AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00007
Edition Number	1
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A phase II, double-blind, placebo-controlled, randomised, 6-way cross-over, single-dose study to investigate the local and systemic effects of 3 doses of inhaled AZD3199 (a β_2-agonist) compared to formoterol in asthmatic patients

Study Dates	First patient enrolled: 11 August 2008 Last patient completed: 29 December 2008
Phase of development	Therapeutic exploratory (II)

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

Study Centres

This study was carried out at 3 centres in Sweden and 1 centre in Denmark.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate the pharmacodynamics of AZD3199 inhaled via Turbuhaler compared to placebo and inhaled formoterol.

The primary variable for local pulmonary effect was Forced Expiratory Volume in 1 second (FEV_1) and the primary variable for systemically mediated effect was potassium concentration.

Heart rate, QT interval corrected for heart rate (QTc), pulse, blood pressure, tremor and palpitations constituted secondary variables for systemically mediated effects.

The secondary objectives of the study were:

- To investigate the safety of single-doses of AZD3199 by assessment of incidence and nature of adverse events (AEs), clinical laboratory assessments and physical examination.

- To investigate drug exposure of AZD3199, by assessment of drug concentration in plasma and calculated pharmacokinetic (PK) parameters.

Study design

This study was a double-blind, placebo-controlled, randomised, 6–way cross-over, single-dose study to investigate the local and systemic effects, drug exposure, tolerability and safety of inhaled AZD3199 in asthmatic patients. The study comprised in total 8 visits, whereof 1 enrolment visit, 6 study drug treatment visits, and 1 follow-up visit.

Target population and sample size

Eligible adult patients were to have mild to moderate persistent asthma with a FEV_1 value equal to or above 60% of predicted normal (PN), and show a step-wise reversibility to salbutamol.

Based on previous experience with formoterol, a coefficient of variation of 3% could be expected for the maximum FEV_1, and a standard deviation (SD) of 0.25 mmol/L for the minimum potassium concentration. Based on this, and using a two-sided test at a 5% significance level, 36 patients were to give a 90% power to detect a pair-wise difference in

maximum FEV_1 of 2.5% or a pair-wise difference in minimum potassium concentration of 0.20 mmol/L. The variability in FEV_1 at 22 to 26 hours was expected to be somewhat higher, 5%, giving a detectable limit of 4%. This detection potential was considered sufficient to study dose-dependent differences in FEV_1 and potassium, and to make a possible estimation of the relative therapeutic index based on these 2 variables.

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

Single doses of AZD3199 (dry powder for inhalation, batch numbers 08-000075AZ [60 µg/dose] and 08-000076AZ [240 µg/dose]), formoterol (dry powder for inhalation, batch number 08-000079AZ [4.5 µg/dose]) and placebo (batch numbers 08-000080AZ and 08-000081AZ) were administered via Turbuhaler.

Duration of treatment

Patients were to inhale 3 single delivered doses of AZD3199 (120, 480, and 1920 µg), 2 single doses of formoterol (9 and 36 µg) and placebo, on 6 separate visits at the clinic.

All single-dose administrations were separated by wash-out periods of 7 to 21 days.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

FEV_1 was the primary variable for local pulmonary effect and potassium concentration was the primary variable for systemically mediated effect.

Heart rate, QTc, pulse, blood pressure, tremor and palpitations were secondary variables for systemically mediated effects.

Standard PK parameters were calculated from AZD3199 concentrations in plasma.

Criteria for evaluation - safety (main variables)

Incidence and nature of AEs.

Clinical laboratory assessments (haematology, clinical chemistry and urinalysis) and physical examination were only performed at the enrolment and follow-up visit.

Statistical methods

The full analysis set (FAS) consisted of all randomised patients with sufficient data collected after intake of investigational product to compute the pharmacodynamic (PD) parameters on at least 2 study visits. The PK data set consisted of all randomised patients with blood sampling performed after at least 1 dose of AZD3199, and with data sufficient to calculate

PK parameters. The safety data set consisted of all randomised patients with safety data collected after intake of investigational product on at least 1 visit.

