AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3199
Study Code	D0570C00003
Edition Number	1
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A 4-week, phase-II, double-blind, placebo-controlled, randomized, parallel group, multi-centre study to assess the efficacy and tolerability/safety of inhaled AZD3199 once daily compared to 9 µg formoterol bid and placebo in patients with moderate to severe COPD

Study Dates	First patient enrolled: 16 June 2009 Last patient completed: 5 March 2010
Phase of development	Therapeutic exploratory (II)

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

Study Centres

A total of 53 sites in Bulgaria, Canada, Japan, Poland and Russia participated in this study.

Publications

None at the time of finalizing this report.

Objectives

Primary objective:
To compare the clinical efficacy of AZD3199 inhaled once daily with 9 µg formoterol twice daily and placebo over a 4-week treatment period in adults with COPD.

Primary variables of primary objective:
-Forced expiratory volume in 1 second (FEV_1) measured as:
-$E_{0–4}$; the average value at visit 5 from before to 4 hours after morning dose (peak effect)
-$E_{24–26}$; the average value at visit 5 between 24 and 26 hours following the morning dose (trough effect)

FEV_1 $E_{0–4}$ was the primary outcome for bronchodilator potency of investigational product, and spirometry was performed at pre-dose, 5, 15 minutes, 1, 2 and 4 hours after dose. The $E_{0–4}$ is the area under the time curve (AUC) of the values from pre-dose to 4 hours after dose. FEV_1 $E_{24–26}$ was the primary outcome for duration of effect (AUC from 24 to 26 hours after dose).

Secondary variables of primary objective:
-E_{pre}; the mean pre-dose FEV_1 from visits 3 to 5
-E_{post} the mean 1 h post-dose FEV_1 from visits 3 to 5
-Forced Vital Capacity (FVC) (same 4 parameters as FEV_1)
-AstraZeneca COPD Symptom Scores
-Clinical COPD Questionnaire (CCQ)
-St George's Respiratory Questionnaire for COPD (SGRQ-C)
-use of reliever medication, (day, night and total).

Secondary objectives:
-to investigate the safety of AZD3199: Variables: nature, incidence and severity of adverse events (AEs), safety laboratory variables, pulse, blood pressure, and ECG.
-to investigate the effect of regular treatment with AZD3199 on the reversibility in FEV_1 after inhalation of salbutamol: Variables: percentage change in FEV_1 from before to after salbutamol administration, and the absolute FEV_1 value after the test.
-to determine the pharmacokinetics of AZD3199 in COPD patients. Variables: maximum plasma concentration (C_{max}); time to C_{max} (t_{max}); the area under the plasma

concentration-time curve from zero to 24 hours ($AUC_{0–24}$), and the apparent clearance CL/F (dose/AUC_{0-24})

Exploratory objectives (not reported in CSR):
-to explore morning and evening PEF and $FEV_{1(eDiary)}$ measurements using an electronic diary device with electronic peak flow device.
-to collect pharmacogenetic samples for possible retrospective pooled analysis, by evaluation of genes or gene categories involved in the response to AZD3199.

Study design

A 4-week randomized, double-blind, placebo controlled, parallel-group multicentre study was performed. The effect of AZD3199 at 3 different dose levels (200, 400 and 800 µg once daily) was evaluated in comparison with placebo and formoterol 9 µg twice daily. Eligible patients started a 2 week run-in, and were then randomized to 1 of the 5 treatment arms. Patients who were on inhaled glucocorticosteriods on a constant dose on inclusion were allowed to continue this during the run-in and treatment periods. A short-acting β_2-agonist (salbutamol) was provided as reliever medication. At the last visit on treatment, serial spirometry measurements were performed and from these the primary variables were calculated. Patients were followed up 2 weeks after the treatment had stopped.

Target patient population and sample size

Men and women of non-childbearing potential (or using highly reliable contraceptives), aged 40 years and above, diagnosed as having moderate to severe COPD, with the post-bronchodilator FEV_1 value between 40 to 80% of the predicted normal, and the post-bronchodilator FEV_1/FVC ratio less than 70%. Patients were to be current or ex-smokers with a smoking history of at least 10 pack-years, and be symptomatic during the run-in period.

The sample size computation was based on the repeated FEV_1 assessments from visit 5. It was estimated that a coefficient of variation of 10% could be expected for the FEV_1 E_{0-4}. With 60 patients per group and a 2-sided test at a 5% significance level, there was an 80% chance to detect a true difference of 5% between any 2 treatments.

