AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8848
Study Code	D0542C00002
Edition Number	1
Date	28 October 2014
EudraCT Number	2012-002809-21

A Phase 1, Single Centre, Double-blind, Randomised, Placebo-controlled, Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics after Administration of Multiple Ascending (MAD) Once Weekly Inhaled Doses of AZD8848 in Healthy Subjects

Study dates:	First subject enrolled: 23 January 2014
	Last subject last visit: 07 February 2014
Phase of development:	Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Study objectives and variables

Objectives			Variables
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD8848 following inhaled administration of multiple ascending doses and to estimate the MTD, if within predefined exposure and dose limits, in healthy subjects	AEs, vital signs (blood pressure, pulse rate, body temperature), ECGs, laboratory variables, spirometry (FEV_1, FVC), DLCO, and pulse oximetry were monitored
Secondary	PK	To characterise the PK after inhaled administration of multiple ascending doses of AZD8848 by determination of plasma and urine concentrations of the sum of AZD8848 and acid metabolite (AZ12432045) (measured as the acid metabolite after allowing the hydrolysis of AZD8848 to go to completion during sample preparation), and if possible AZD8848 alone in plasma.	The following parameters were calculated for AZD8848 and AZ12432045 combined (measured as total AZ12432045) after the 1st dose[a]: C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, CL/F, V_z/F, CL_R, and Ae; % dose, $t_{1/2}$, λ_z
Secondary	PD	To characterise the PD effect after multiple doses of inhaled AZD8848 in healthy subjects by assessment of the PD biomarker CXCL10, in plasma	CXCL10 concentration and change-from-baseline ratios in plasma
Exploratory	PGx	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to inhaled AZD8848	Not applicable
	PK	To collect and store plasma and urine samples for possible exploratory analysis of metabolites of AZD8848 (other than AZ12432045)	Not applicable
	PK	To collect blood for possible explorative analysis of markers of lung activity, eg. SP-A and SP-D and/or KL-6 or other markers considered to be of greatest value and robustness at the time of evaluation	Not applicable

Table S1 Study objectives and variables

Objectives			Variables
Priority	**Type**	**Description**	**Description**
	PGx	To collect and store blood for possible explorative analysis of changes in RNA expression of markers involved in inflammatory respiratory diseases, eg, interferon inducible genes	Not applicable

AE: Adverse events; Ae; % dose: Amount of drug excreted as AZD8848 or AZD8848 and AZ12432045 combined (measured as total AZ12432045); AUC: Area under the plasma concentration time curve from zero to infinity; $AUC_{(0-t)}$: Area under the plasma concentration time curve from zero to the time of last quantifiable concentration; CL/F: Apparent plasma clearance; CL_R: apparent renal clearance; C_{max}: Maximum plasma concentration; CXCL10: Chemokine (C-X-C motif) ligand 10; DLCO: Diffusion capacity of carbon monoxide; DNA: Deoxyribose nucleic acid; ECG: Electrocardiogram; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; KL: Krebs von den Lungen; MTD: Maximum tolerated dose; PD: Pharmacodynamics; PGx: Pharmacogenetics; PK: Pharmacokinetics; RNA: Ribonucleic acid; SP: Surfactant protein; t_{max}: time to C_{max}; $t_{1/2}$: Half-life; V_z/F: Apparent volume of distribution during terminal phase; λ_z: Apparent terminal rate constant.

[a] Pharmacokinetic parameters were also planned to be determined after the 4th dose, but were not, as the study was terminated early.

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy male and female subjects conducted at a single study centre. The study design allowed a gradual escalation of AZD8848 inhaled administrations with intensive safety monitoring to ensure the safety of the subjects. Up to 24 healthy subjects aged 18 to 50 years (inclusive) were to participate in a maximum of 3 cohorts with 8 subjects per cohort (6 administered AZD8848 and 2 placebo). Each subject was to receive 4 repeated once-weekly administrations of the investigational product.

The study comprised of 8 visits:

- **Screening visit (Visit 1)** conducted within 42 days of Day -1 of Visit 2
- **Treatment visits (Visit 2 to Visit 5)** during which the subjects were to be resident at the study centre from the day before each administration of the investigational product (Day -1; admission) until discharge (Day 2, Day 9, Day 16, and Day 23 of the respective periods) 24 hours after each administration of the investigational product. Subjects were to visit the study centre 48 hours after each investigational product administration on Day 3, Day 10, Day 17, and Day 24 for the collection of 48-hour blood samples. The investigational product was to be administered on Day 1, Day 8, Day 15, or Day 22 of the respective periods
- **Treatment follow-up visit (Visit 6)** 7 to 13 days after the last administration of the investigational product to assess the safety variables
- **Additional telephonic contact for females only (Visit 7)**: Female subjects were additionally followed up regarding a possible pregnancy (urine dipstick to be provided in advance) and contraceptive history 3 months after the last administration of the investigational product by a telephone contact
- **Long-term safety follow-up (Visit 8)** at the study centre was to be performed 5 to 7 months after the last administration of the investigational product to obtain information on any serious adverse events (SAEs) (a confirmed diagnosis of an autoimmune disorder was also to be reported as an SAE), adverse events (AEs) (only those AEs suggesting autoimmune disorders), vaccinations and/or concomitant medications used as treatment for SAEs and also to collect blood samples for auto antibodies (anti-nuclear antibodies [ANA], rheumatoid factor [RF], anti double stranded deoxyribonucleic acid [anti dsDNA]) and not prespecified auto antibodies
- **Long-term safety telephonic follow-up (Visit 9)** at 11 to 13 months after the last administration of the investigational product to obtain information on any SAEs (a confirmed diagnosis of an autoimmune disorder was also to be reported as an SAE), AEs (only those AEs suggesting autoimmune disorders), and vaccinations and/or concomitant medications used as treatment for SAEs

