Clinical Study Report Synopsis

Drug Substance	AZD8848 inhaled
Study Code	D0542C00001
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A Double-blind, Placebo-controlled, Randomised Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Inhaled Doses of AZD8848 in Healthy Subjects

Study dates: First subject enrolled: 27 May 2012
Last subject last visit: 28 July 2014

Phase of development: Clinical Pharmacology (I)

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

Publications

Not applicable

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD8848 after inhaled administration of single ascending doses and to estimate the maximum tolerated dose (MTD), if within predefined exposure and dose limits, in healthy subjects	Adverse events (AE), vital signs (blood pressure and pulse rate, body temperature), laboratory variables (haematology, clinical chemistry, urinalysis), antibody, 12-lead electrocardiogram (ECG), dECG, pECG, and spirometry
Secondary	PK	To investigate the pharmacokinetics (PK) after inhaled administration of single ascending doses of AZD8848 by determination of the plasma concentrations of total AZ12432045 (which represents the sum of AZD8848 and its acid metabolite AZ12432045, after allowing the hydrolysis of AZD8848 to complete during sample preparation) and, if possible, AZD8848 alone	The following parameters were calculated for AZD8848 and AZ12432045 combined (measured as total AZ12432045) and, if possible, for AZD8848 alone: C_{max}, t_{max}, λ_z; $t_{½\lambda,z}$, $AUC_{(0\text{-}t)}$, AUC, CL/F, V_z/F
	PD	To investigate the pharmacodynamic (PD) effect after inhaled administration of single ascending doses of AZD8848 in healthy subjects by assessment of the PD biomarker, chemokine (C-X-C motif) ligand 10 (CXCL10), in blood and sputum	CXCL10 concentration and ratio-to-baseline in blood and induced sputum
Exploratory[a]		To collect and store plasma and urine samples for possible exploratory analysis of metabolites of AZD8848	PK

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence the response (ie, distribution, safety, tolerability and efficacy) to inhaled AZD8848	Pharmacogenetics
		To collect blood for potential analysis of biomarkers for lung activity, eg surfactant protein A (SP-A), SP-D and/or KL-6 or other markers considered to be of greatest value and robustness at the time of the evaluation	
		To analyse sputum supernatants produced during screening for CXCL10 and other potential biomarkers of lung activity. This will be used to research into sputum quality (measured by cell viability, cell number, and squamous cell contamination) and changes in baseline levels of measurable biomarkers	
		To collect cells produced after sputum processing in order to measure messenger ribonucleic acid for markers of lung activity	

AE: Adverse event; AUC: Area under the plasma concentration-time curve from zero extrapolated to infinity; $AUC_{(0-t)}$: Area under the plasma concentration-time curve from zero to the time of the last measurable concentration; C_{max}: Maximum plasma concentration; CL/F: Apparent systemic plasma clearance; CLCX10: Chemokine ligand 10; CSP: Clinical study protocol; dECG: Digital electrocardiogram; ECG: Electrocardiogram; KL-6: Krebs von den Lungen-6; MTD: Maximum tolerated dose; pECG: Paper electrocardiogram; PK: pharmacokinetic; PD: Pharmacodynamic; t_{max}: Time to C_{max}; $t_{½λz}$: Terminal half-life; V_z/F: Apparent volume of distribution during terminal phase; λ_z: Terminal rate constant

[a] Results from the exploratory objectives are not reported in this CSR

Study design

This was a Phase I, randomised, double-blind, placebo-controlled study conducted at a single study centre with single ascending dose levels of inhaled AZD8848 in healthy subjects. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure

the safety of the subjects. Staggered dosing was used, ie, not all subjects received the investigational product at the same time.

The study comprised 5 visits:

- Screening visit (Visit 1) conducted over 2 or more days (only on 1 day for Cohort 8) during a 30-day screening period with an induced sputum sampling from Day -5 to Day -2 for all subjects (no induced sputum sampling for Cohort 8)

- Treatment visit (Visit 2) during which the subjects were resident at the study centre from the day before administration of the investigational product (Day -1; admission) until discharge (Day 3), 48 hours after administration of the investigational product. The investigational product was administered on Day 1

- Follow-up visit (Visit 3) 7 to 13 days after administration of the investigational product to assess the safety variables

- Additional visit for females only (Visit 3b): Female subjects were additionally followed-up regarding a possible pregnancy (urine dipstick was provided in advance) and contraceptive history 3 months after administration of the investigational product by a telephone contact

- Long-term safety follow-up (Visit 4) at the study centre was performed 5 to 7 months after administration of the investigational product

- Telephone contact (Visit 5) at 11 to 13 months after administration of the investigational product

Initially approximately 36 male and female subjects (6 cohorts with an optional 5 additional cohorts) were to be randomised in the study, with 6 subjects per cohort (4 subjects administered AZD8848 and 2 subjects placebo). After each cohort, a SRC reviewed and assessed all the available safety and PK data relevant to safety from at least 5 subjects (AZD8848 and/or placebo) to make a decision on the dose level for the next cohort of subjects. This evaluation was primarily based on the safety (of the first 48 hours) and PK (up to 24 hours) data after administration of the investigational product (see Section 3.1.2 of the CSP).

