AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9164
Study Code	D1882C00003
Edition Number	1
Date	10 March 2010

A double-blind, double-dummy, placebo-controlled, randomised, multi-centre, 5-way cross-over, single-dose study to investigate the local and systemic effects of inhaled AZD9164 compared to tiotropium in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Study Dates	First healthy subject enrolled: 23 June 2009 Last healthy subject completed: 26 November 2009
Phase of development	Therapeutic exploratory (IIa)

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

Study Centres

The study was performed at 4 study centres in Sweden.

Publications

None at the time of writing this report.

Objectives

Table 1 Primary and secondary objectives and variables

Objectives	Variables	Type
Primary		
To investigate the pharmacodynamics of inhaled AZD9164 compared to placebo and tiotropium.	• Pulmonary effects: FEV_1 ($E_{av\ 0\text{-}24}$, E_{max}, $E_{22\text{-}26}$) • Systemic effects: heart rate, QTc, pulse and blood pressure (average 0-4 h)	PD
Secondary		
To investigate the safety of single doses of AZD9164	• Adverse events • Clinical laboratory variables: clinical chemistry, haematology, urinalysis • Blood pressure, pulse • ECG parameters • Physical examination	Safety
To investigate drug exposure of AZD9164	• $AUC_{0\text{-}24}$, C_{max}, t_{max}	PK
Exploratory[a]		
To collect and store DNA for possible future exploratory research into genes/genetic variation that may influence response to AZD9164 (ie, distribution, safety, tolerability and efficacy) and/or susceptibility to COPD.		PGx

PK Pharmacokinetics; PD Pharmacodynamics; E_{max}, peak effect, $E_{22\text{-}26}$ trough effect (average of 22-26h), $E_{av\ 0\text{-}24}$ average effect 0-24 h, AUC Area under plasma concentration time curve; C_{max} Maximum plasma concentration; t_{max} Time to maximum plasma concentration.

a With regard to exploratory objectives, samples for possible future pharmacogenetic investigation were collected - this has not been further addressed in the clinical study report.

Study design

A double-blind, double-dummy, placebo-controlled, randomised, multi-centre, 5-way cross-over, single-dose study to investigate the local and systemic effects and safety of inhaled AZD9164 (a muscarinic receptor antagonist) in chronic obstructive pulmonary disease (COPD) subjects.

Target healthy volunteer population and sample size

Eligible subjects were male or post-menopausal women aged ≥40 years, with COPD diagnosis, with a post-bronchodilatory FEV_1 value in the range 40% to 80% of predicted normal and post-bronchodilatory FEV_1/FVC <70%. The subjects were required to demonstrate an airway obstruction reversible to ipratropium at 2 separate occasions.

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

AZD9164 (AZD9164 bromide in 20 mM citrate buffer/0.72% sodium chloride; solution for nebulisation, 10 mg/g, batch number 09-000472AZ) and placebo for AZD9164 (sodium chloride, solution for injection, 9 mg/mL; batch number 09-003385AZ) were administered via Spira nebulariser. Tiotropium 18 µg/dose (Spiriva®, powder for inhalation [hard capsules], batch numbers 09-003386AZ and 09-006044AZ) and matching placebo (powder for inhalation [hard capsules], batch number 09-002635AZ) were administered via a HandiHaler® device.

Due to the way in which the formulation was prepared subjects received increasing amounts of citrate as the dose of AZD9164 increased. Subjects inhaled 3 different single doses of AZD9164 (100, 400 and 1200 µg, expressed as lung deposited doses) delivered via nebulisation, 1 single dose of placebo and 1 single dose of tiotropium (18 µg) from a dry-powder inhaler on 5 separate visits to the clinic. At each treatment visit the subject inhaled from both Spira nebuliser and HandiHaler® device in a double-dummy fashion.

Duration of treatment

5 single-dose administrations (on 5 overnight visits to the clinic) were to be separated by wash-out periods of 7 to 14 days.

Statistical methods

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. Pharmacodynamic (PD) parameters (peak effects and average effects) were compared using analysis of variance (ANOVA) with fixed factors for treatment, period and subject, 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 pharmacokinetic (PK) data were summarised using descriptive statistics.

All 28 randomised subjects completed the study and were analysed for safety, PD and PK.

Subject population

Of the 28 subjects allocated to treatment, all were White and 13 (46%) were men. Their average age was 64.2 years (range: 51 to 71) and their average body mass index (BMI) was 25.7 kg/m^2 (range: 20 to 34). Subjects were former (15 [54%]) or current smokers with a smoking history of at least 10 pack years, with the median time since diagnosis of COPD of 6 years (range: 1 to 20). In total, 21 (75%) subjects used inhaled corticosteroids, 18 (64%) subjects were on treatment with long-acting β_2 -agonists and 14 (50%) subjects were on treatment with long-acting anticholinergics prior to the study.