The treatment part of the study including 3 cohorts was anticipated to be a minimum of 9 weeks excluding the screening period. The total duration of the study including the long-term safety follow-up period was estimated to be approximately 15 months.

The study was to comprise of up to 3 cohorts. Eight (8) healthy subjects in each cohort were to be administered 4 once-weekly inhalations at each dose level. Each cohort was to employ a new cohort of 8 healthy subjects randomised in a 6:2 ratio (6 subjects were to receive AZD8848 and 2 subjects placebo).

Dose escalation to the next level was to proceed only after a Safety Review Committee (SRC) review as described in Section 3.1.2 of the clinical study protocol (Clinical Study Report Appendix 12.1.1) and it was estimated to take approximately 7 days between the safety data generation in the previous cohort and the first investigational product administration in the next cohort.

The starting dose in this MAD study was 30 µg based on the evaluation of data generated in the single ascending dose (SAD) study. The highest dose in this MAD study was to not exceed 106 µg.

The SRC decision was to be generally made without breaking the randomisation code. However, if judged necessary by the SRC, the randomisation code for an individual or a completed dose panel could have been broken.

If any of the stopping criteria were met, the study was to be terminated.

Dose escalation was to continue until significant possibly drug related clinical symptoms occurred, predefined top dose was reached or until the defined maximum exposure (area under the plasma concentration-time curve from zero extrapolated to infinity [AUC] or maximum plasma concentration [C_{max}]) of the sum of the acid metabolite and AZD8848 (measured as the acid metabolite) and/or dose of AZD8848 was reached or predicted to be reached.

Overall, 8 subjects were enrolled in Cohort 1 and randomised in a 6:2 ratio to receive 30 µg AZD8848 and placebo, respectively. At Visit 2 and Visit 3, the subjects were resident at the study centre from the day before each administration of the investigational product (Day -1; admission) until discharge (Day 2 and Day 9 of the respective periods) 24 hours after each administration of the investigational product. Subjects visited the study centre 48 hours after each investigational product administration on Day 3 and Day 10 of the respective periods, for the collection of the 48-hour blood samples. The investigational product was administered on Day 1 and Day 8 of the respective periods. The further administration of investigational product was stopped after the Day 8 treatment administration due to the SRC decision, which was based on the stopping criterion of 'two or more subjects, who received AZD8848 had influenza-like symptoms of severe intensity, in the absence of any other explanation' being met.

The long term safety follow-up of the study is ongoing at the time of this report and the data from Visit 7 until Visit 9 (long-term safety follow-up) including ANA, RF and anti-dsDNA results will be reported as an addendum to the CSR

Target subject population and sample size

The study was conducted in healthy male and female subjects to avoid interference from disease processes or other drugs. The selection criteria were defined such that subjects selected for participation in the study are known to be free from any significant illness.

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

Table S2 Details of investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD8848	Concentrate for nebuliser solution 10 mg/mL (as AZD8848 hydrochloride 10.6 mg/mL)	AstraZeneca	132648131
Placebo	0.9% sodium chloride solution for injection	B. Braun	P Lot ID: 13-001282AZ; F Lot ID: 13-000372AZ

AZD8848 concentrate for nebuliser solution was supplied as study specific labelled bulk by AstraZeneca Research and Development, Mölndal, Sweden. Commercial 0.9% sodium chloride solution was used as placebo and for dilution of the AZD8848 concentrate for nebuliser solution. The sodium chloride solution was sourced locally by the study centre. The responsible personnel at the study centre diluted and dispensed the investigational products into subject specific labelled dosing containers, according to the randomisation scheme and handling instructions, provided by AstraZeneca.

Duration of treatment

The treatment part of the study including 3 cohorts was anticipated to be minimum 9 weeks excluding the screening period. The total duration of the study including the long-term safety follow-up period was estimated to be approximately 15 months.

Statistical methods

Since the study was terminated in first cohort, no statistical analysis was performed. However, descriptive statistics and graphical presentations were provided as appropriate for safety, pharmacokinetic (PK) and pharmacodynamic (PD) parameters.