All hypothesis testing was done using two-sided alternative. P-values less than 5% were considered statistically significant. Differences between treatment were described using 95% confidence interval. PD parameters (peak effects and average effects) were compared using analysis of variance (ANOVA) with fixed factors for treatment, period and patient, and using baseline as covariate. Additive models were used for measures of systemic effects, while FEV_1 was analysed using multiplicative models.

Adverse event were analysed by descriptive statistics and qualitative analysis. Other safety and PK data were summarised using descriptive statistics.

Subject population

Of the 37 patients allocated to treatment, all were white except 2 and 32 (86%) were men. Their average age was 40.3 years and their average body mass index (BMI) was 26.5 kg/m^2. The median duration of the patients' asthma diagnoses was 25 years. The patients' average FEV_1 at inclusion was 77.5% of PN and the average total reversibility (stepwise after 100 + 900 µg salbutamol pressurised metered dose inhaler [pMDI]) was 24.4%. In total, 32 patients used inhaled corticosteroids at a median daily dose of 567 µg, and 20 patients were on treatment with long-acting β_2-agonists prior to the study.

Two (2) patients were withdrawn from the study (voluntary discontinuation and lost to follow-up), both after completing only 1 study treatment visit (placebo respective AZD3199 120 µg). In all, 37 patients were analysed for safety, 35 were analysed for pharmacodynamics and 36 were analysed for pharmacokinetics.

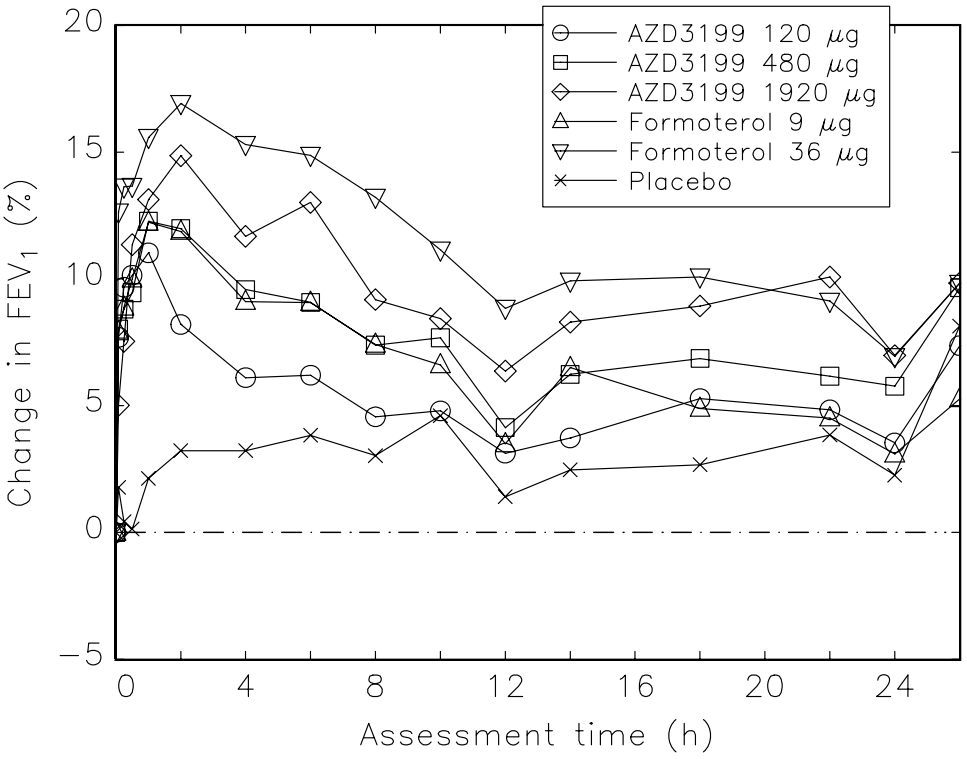
Summary of pharmacokinetic results

Systemic exposure of AZD3199 was dose proportional. AZD3199 was quantifiable in plasma longer than the wash-out periods.

