AEs) and clinically significant abnormalities in ECG parameters, blood pressure, pulse, lung function, body temperature and laboratory variables (clinical chemistry, haematology and urinalysis).

The secondary objectives of the study were:

- To investigate the pharmacokinetics (PK) of multiple ascending doses of AZD3199 by assessment of the degree of accumulation, dose proportionality and time linearity
- To investigate β2- adrenoreceptor mediated effects of multiple ascending doses of AZD3199 by assessment of potassium and lactate concentrations, tremor and palpitations, heart rate, QTc, pulse and blood pressure and FEV_1

The exploratory objective of the study was to obtain material for possible exploratory analysis of metabolites of AZD3199 in urine and plasma. (The exploratory data do not form part of the clinical study report.)

Study design

This was a phase I, double-blind, parallel-group, randomised, placebo-controlled study in healthy men to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of inhaled AZD3199. Multiple ascending doses of AZD3199 (240 μg, 720 μg and 1680 μg delivered dose [1]) were given sequentially to 3 cohorts of subjects. In each dose cohort, 6 subjects received active treatment and 3 placebo.

Target healthy volunteer population and sample size

27 healthy, non-smoking male subjects, 18-45 years of age, were to be allocated to 3 dose cohorts of 9 subjects each.

[1] Delivered dose is the amount of drug that leaves the mouthpiece of inhaler during inhalation.

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

AZD3199 and its placebo were formulated as dry powder for inhalation. Multiple doses of AZD3199 (240 µg, 720 µg and 1680 µg delivered dose) or placebo were administered once daily via Turbuhaler.

AZD3199 Turbuhaler M3 plus 60, (60 µg/inhalation), 60 doses, Batch number 08-013153AZ

AZD3199 Turbuhaler M3 plus 240, (240 µg/inhalation), 60 doses,
Batch number 08-013155AZ

Placebo Turbuhaler, 60 doses, Batch number 07-012008AZ

Duration of treatment

At each dose level the subjects first received a single dose of AZD3199/placebo on Day 1. There was no dosing on Day 2. On Day 3 repeated, once daily dosing started and continued to Day 14.

Criteria for evaluation - pharmacokinetics and pharmacodynamics (main variables)

- Plasma concentration and urinary excretion of AZD3199
- Potassium and lactate plasma concentrations, tremor and palpitations, heart rate, QTc Bazett, pulse and blood pressure, and FEV_1

Criteria for evaluation - safety (main variables)

Incidence and nature of adverse events and clinically significant abnormalities in ECG parameters, blood pressure, pulse, lung function, body temperature and laboratory variables (clinical chemistry, haematology and urinalysis)

Statistical methods

Safety and pharmacokinetic data were summarised using descriptive statistics. Pharmacodynamic data were reduced to pharmacodynamic 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.

Subject population

All 27 subjects allocated to treatment were male, aged 20 to 44 years (mean 27.7 years), and all but one (Asian) were White. Twenty-five (25) subjects completed the study and received all 13 doses of investigational product; 2 subjects at the lowest dose level withdrew consent prematurely due to personal reasons unrelated to the study. All 27 randomised

subjects were analysed for safety and pharmacodynamics, and all 18 subjects on active treatment had data on PK.

Summary of pharmacokinetic results

Inhaled AZD3199 appeared fairly rapidly in the systemic circulation; the maximum plasma concentration was reached after about 30 min. The results suggest dose-proportional and time-independent pharmacokinetics. The terminal elimination half-life was long, on average 142 h as suggested by data after the last dose; steady state was not fully reached within the 12-day treatment period. Different accumulation indices were obtained for C_{max}, $AUC_{0\text{-}24h}$, and C_{min}, as an expected consequence of the multi-phasic disposition of AZD3199. Urinary recovery constituted on average 1 to 2% of the nominal delivered dose; renal clearance marginally contributed to the overall elimination of the parent drug.

Summary of pharmacodynamic results

Repeated administration of AZD3199 did not produce any consistent systemic effects, as determined by assessments of potassium and lactate plasma concentrations, tremor, palpitations, heart rate, QTc, pulse and blood pressure during the first 4 hours after inhalation of AZD3199. The only statistically significant effects observed were a decrease in plasma potassium, found at all 3 dose levels after the last (13^{th}) dose, and an increase in QTc Bazett intervals, seen after the first dose in the highest dose cohort. No or minimal effects were observed on tremor and palpitations, lactate concentrations, heart rate and blood pressure. Regarding the local effects of AZD3199 in healthy men, all doses provided small but consistent brochodilating effect from Day 1, and the magnitude of effect was maintained after 12 days of repeated dosing.

Summary of safety results

AZD3199 inhaled once daily at doses up to 1680 µg was well tolerated, both at single doses and during multiple dosing over 12 days. The adverse events profiles were similar across the dose groups and the majority of AEs were mild in intensity. There were no clinically important differences discernible in the pattern of reported AEs across the dose groups. The most commonly reported AE was headache (19%), followed by nasopharyngitis (15%). One SAE in this study, a case of appendicitis, which occurred in a subject on the lowest dose, was considered unrelated to the study drug. There were no clinically relevant findings in vital signs, ECG or safety laboratory variables and no subject discontinued the study due to an AE.