Subject population

A total of 8 subjects were randomised in a 6:2 ratio to receive AZD8848 and placebo, respectively. An equal ratio of male and female subjects received placebo (1:1) and AZD8848 (3:3). The mean age of the subjects in both the AZD8848 group and placebo group was similar (35 years and 38 years). The mean body mass index in both the groups was within the protocol defined criteria of 18 and 32 kg/m^2. All the subjects in the placebo group and majority of the subjects in the AZD8848 group (4/6; 66.7%) were Whites. All the subjects in both the groups belonged to the ethnic category of 'not Hispanic or Latino'

All the 8 subjects received 30 µg AZD8848 or placebo, per the randomisation scheme, on Day 1 and Day 8. The administration of investigational product was stopped after the Day 8 treatment administration due to the SRC decision, which was based on the stopping criterion of 'two or more subjects, who received AZD8848 had influenza-like symptoms of severe intensity, in the absence of any other explanation' being met.

Summary of pharmacokinetic results

The PK parameters of total AZ12432045 after inhalation of 30 µg of AZD8848 appeared to be similar to those observed during the previously completed SAD study at the same dose level. Total AZ12432045 was rapidly formed (t_{max} ranged from 0.08 hours to 0.18 hours) and quickly eliminated. On average, 18.4% of the nominal inhaled dose was excreted in the urine as total A12432045, mostly within 6 hours of dose administration.

As this study was terminated after the second dose in the first cohort, the PK of total AZ12432045 after administration of multiple AZD8848 doses was not assessed. Additionally, parent AZD8848 was not quantifiable in the samples collected.

Summary of pharmacodynamic results

The chemokine (C-X-C motif) ligand 10 (CXCL10) ratio-to-baseline was similar and close to 1 for the placebo group throughout the sampling period.

Inhalation of 30 µg AZD8848 resulted in a CXCL10 ratio-to-baseline higher than placebo at 24 and 48 hours after the first and second doses. Although the CXCL10 ratio-to-baseline was similar to 1 before the second dose, the increase was 1.8-fold higher 24 hours after the second dose than on the first dose. However, this trend was highly variable and only observed in 4 out of the 6 subjects.

The increase at 48 hours postdose was similar after both the first and second doses and CXCL10 returned to baseline at follow-up.

Summary of safety results

- The study was stopped after 2 doses in the Cohort 1 due to poor tolerability (influenza-like symptoms) of 30 µg repeated dose of AZD8848
- No deaths or serious adverse events (SAEs) were reported in this study
- All the subjects (6/6; 100%) in the AZD8848 group reported at least 1 AE and 1 subject (1/2; 50%) in the placebo group reported at least 1 AE
- In the AZD8848 group, the most commonly reported AE belonged to the system organ class of nervous system disorders (5/6; 83.3%) with headache being reported by 4 of the 6 subjects (66.7%). In the placebo group, 1 subject reported an AE of headache which was considered to be mild intensity and causally not related to the investigational product
- All subjects in the AZD8848 group reported AEs which were considered to be casually related to the investigational product by the investigator. Most of the AEs, such as pain, nausea, abdominal discomfort, arthralgia, musculoskeletal stiffness reported in the AZD8848 group were mild or moderate in intensity except for 2 AEs of pyrexia which were of severe intensity. Subjects E0001010 and E0001015 reported feeling “cold and shaky” and “chills and rigor”, respectively, on Day 8

postdose and severe AEs of pyrexia were reported for both the subjects. The further administration of investigational product was stopped after the Day 8 investigational product administration due to the SRC decision, which was based on the stopping criterion of 'two or more subjects, who received AZD8848 had influenza-like symptoms of severe intensity, in the absence of any other explanation' being met. All the AEs reported in this study resolved by the end of the study.

- An increase in the body temperature from predose to Day 8 postdose was seen in Subjects E0001010 and E0001015, which resolved on the same day in Subject E0001010 and on Day 9 in Subject E0001015. Pyrexia of severe intensity was reported for both the subjects, which was assessed to be causally related to the investigational product, by the investigator. This met the stopping criterion of 'two or more subjects, who received AZD8848 had influenza-like symptoms of severe intensity, in the absence of any other explanation' which led to the decision by the SRC to stop further administration of the investigational product

- All the AEs reported in this study resolved by the end of the study

- Elevations in individual serum C-reactive protein levels were observed 24 hours postdose after both the first and second dose administrations in the AZD8848 group, whilst in the placebo group the individual serum CRP levels remained almost the same

- It was observed that AZD8848 caused a transient decrease in blood lymphocytes commensurate with the interferon response. A decline in the blood lymphocytes was observed at 24 hours postdose, on Day 2 and Day 8, after the first and second administrations of the investigational product, respectively, with a greater decline observed on Day 8, 12 hours after administration of the second dose

- A QT mean increase of >30 msec, from baseline, but not in QTcF, was observed in 1 subject on Day 8 which was assessed to be within normal range by the investigator