AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00011
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A Randomised, Double-blind, Double-dummy, Placebo-controlled, Multicentre, 6-way Crossover, Single-dose, Phase IIa Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Different Dry Powder Inhalation Formulations of AZD3199 Administered via Single Inhalation Device Compared to AZD3199 Administered via Turbuhaler™[1] Inhaler in Patients With Asthma

Study dates: First patient enrolled: 26 May 2011
Last patient last visit: 27 February 2012

Phase of development: Therapeutic exploratory (IIa)

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

[1] Turbuhaler is a trademark of the AstraZeneca group of companies. Turbuhaler is a registered trademark in Sweden where the study was performed.

Study centres

This study was conducted at 3 centres in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Study objectives and outcome variables are summarised in Table S1

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the pharmacokinetics and pharmacodynamics of single doses of 3 different dry powder inhalation formulations of AZD3199 administered via SID compared to AZD3199 administered via Turbuhaler™[1] inhaler and compared to placebo in patients with persistent asthma	For evaluation of pharmacokinetics: AUC, C_{max}, t_{max}, $t_{1/2}$ For evaluation of pharmacodynamics: E_{max}, $E_{22\text{-}26h}$, t_{Emax}, E_{5min}, $E_{0\text{-}24h}$ of FEV_1 and E_{max}, $E_{0\text{-}4h}$ of pulse	Pharmacokinetics and Pharmacodynamics
Secondary	**Secondary**	
To investigate the safety and tolerability of different dry powder formulations of AZD3199 compared to placebo after single dose administration	AE, clinical laboratory assessments and physical examination.	Safety

AE Adverse event; AUC Area under plasma concentration curve from zero to infinity; C_{max} Maximum plasma drug concentration; E_{max} (FEV_1) Maximum value of FEV_1 for every treatment visits; E_{max} (pulse) Maximum value of pulse for every treatment visits; E_{5min} The value of FEV_1 at 5 minutes for every treatment visit; $E_{0\text{-}4h}$ The average of pulse between zero and 4 hours for every treatment visit; $E_{0\text{-}24h}$ The average of the FEV_1 values between zero and 24 hours for every treatment visit; $E_{22\text{-}26h}$ The average of the FEV_1 values between 22 and 26 hours for every treatment visit; FEV_1 Forced expiratory volume during the first second; SID Single inhalation device; t_{max} Time to maximum plasma concentration; t_{Emax} Time to maximum value of FEV_1 for every treatment visit; $t_{1/2}$ Terminal half-life.

Study design

This was a randomised, double-blind, double-dummy, placebo-controlled, multicentre, 6-way crossover, single-dose, Phase IIa study in patients with persistent asthma. The study

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comprised a total of 8 visits: 1 enrolment visit, 6 study drug treatment visits, and 1 follow-up visit.

Target subject population and sample size

Males and females, ≥18 years of age, having a history of asthma for at least 6 months, with a pre-bronchodilator Forced Expiratory Volume in 1 second (FEV_1) ≥60% of the predicted normal (PN) value, and having a step-wise reversible airway obstruction; a minimum of 5% increase in FEV_1 after each of the 2 consecutive doses of salbutamol (100 µg and 900 µg) with a total increase of at least 15% relative to baseline, were enrolled in the study.

Based on a previous study with AZD3199, a coefficient of variation of 4% was expected for both, the maximum value of FEV_1 (FEV_1 E_{max}) and the average of the FEV_1 values between 22 and 26 hours (FEV_1 $E_{22\text{-}26h}$). Based on this, and using a 2-sided test at a 5% significance level, 24 patients were expected to give an 80% power to detect a pair wise difference in FEV_1 of 3.4%.

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

The details of the IP and other study treatment are given in Table S2

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength[a], and route of administration	Manufacturer	Formulation number	Batch number
AZD3199 Turbuhaler	Inhalation powder 100 µg/dose and 400 µg/dose	AstraZeneca	2100700/ 190032854 2100705/ 190033054	11-000629AZ 11-000630AZ
Placebo Turbuhaler	Inhalation powder	AstraZeneca	2154099/P1765-0	11-000785AZ
AZD3199 SID	Inhalation powder 350 µg (0% excipient) and 220 µg (0.5% excipient) and 200 µg (2.5% excipient)	AstraZeneca	D1000362 D1000363 D1000364	11-000029AZ 10-006446AZ 10-006402AZ
Placebo SID	Inhalation powder (0% excipient)	AstraZeneca	D1000361	10-006231AZ

[a] Strength per dose was referred to AZD3199 delivered dose from the inhalers. One gram of AZD3199 was equivalent to 1.28 gram of AZD3199 dihydrobromide.
SID Single inhalation device.