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

The following treatment regimens were used:

- AZD3199 Turbuhaler 100 µg, 2 inhalations in the morning, Placebo Turbuhaler, 2 inhalations in the evening, daily dose 200 µg

- AZD3199 Turbuhaler 200 µg, 2 inhalations in the morning, Placebo Turbuhaler, 2 inhalations in the evening, daily dose 400 µg
- AZD3199 Turbuhaler 400 µg, 2 inhalations in the morning, Placebo Turbuhaler, 2 inhalations in the evening, daily dose 800 µg
- Formoterol Turbuhaler 4.5 µg, 2 inhalations in the morning and 2 inhalations in the evening, daily dose 18 µg
- Placebo Turbuhaler, 2 inhalations in the morning and 2 inhalations in the evening

The batches used for this study are described in Appendix 12.1.6 of the CSR.

Duration of treatment

The run-in was 2 weeks, the treatment period was 4 weeks and the follow-up period 2 weeks.

Statistical methods

All tests were two-sided at a 5% significance level.

The efficacy variables were compared between treatments using analysis of variance (ANOVA) models with treatment and country as fixed factors and baseline as a covariate. Pairwise treatment contrasts were calculated including estimated mean differences with 95% confidence intervals and p-values. AZD3199 was compared with placebo using a closed test procedure starting at the top dose.

Pharmacokinetic parameters were summarised using descriptive statistics for each dose level.

AEs were summarised by preferred term and system organ class using MedDRA vocabulary. Furthermore, on preferred term level, listings of serious AEs (SAEs), AEs leading to discontinuation of investigational product (DAE), withdrawals from study due to AE, AEs with severe intensity and AEs causally related to investigational product, as judged by the investigator, were made.

Patient population

A total of 490 patients were enrolled. 329 patients were randomized and 22 discontinued the study. Slightly more patients discontinued from the formoterol and placebo groups (6 from each) than from the AZD3199 groups (4, 3 and 3, respectively, from the 200 400 and 800 µg groups).

Of the 329 patients allocated to treatment, 75.1% were males and 24.9% were females; 75.7% were white and 24.3% were Asian. Their average age was 64.1 years (range: 40 to 92) and the median time since diagnosis of COPD was 4 years (range: 0 to 29). The

patients' average FEV_1 at inclusion was 61.2% (range: 40 to 80) of predicted normal, 31% of the patients had a reversibility relative to pre-dose of 12% or more, 47% of the patients were previous smokers and 53% were current smokers. Some differences were noted at entry regarding distribution of sex, FEV_1 and reversibility, but these were not considered to affect the conclusions of the study.

Summary of efficacy results

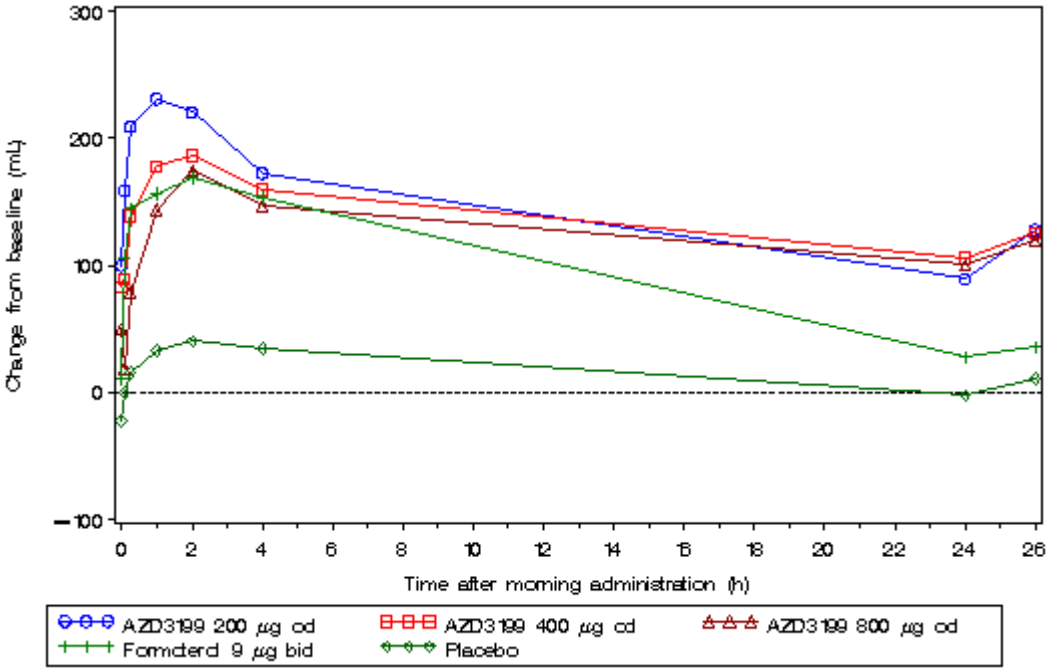
Primary efficacy variables

The study showed that all doses of AZD3199 were effective at peak and had a 24-hour duration of bronchodilation.

Mean value curves for serial FEV_1 as change from baseline in mL are shown in Figure 1. The FEV_1 results of the statistical comparison between the treatment groups are summarised in Table 1.