Summary of pharmacodynamic results

All doses of AZD3199 and formoterol statistically significantly and dose-dependently increased peak FEV_1 relative placebo (Figure S1). The estimated relative dose potency between AZD3199 and formoterol regarding peak effect was 50 on the µg scale.

Figure S1 Mean value graphs of change in FEV_1 by treatment



FEV_1=Forced expiratory volume in 1 second

AZD3199 480 and 1920 µg, and formoterol 36 µg statistically significantly and dose-dependently increased average 22 to 26 hours FEV_1 relative placebo. The estimated relative dose potency between AZD3199 and formoterol regarding 22 to 26 hours FEV_1 was 11 on the µg scale. Thus, at comparable peak effects, AZD3199 showed a longer duration of bronchodilatation.

Use of rescue medication (inhaled terbutaline) was less frequent during active treatments, particularly after AZD3199 480 and 1920 µg.

Early response (5 min) of AZD3199 was not dose-dependent contrary to formoterol. Thus, no firm conclusion could be drawn regarding the relative onset properties.

Statistically significant systemic effects were only seen after formoterol 36 µg and AZD3199 1920 µg. On serum potassium and tremor formoterol gave the largest effects whereas on heart rate and QT interval corrected for heart rate using the Bazett formula (QTcB) effects were of similar magnitude. Overall, at comparable peak effects on FEV_1, AZD3199 showed to be beneficial regarding systemic effects compared to formoterol.

Summary of safety results

AZD3199 was safe and well tolerated in asthmatic patients at the studied dose ranges. The most commonly reported AEs were headache and nasopharyngitis (Table S1).

Table S1 **Adverse events by preferred term. Number (%) of patients reporting AEs, sorted by decreasing order of frequency as summarised over all treatment groups**

Preferred term	A 120 µg n=36	A 480 µg n=35	A 1920 µg n=35	F 9 µg n=35	F 36 µg n=35	Placebo n=36
Headache	1 (3%)	3 (9%)	4 (11%)	2 (6%)	3 (9%)	2 (6%)
Nasopharyngitis	3 (8%)	1 (3%)	4 (11%)	0	1 (3%)	4 (11%)
Throat irritation	0	0	4 (11%)	0	0	0
Venipuncture site thrombosis	1 (3%)	0	0	0	1 (3%)	0
Nasal congestion	1 (3%)	0	1 (3%)	0	0	0
Dyspepsia	0	0	1 (3%)	0	0	1 (3%)

Only AEs that occurred in at least 2 patients are included in the table
A=AZD3199; AE=Adverse event; F=Formoterol

The majority of AEs were mild or moderate in intensity. The total number of AEs and causality related AEs were more frequently reported after AZD3199 1920 µg (Table S2). Specifically, throat irritation was only reported after AZD3199 1920 µg.

Table S2 **Causality related adverse events (as judged by the investigator) by preferred term. Number (%) of patients, sorted by decreasing order of frequency as summarised over all treatment groups**

Preferred term	A 120 µg n=36	A 480 µg n=35	A 1920 µg n=35	F 9 µg n=35	F 36 µg n=35	Placebo n=36
Throat irritation	0	0	4 (11%)	0	0	0
Headache	0	1 (3%)	1 (3%)	1 (3%)	1 (3%)	0
Respiratory distress	0	0	1 (3%)	0	0	0
Dyspepsia	0	0	0	0	0	1 (3%)
Cough	0	0	1 (3%)	0	0	0
Dysphonia	0	1 (3%)	0	0	0	0

A=AZD3199; F=Formoterol

No serious adverse event (SAE) was reported and no patient discontinued the treatment/study due to an AE.

No safety concerns were identified based on laboratory analyses and physical examination. There were no persistent clinically relevant changes in serum potassium or QT interval corrected for heart rate using the Fridericia correction (QTcF) in patients after AZD3199 dosing.

Date of the report

9 April 2009