The following 6 delivered doses were inhaled in random order:

- AZD3199 1400 µg (4 x 350 µg; 0% new excipient) administered via Single Inhalation Device (SID)
- AZD3199 880 µg (4 x 220 µg; 0.5% new excipient) administered via SID
- AZD3199 800 µg (4 x 200 µg; 2.5% new excipient) administered via SID
- AZD3199 300 µg (3 x 100 µg) administered via Turbuhaler inhaler
- AZD3199 1200 µg (3 x 400 µg) administered via Turbuhaler inhaler
- Placebo, administered via SID and Turbuhaler inhaler.

Study drug was given in the morning of each treatment visit (Visit 2 to Visit 7). To maintain blinding, patients were to inhale from 4 SIDs and 1 Turbuhaler inhaler at each visit; 1 inhalation from each of the 4 SIDs, and 3 inhalations from the Turbuhaler inhaler (7 inhalations in total during each visit).

Duration of treatment

Six single doses (1 dose each on Visit 2 to 7) of AZD3199 or matching placebo were administered via SID or Turbuhaler inhaler. The single dose inhalations were separated by wash-out periods of 21 to 28 days. The total study period for 1 patient was 21 to 27 weeks.

Statistical methods

Where not otherwise stated, a 5% significance level was used; all tests were 2-sided and 90% or 95% Confidence Intervals (CIs) were calculated.

Pharmacodynamics (PD): Additive models were used for pulse, while FEV_1 was analysed using multiplicative models. Comparisons of AZD3199 SID and AZD3199 Turbuhaler were based on the dose-response pattern of AZD3199 Turbuhaler, by calculating the dose of AZD3199 Turbuhaler giving a corresponding effect as the different AZD3199 SID treatments.

Pharmacokinetics (PK): PK parameters were summarised using descriptive statistics for each dose level. Area under plasma concentration curve from zero to infinity (AUC) and maximum plasma drug concentration (C_{max}) were compared between active treatments using a multiplicative ANOVA (Analysis Of Variance) model with patient, period, and treatment as factors.

Subject population

Of the 39 patients enrolled, 26 patients were randomised to the study treatment. In total, 25 patients completed the study; one patient was withdrawn from the study due to an AE, after completing only 1 study treatment (AZD3199 SID 1400 µg [0% excipient]). In all, 26 patients were included in the safety and PK analysis sets and 25 patients were included in the PD analysis set.

The majority of the patients (20 [76.9%]) were male. Except 2 patients, all the patients were White. The mean age of the patients was 36.5 years (range 18 to 62 years), with a mean body mass index of 25.2 kg/m^2 (range 21 to 30 kg/m^2). A total of 19 (73.1%) patients were non-smokers and 7 (26.9%) patients were ex-smokers. The duration of asthma was more than 30 months for all the patients. The mean FEV_1 at baseline was 89.20% of PN (range 60.57 to 120.14%) and the mean total reversibility was 26.98% (range 14.79 to 58.20%).

Summary of pharmacokinetic results

There was no difference in the terminal half-life across treatments, suggesting that the amount of inhaled AZD3199 or the inhalation device did not influence systemic rate of elimination after inhalation of AZD3199. The PK of AZD3199 inhaled via Turbuhaler showed dose proportionality (AUC, C_{max}) in the tested dose range (300 µg to1200 µg), whereas the PK of AZD3199 inhaled via SID showed similar exposure (AUC, C_{max}) across the 3 SID treatments (AZD3199 SID 800 µg [2.5% excipient]; AZD3199 SID 880 µg [0.5% excipient]; AZD3199 SID 1400 µg [0% excipient]). The estimated relative systemic bioavailability between SID and Turbuhaler was similar with respect to AUC and C_{max} of AZD3199.

