
Clinical Study Report Synopsis

Drug Substance	AZD9164
Study Code	D1882C00002
Edition Number	1
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A Phase I, Multi-Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Multiple Ascending Doses of AZD9164 given once daily as Inhaled Formulation via Turbuhaler for 13 days in Healthy Male and Female Subjects and in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study dates: First subject enrolled: 16 December 2009
Last subject last visit: 18 June 2010

Phase of development: Clinical pharmacology (I)

Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 2 centres in Sweden: Berzelius Clinical Research Center AB, Berzelius Science Park, SE-582 25 Linköping and Quintiles Hermelinen, Varvsgatan 53, SE-972 33 Luleå.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary objective

To investigate the safety and tolerability of AZD9164 following inhaled administration of multiple ascending doses delivered via Turbuhaler in healthy subjects and chronic obstructive pulmonary disease (COPD) patients.

Secondary objectives

1. To characterise the multiple dose pharmacokinetics (PK) of AZD9164 delivered via Turbuhaler by assessment of the degree of accumulation, and the time dependency of the PK in healthy subjects. To characterise the multiple dose PK of AZD9164 delivered via Turbuhaler in COPD patients.
2. To investigate the pharmacodynamics (PD) effects of inhaled multiple ascending doses of AZD9164 delivered via Turbuhaler in healthy subjects and COPD patients.

Exploratory objectives

1. Exploratory analysis of metabolites of AZD9164 in plasma and urine in healthy subjects.
2. To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, safety, tolerability, PK and PD) to AZD9164 (see Appendix D of the CSP).

Results from exploratory objectives are not included in the report.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	Primary	
To investigate the safety and tolerability of AZD9164 following inhaled administration of multiple ascending doses delivered via Turbuhaler in healthy subjects and COPD patients.	Adverse events, laboratory variables, physical examination, vital signs, ECG, FEV ₁ and FVC	Safety
Secondary	Secondary^a	
To characterise the multiple dose PK of AZD9164 delivered via Turbuhaler by assessment of the degree of accumulation, and the time dependency of the PK in healthy subjects. To characterise the multiple dose PK of AZD9164 delivered via Turbuhaler in COPD patients.	AUC ^c , AUC ₀₋₂₄ , AUC _{0-t} ^b , %AUCextra ^b , C _{max} , C _{max} /dose, t _{max} , t _{1/2λz} , CL/F, V _z /F ^b , MRT ^b , LI, R _{ac} , C _{av} , A _e , A _e /dose, CL _R . CL/F and V _z /F were also reported after adjustment for body weight.	PK
To investigate the PD effects of inhaled multiple ascending doses of AZD9164 delivered via Turbuhaler in healthy subjects and COPD patients	FEV ₁ , FVC, supine systolic and diastolic blood pressure, heart rate, QTcF, E _{av} and E _{max} (E _{min} for diastolic blood pressure).	PD

^a Due to the premature interruption of cohort 4, none of the planned PK analyses were possible to perform for the COPD patients.

^b Single dose only.

A_e amount unchanged drug excreted into urine; AUC area under the plasma concentration time curve from zero to infinity; AUC₀₋₂₄ area under the plasma concentration time curve from zero to 24 h; AUC_{0-t} area under the plasma concentration time curve from zero to time of last quantifiable concentration; %AUCextra % of AUC extrapolated; C_{av} average concentration at last dose; CL/F apparent plasma clearance; CL_R renal clearance; C_{max} maximum plasma concentration; C_{max}/dose dose adjusted maximum plasma concentration; E_{av} average effect; ECG electrocardiogram; E_{max} maximum effect; E_{min} minimum effect; FEV₁ forced expiratory volume in 1 second; FVC forced vital capacity; LI linearity index; MRT mean residence time; QTcF QT interval for heart rate using Fridericia's formula; R_{ac} accumulation ratio; t_{1/2λz} terminal half-life; t_{max} time to C_{max}; V_z/F apparent volume of distribution during terminal phase

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, multiple ascending dose (MAD) study conducted at 2 centres in Sweden.

Healthy subjects were randomised 6:3 to active treatment or placebo in 3 cohorts. The starting dose of AZD9164 in cohort 1 was 400 µg delivered dose inhaled via Turbuhaler. The doses in cohorts 2 and 3 were 1000 and 2800 µg delivered dose, respectively. After each cohort, a Safety Review Committee (SRC) evaluated available safety, tolerability, PK and PD data and made a decision on the next dose. Each healthy subject participated in 1 cohort only.