The subjects average post-bronchodilator FEV_1 at Visit 2 was 61.1% predicted normal (range: 41 to 80). The average reversibility (after 120 µg ipratropium) was 20.9% (range: 11 to 61) and 22.1% (range: 10 to 50) at Visits 2 and 3, respectively.

Summary of pharmacokinetic results

Inhaled AZD9164 showed a relatively fast absorption rate from the lung, as indicated by the median t_{max} between 15 and 60 minutes. The systemic exposure of AZD9164, as determined by C_{max} and AUC_{0-24}, increased slightly more than dose-proportionally after inhalation of 100 µg to 1200 µg as nebulised solution.

Summary of pharmacodynamic results

All 3 tested doses of AZD9164 (1200 µg, 400 µg and 100 µg lung deposited doses) delivered via nebulisation produced statistically significant increases in peak, trough (average 22-26 h) and 24-h average FEV_1 versus placebo (Figure 1). The largest effects were obtained with the 400 µg dose. Statistically significant increases in peak and average but not trough FEV_1 (borderline, p=0.07) versus placebo were observed with tiotropium 18 µg. Numerically, all three doses of AZD9164 showed larger increases in peak and trough FEV_1 than tiotropium 18 µg. The difference between AZD9164 and tiotropium for trough FEV_1 was statistically significant for 1200 µg and 400 µg. An AZD9164 dose of 100 µg best approximated the effect of tiotropium 18 µg.

Administration of AZD9164 was associated with a transient, dose-dependent drop in FEV_1 within the first 2 hours following inhalation (Figure 2). This negative effect on FEV_1 was accompanied by a dose-related increase in the incidence of AE, mostly due to increase in respiratory-related AEs (see below). On the individual level, there was no clear association between degree of fall in FEV_1 and occurrence of AEs; however AEs generally were reported shortly after inhalation, and use of rescue medication was also higher after inhalation of the

1200 µg dose. First rescue inhalation after AZD9164 was in most cases used within 30 min, whereas the use of rescue medication after tiotropium peaked during the night. With regard to class-related systemic effects, statistically significant increases in heart rate, pulse and systolic blood pressure compared to placebo were only seen after AZD9164 1200 µg.