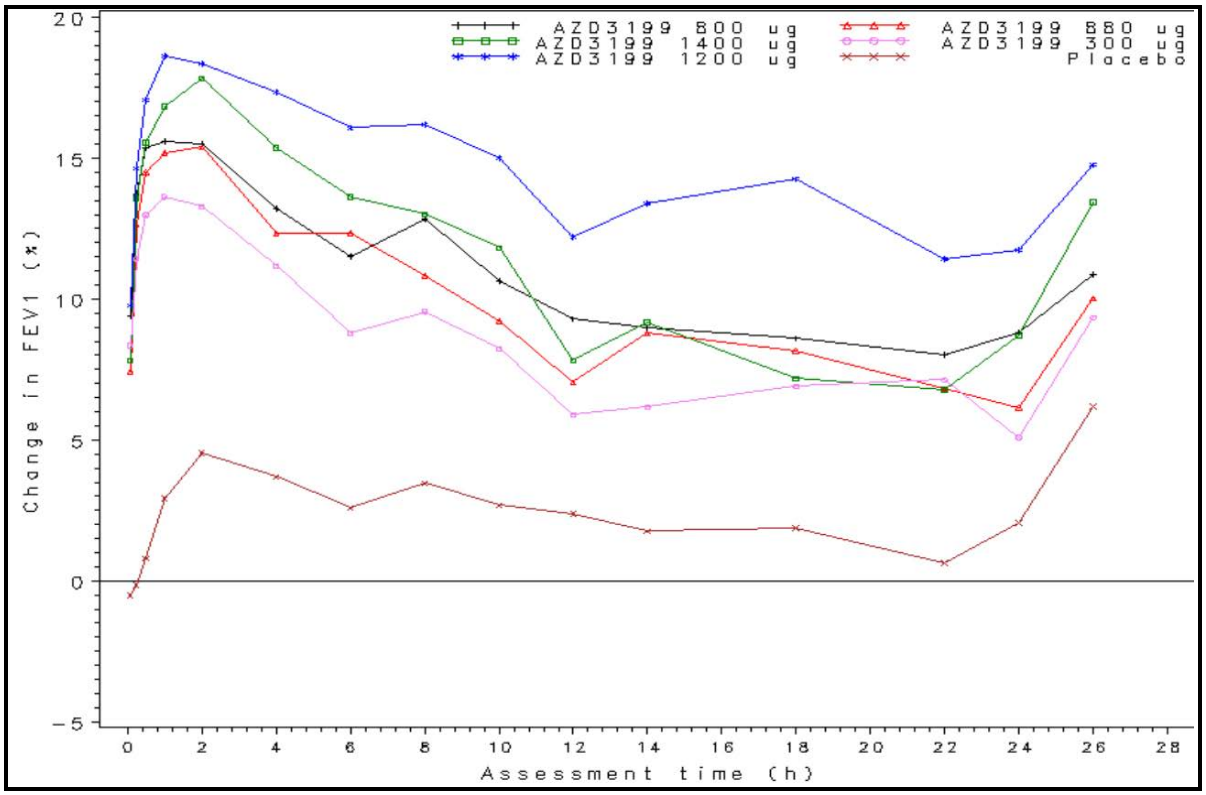
Summary of pharmacodynamic results

AZD3199 inhaled via Turbuhaler and SID resulted in a statistically significantly higher mean FEV_1E_{max}, $FEV_1E_{22\text{-}26h}$, $FEV_1E_{0\text{-}24h}$, and FEV_1E_{5min} compared to placebo (Figure S1).

The effects of AZD3199 Turbuhaler were dose-dependent. The effects of the 3 doses inhaled via SID were in between the effects observed from the 2 doses inhaled via Turbuhaler. There was no statistically significant difference between the effects of the 3 doses inhaled via SID. The dose potency of SID was slightly lower than that predicted for Turbuhaler with regard to lung function (less than a 2-fold difference) as determined by FEV_1 E_{max}, FEV_1 $E_{22\text{-}26h}$, and FEV_1 $E_{0\text{-}24h}$.

No dose-response relationship was observed between Turbuhaler 300 µg and Turbuhaler 1200 µg for FEV_1 E_{5min}. Therefore, no Turbuhaler equi-effective dose by SID could be established for FEV_1 E_{5min}. There were no statistically significant changes in the mean values for pulse at E_{max} and $E_{0\text{-}4h}$ for the AZD3199 treatments as compared to placebo.

Figure S1 **Mean change in FEV_1 over time after a single inhalation of AZD3199 (800 µg / 880 µg / 1400 µg) inhaled via SID, AZD3199 (300 µg / 1200 µg) inhaled via TBH and placebo (PD analysis set)**



FEV_1 Forced expiratory volume during the first second; PD Pharmacodynamics; SID Single inhalation device; TBH Turbuhaler.

Summary of safety results

Single doses of the 3 different dry powder inhalation formulations of AZD3199 administered via SID and 2 doses of AZD3199 administered via Turbuhaler were generally safe and well tolerated.

The number of patients reporting AEs was somewhat higher following AZD3199 1200 µg Turbuhaler than following the other treatments. The most frequently reported AEs were dysguesia, nasopharyngitis and headache. The AE pattern was similar across treatments with the exception for dysguesia, which was reported only in the active treatment periods.

No deaths or SAEs were reported in this study. A single DAE was reported in this study. This was an anaphylactic reaction due to a wasp sting. This occurred in the washout period after the treatment with AZD3199 SID 1400 µg (0% excipient), and was judged to be unrelated to the treatment. There were no OAEs identified in this study. No clinically relevant changes in clinical laboratory findings, physical examination, electrocardiogram, or vital signs were observed in this study.