Regarding peak FEV_1 $E_{0\text{-}4}$ there were statistically significant differences for all 3 doses of AZD3199 and formoterol 9 µg compared to placebo. At trough, for FEV_1 $E_{24\text{-}26}$ there were statistically significant differences (about 95 to 110 mL) for all AZD3199 treatment groups compared to placebo. The largest response was shown for AZD3199 400 µg, and no dose-response could be seen. No effect could be seen for formoterol at trough, ie the duration of effect for formoterol was less than 12 hours. All doses of AZD3199 were numerically better than formoterol 9 µg with differences of about 80 to 90 mL, but these differences were not statistically significant.

Figure 1 Mean value curves for FEV_1 at visit 5



NB Since there were no FEV_1 measurements between 4 and 24 hours, the presumed formoterol peak after evening administration (12h) is not captured in the figure

Table 1 **Treatment estimates and pairwise contrasts for FEV_1 E_{0-4} and E_{24-26} (mL)**

			Treatment contrasts			
Variable	**Treatment**	**Baseline diff (mL)**		**Diff (mL)**	**95% CI**	**P-value**
FEV_1, E_{0-4}	AZD3199 200 µg od	199.7	AZD3199 200 vs Placebo	171.0	(69.2, 272.9)	0.001
	AZD3199 400 µg od	163.2	AZD3199 400 vs Placebo	134.5	(34.7, 234.3)	0.008
	AZD3199 800 µg od	134.3	AZD3199 800 vs Placebo	105.7	(4.6, 206.8)	0.041
	Formoterol 9 µg bid	142.8	Formoterol 9 vs Placebo	114.2	(12.8, 215.6)	0.027
	Placebo	28.6	AZD3199 200 vs Formoterol 9	56.9	(-42.7, 156.4)	0.262
			AZD3199 400 vs Formoterol 9	20.4	(-77.4, 118.2)	0.682
			AZD3199 800 vs Formoterol 9	-8.5	(-107.2, 90.3)	0.866
FEV_1, E_{24-26}	AZD3199 200 µg od	104.1	AZD3199 200 vs Placebo	98.6	(2.4, 194.9)	0.045
	AZD3199 400 µg od	115.9	AZD3199 400 vs Placebo	110.4	(16.0, 204.7)	0.022
	AZD3199 800 µg od	102.1	AZD3199 800 vs Placebo	96.5	(0.5, 192.5)	0.049
	Formoterol 9 µg bid	23.4	Formoterol 9 vs Placebo	17.9	(-78.0, 113.7)	0.714
	Placebo	5.5	AZD3199 200 vs Formoterol 9	80.8	(-13.4, 174.9)	0.092
			AZD3199 400 vs Formoterol 9	92.5	(0.1, 185.0)	0.050
			AZD3199 800 vs Formoterol 9	78.7	(-15.0, 172.4)	0.100

Secondary efficacy variables

The FEV_1 E_{pre} and E_{post} data supported the results for FEV_1 E_{0-4} and E_{24-26}; and the analysis of FVC generally confirmed the evaluation based on FEV_1.

AZD3199 800 µg and formoterol 9 µg statistically significantly reduced the overall mean CCQ scores compared to placebo, as measured at clinic visits. All active treatment groups improved total SGRQ-C scores from visit 5 compared to placebo, but no statistical significance was reached. AZD3199 800 µg statistically significantly reduced breathlessness, chest tightness, awakenings and total symptom scores compared to placebo, as measured by daily diary recordings.

All doses of AZD3199, but not formoterol, statistically significantly reduced daily use of reliever inhalations (salbutamol). Four weeks of regular treatment with AZD3199 once daily and formoterol twice daily did not impair the acute bronchodilating effect of inhaled salbutamol.

Summary of pharmacokinetic results

Steady-state systemic exposure of AZD3199 was found to be dose proportional. The magnitude of exposure was lower than predicted from previous studies in healthy subjects and asthma patients.

Summary of safety results

In this study AZD3199 was well tolerated at all dose levels and no safety concerns were raised. There was 1 death in the placebo group. SAEs and DAEs were few and evenly distributed between the different treatment groups. AEs were few, and only 6 of the 128 AEs were of severe intensity. The number of AEs were considered evenly distributed between treatment groups, with lowest incidence in the AZD3199 200 µg group. The most commonly reported AEs were nasopharyngitis, cough and COPD (= COPD exacerbation). Seven patients reported 9 SAEs other than death. Of these 9 SAEs, 8 were serious due to hospitalisation, and 2 were considered causally related by the investigator. There were 11 DAEs reported with the highest number in the placebo and formoterol groups, and none in the AZD3199 200 µg group. Of the 11 DAEs, 7 were due to COPD exacerbation, all fulfilling the study specific discontinuation criterion. There were no consistent clinically significant changes across groups in vital signs, ECG or laboratory parameters.

Date of the report

28 September 2010