Figure 1 Mean value graphs of change from baseline in FEV_1 by treatment

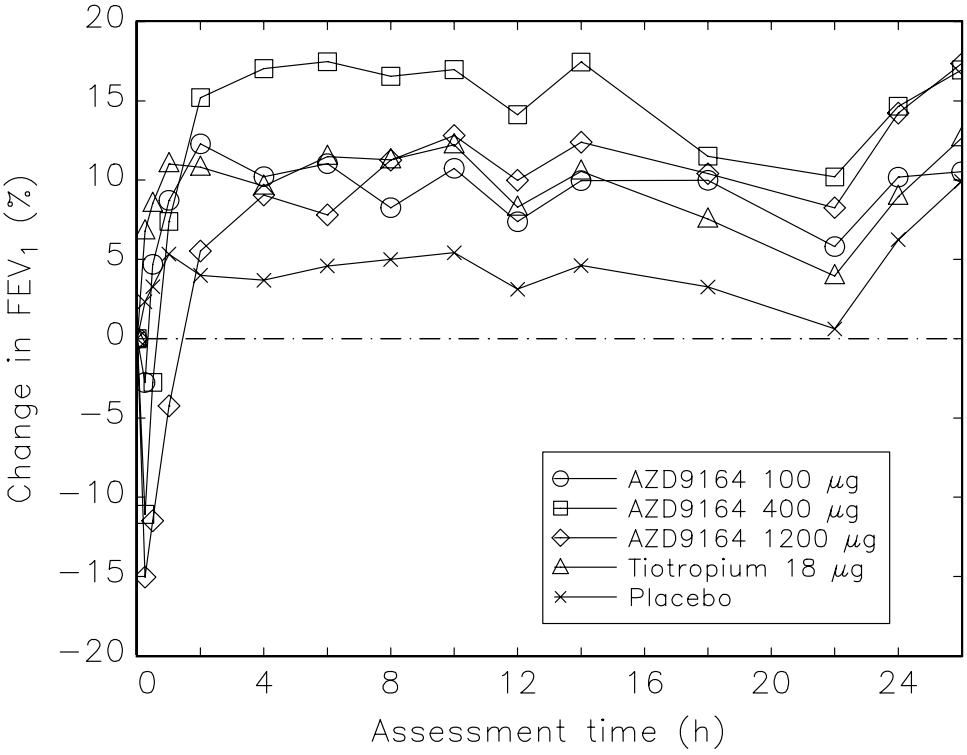
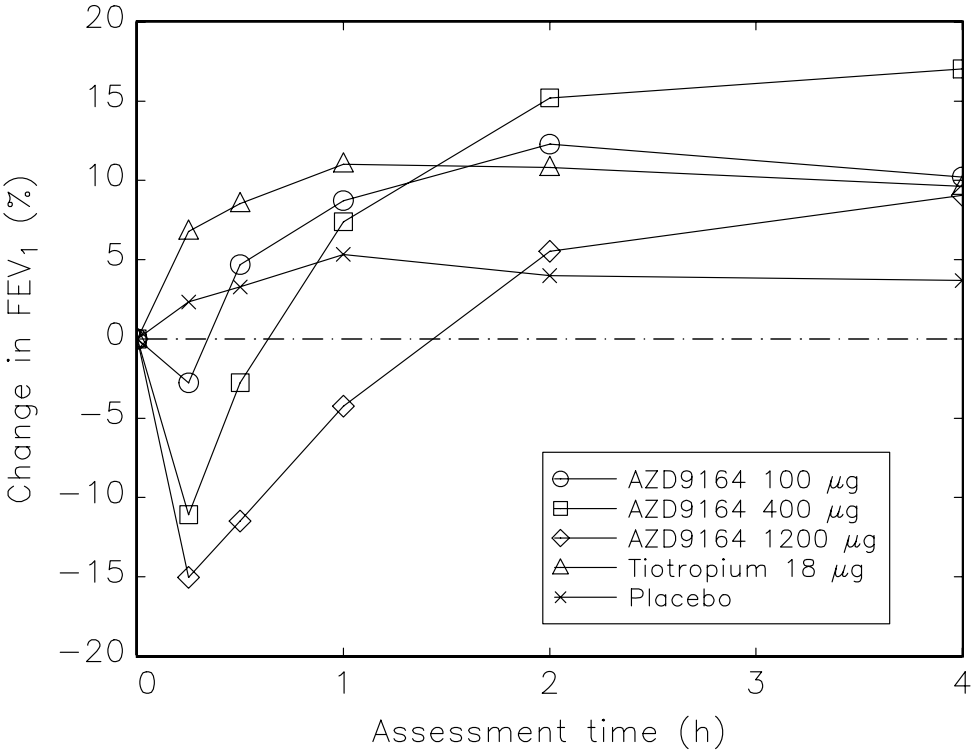


Figure 2 **Mean value graph of change in FEV_1 during first 4 hours, by treatment**



Summary of safety results

There were no deaths, SAE or DAE reported for randomised subjects. However, a dose-related increase in the incidence of AEs was observed with AZD9164 (21% after AZD9164 100 µg, 57% after 400 µg and 96% after 1200 µg as compared to 25% after placebo and 21% after tiotropium). The increase was mainly due to respiratory-related AEs such as cough, throat irritation and dyspnoea (Table 2), appearing shortly after inhalation.

Table 2 **Adverse events by preferred term. Number (%) of subjects reporting AEs, sorted by decreasing order of frequency as summarized over all treatment groups**

Preferred term	A 100 µg n=28	A 400 µg n=28	A 1200 µg n=28	T 18 µg n=28	Placebo n=28
cough	0	6 (21%)	18 (64%)	1 (4%)	0
throat irritation	0	5 (18%)	8 (29%)	0	0
dyspnoea	1 (4%)	2 (7%)	7 (25%)	0	0
headache	1 (4%)	3 (11%)	2 (7%)	1 (4%)	1 (4%)
nasopharyngitis	2 (7%)	3 (11%)	0	0	2 (7%)
chest discomfort	0	2 (7%)	4 (14%)	0	0
thrombophlebitis	0	2 (7%)	1 (4%)	0	0
chronic obstructive pulmonary disease	0	0	2 (7%)	0	0
tremor	0	0	2 (7%)	0	0
gingivitis	1 (4%)	0	0	0	1 (4%)
palpitations	0	0	1 (4%)	1 (4%)	0
puncture site haemorrhage	1 (4%)	0	1 (4%)	0	0

Only AEs that occurred in least 2 subjects, or in 1 subject after 2 treatments, are included in the table.

The majority of AEs were of mild to moderate intensity; the most common AE of severe intensity was dyspnoea. Most of the reported respiratory-related AEs were judged by Investigator as causally related to investigational product.

There were no consistent clinically significant changes in blood pressure, pulse, ECG or clinical laboratory parameters.

Date of the report

10 March 2010