Nine COPD patients were to be randomised 6:3 to active treatment or placebo in cohort 4. The patients were to receive the mid dose (1000 µg) given to healthy subjects. The study was

prematurely interrupted after administration of 1 single dose of AZD9164 to 3 COPD patients and 1 single dose placebo to 1 COPD patient.

Target subject population and sample size

The main criteria for inclusion of healthy subjects were: healthy male or female volunteers aged 18 to 45 years inclusive with a body mass index (BMI) between 18 and 30 kg/m² who were able to inhale from the Turbuhaler according to given instructions. Females were to be of non-childbearing potential.

The main criteria for inclusion of COPD patients were: male or female patients aged 40 years or above with a BMI between 18 and 32 kg/m² with a clinical diagnosis of COPD for more than 1 year at Visit 1 according to GOLD guidelines. Patients were to be able to inhale from the Turbuhaler according to given instructions and were to have a post-bronchodilator FEV₁ 40 to 80% of the predicted normal value and post bronchodilator FEV₁/FVC <70%. Females were to be of non-childbearing potential.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength ^a , and route of administration	Manufacturer	Batch number
AZD9164 Turbuhaler [®]	Dry powder for inhalation 200 µg/dose	AstraZeneca	09-007181AZ
AZD9164 Turbuhaler [®]	Dry powder for inhalation 500 µg/dose	AstraZeneca	09-007182AZ
Placebo Turbuhaler [®] M3	Dry powder for inhalation	AstraZeneca	09-002533AZ

^a Strength per dose refers to delivered dose from Turbuhaler

Duration of treatment

Each of the healthy subjects received a single dose of AZD9164 or placebo on Day 1 and subsequent single doses once daily between Day 4 and Day 15, ie, 13 doses of AZD9164.

The COPD patients were to receive AZD9164 or placebo for 13 consecutive days. Only 1 single dose of AZD9164 and 1 single dose of placebo were administered to 4 COPD patients before termination of the study.

Statistical methods

The safety, tolerability, PK and PD data were summarized using descriptive statistics. Adverse events were summarised by preferred term (PT) and system organ class (SOC) using Medical dictionary for regulatory activities (MedDRA).

Analysis of dose-proportionality was data driven. Dose-normalised AUC and C_{\max} values were graphically presented.

Where data allowed, the average effect over the first 4 h (E_{av}) was determined for each PD variable. The maximum effect during the first 4 h (E_{max}) was calculated for all PD variables except for diastolic blood pressure for which the minimum value (E_{min}) was determined. The average effect, E_{max} and E_{min} were analysed using an analysis of variance (ANOVA) model with fixed factor treatment and the baseline value as a covariate. Multiplicative models were used for FEV₁ and FVC whereas additive models were used for the other variables.

Subject population

Healthy subjects: 27 white healthy male subjects, aged 19 to 39 years, were randomised into the study at 1 study site. All but 3 healthy subjects randomised to treatment completed the study and received 13 administrations of AZD9164 or placebo. There were 2 discontinuations of investigational product due to adverse events (DAEs: winter vomiting disease and ventricular tachycardia), of which 1 was due to a serious AE (SAE: ventricular tachycardia). In both cases, the subjects had received placebo. One additional healthy subject was discontinued from investigational product due to the study specific discontinuation criterion: "Fall in FEV₁ \geq 30% compared with the pre-dose value on the same day within 4 h after administration of investigational product". The subject had received 1 dose of AZD9164 (2800 μ g). The safety analysis set included all randomised healthy subjects and there were no protocol deviations or incidents that led to exclusion of subjects from the PK or PD analysis sets. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

COPD patients: 1 white male and 4 white non-fertile female COPD patients, aged 57 to 71 years, were randomised into the study at 2 study sites. Due to the premature termination of the study, one randomised COPD patient was not dosed and therefore not included in the safety analysis set. None of the COPD patients randomised to treatment completed the study as the study was prematurely stopped after 1 single dose administration of investigational product to 4 patients. There was 1 DAE (anxiety). Two patients, of which one constituted the DAE, fulfilled the study specific discontinuation criterion: "Fall in FEV₁ \geq 30% compared with the pre-dose value on the same day within 4 h after administration of investigational product". No patient received more than 1 dose of AZD9164. The safety analysis set included all randomised COPD patients who received investigational product, ie, 4 patients.

Summary of pharmacokinetic results

The plasma concentration-time profiles of AZD9164 were characterised by a rapid absorption phase and a multi-phasic, generally parallel, decline with a slow terminal phase. Scarce sampling was obtained from COPD patients. The plasma concentrations at 1 h were consistently higher in COPD patients compared to those in healthy subjects; however the levels were within one doubling dose (assuming dose linearity). The concentrations at 24 h were similar in COPD patients and healthy subjects.

For healthy subjects, the predefined maximum exposure limits for AUC (single dose) or AUC₀₋₂₄ (last dose) and C_{max} were not reached based on geometric mean estimates. In the highest dose group the geometric mean AUC (single dose) was 54.5 h*nmol/L and the geometric mean AUC₀₋₂₄ (last dose) was 58.6 h*nmol/L. The corresponding geometric mean C_{max} was 13.3 nmol/L (single dose) and 16.0 nmol/L (last dose).

The absorption of AZD9164 from the lung was rapid and comparable between doses with median t_{max} of 5 to 11 minutes both after single dose and after last dose. The geometric mean t_{1/2λz} after last dose was 131 to 189 h. The A_e/dose constituted less than 1% of nominal delivered dose.

Steady-state was considered to have been reached in a majority of the subjects within the study time period. In all dose groups the geometric mean linearity index was close to unity, indicating the PK properties of AZD9164 to be time-independent. By visual inspection of dose-normalised estimates of C_{max} and AUC (single dose) or AUC₀₋₂₄ (last dose) versus dose, there were no indications of deviations from dose-proportionality in the present dose range studied.

Summary of pharmacodynamic results

Healthy subjects: There were no statistically significant effects on any of the PD variables compared to placebo after administration of single doses of 400, 1000 and 2800 µg AZD9164. Following administration of the last dose of AZD9164, a numerical improvement of 5 to 10% in FEV₁ E_{max} compared to placebo was observed. The increase was statistically significant for the highest dose (2800 µg).

There was no evidence of systemically-mediated effects, with the exception of a statistically significant difference in mean systolic blood pressure (SBP) (8 mmHg) between healthy subjects receiving AZD9164 (2800 µg) and healthy subjects receiving placebo after the last dose (mean estimate: -6.27 mmHg for 2800 µg AZD9164 versus -14.3 mmHg for placebo).

COPD patients: For COPD patients, spirometry results are presented in a safety context below.

Summary of safety results

Healthy subjects: All planned dose panels were completed. No safety or tolerability concerns were identified up to the highest dose given (2800 µg). There was 1 SAE (arrhythmia: ventricular tachycardia), 2 DAEs, of which 1 was due to the SAE, but no deaths or other significant AEs (OAEs). Both subjects with DAE had received placebo.

The AE frequency was highest in the placebo group. The smallest number of AEs was reported in the lowest dose group (400 µg). Most AEs were of mild intensity. All of the causally related AEs (n=7) occurred in the highest dose group and included dry mouth, throat irritation, cough and flushing. Six (6) healthy subjects receiving AZD9164 reported in total 10 (including multiple events within one individual) respiratory-related AEs (ie AEs within the respiratory, thoracic and mediastinal disorders SOC), of which the most common was

throat irritation. One (1) healthy subject receiving placebo reported 1 respiratory AE (throat irritation). Five (5) of the respiratory related AEs (throat irritation: 3 events and cough: 2 events) were reported by 2 subjects in the highest dose group (2800 µg). All of these events occurred in close association with either first or second dose and were assessed as causally related to treatment by the investigator. All of the respiratory AEs following administration of AZD9164 were mild in intensity and none were associated with a drop in FEV₁ or FVC.

Two healthy subjects experienced a fall in FEV₁ ≥ 30% within 1 hour of dosing, of which 1 lead to discontinuation of investigational product.

There were no clinically important changes or trends in any laboratory variables, vital signs, ECG or physical examination.

COPD patients: There was 1 DAE but no deaths, other SAEs or OAEs among the COPD patients in the study. Three out of 5 randomised COPD patients received 1 dose of AZD9164, 1 received placebo and 1 was not dosed. In total, 8 AEs, of which 3 were respiratory related (dyspnoea [reported 2 times] and cough), were reported by patients receiving AZD9164. The respiratory related AEs were of mild intensity and were assessed by the investigator as being causally related to the study drug.

The 3 COPD patients receiving AZD9164 experienced a fall in FEV₁ of 34%, 34% and 28%, respectively, 5 to 15 minutes after inhalation of the first dose whereas the patient receiving placebo did not. Out of the 3 patients who received AZD9164, 2 met the discontinuation criterion: "Fall in FEV₁ ≥ 30% compared with the pre-dose value on the same day within 4 h after administration of investigational product". Because of this the following stopping criterion was met: "Two or more subjects, who receive AZD9164, have other clinically significant changes in laboratory values or other safety parameters", a decision was made to permanently stop the study.

There were no clinically important changes in available laboratory variables, vital signs, ECG or physical examinations.

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