Dose escalation was planned with at least 7 days between the start of the investigational product administration in subsequent cohorts to allow sufficient time for the review of the data.

Target subject population and sample size

Healthy male and female subjects aged 18 to 50 years (inclusive) with suitable veins for cannulation or repeated venepuncture were enrolled in the study.

Overall, 47 male and female subjects (6 cohorts with an optional 2 additional cohorts) were randomised in the study. There were 6 subjects per cohort (4 subjects received AZD8848 and 2 subjects received placebo), with the exception of Cohort 3 (1.5 μg), where 3 subjects received AZD8848 and 2 subjects received placebo.

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD8848	Concentrate for nebuliser solution 1.0 mg/mL (as AZD8848 hydrochloride 1.06 mg/mL)	AstraZeneca	12-001066AZ/12-000158AZ
AZD8848	Concentrate for nebuliser solution 10 mg/mL (as AZD8848 hydrochloride 10.6 mg/mL)	AstraZeneca	12-001071AZ/12-000159AZ 13-000488AZ/13-000372AZ
Placebo	0.9% Sodium chloride solution for injection	B. Braun	12-001333AZ/12-001339AZ

The investigational product was supplied as study specific labelled bulk by AstraZeneca R&D Mölndal Sweden.

Duration of treatment

Each subject received a single dose of AZD8848 or placebo.

Statistical methods

No formal statistical hypothesis testing was performed for safety and tolerability. All safety, tolerability, pharmacokinetic and pharmacodynamic data recorded during the study were listed and summarised as appropriate. Continuous variables were summarised using descriptive statistics by dose group and by time points where applicable. Categorical variables were summarised in frequency tables by treatment group. Graphical presentations were used as appropriate.

Statistical analysis was performed for one primary and two secondary endpoints.

- Analysis to check if inhaled AZD8848 is safe and well tolerated was performed as per the stopping criteria. The end results of the criteria were derived for each cohort used to decide if significant possibly drug related clinical symptoms occurred and the study were to be terminated

- Analysis to test if inhaled AZD8848 shows dose-proportional pharmacokinetics was performed using power model

- Analysis to test if inhaled AZD8848 showed dose versus placebo pharmacodynamics in blood and sputum was performed using an analysis of covariance (ANCOVA) model.

Subject population

The proportion of male and female subjects was similar for AZD8848 and placebo group. The age of the subjects ranged from 20 to 45 years and their BMI ranging from 20.27 to 31.68 kg/m^2 with a minimum weight of 53.8 kg. Most of the randomised subjects were white.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Exposure of total AZ12432045 appeared to be dose proportional with regards to C_{max} in the AZD8848 predicted lung deposited dose range of 0.5 to 30 µg and nearly dose proportional with regards to AUC and $AUC_{(0-t)}$ in the AZD8848 predicted lung deposited dose range of 5 to 30 µg.

Table S3 Summary of pharmacokinetic dose proportionality for total AZ12432045

			Slope			
Dose range	**Parameter (unit)**	**n**	**Estimate**	**SE**	**90% CI**	**Coefficient of determination**
5 to 30 µg	AUC (nmol*h/L)	13	0.81	0.10	(0.63, 1.00)	0.8465
5 to 30 µg	$AUC_{(0-t)}$ (nmol*h/L)	13	0.84	0.11	(0.65, 1.04)	0.8469
0.5 to 30 µg	C_{max} (nmol/L)	20	0.95	0.05	(0.87, 1.04)	0.9536

CI = confidence interval; SE = standard error.
Due to limited AZD8848 quantifiable data, no PK parameters were calculated for the AZD8848 analyte. All parameters presented are for the AZ12432045 metabolite. Cohort 7 was not included in this analysis due to different dosing conditions (a single inhalation versus multiple inhalations). Dose levels with less than 3 valid PK parameter values were excluded.
The linear model used was log (Y) = intercept + slope x log (dose). Exponentiation of both sides produces the usual form of the power model: Y = exp(intercept) x (dose)**slope. Estimates are derived from random intercepts linear mixed model.

Summary of pharmacodynamic results

For all pharmacodynamic comparisons, definitive conclusions could not be drawn due to small sample size.

Lower predicted lung deposited doses of AZD8848 (0.15 µg, 0.5 µg, and 1.5 µg) had a CXCL10 ratio-to-baseline that appeared similar to placebo in plasma at 24 hours and 48 hours postdose and sputum at 24 hours postdose.

At 24 hours postdose, the 5 µg, 15 µg, and 30 µg AZD8848 predicted lung deposited dosing groups appeared to have a higher CXCL10 ratio-to-baseline than placebo in both plasma and sputum, and the geometric least-squares mean ratio increased with increasing dose.

At 48 hours postdose, while the 5 µg dose and 15 µg dose via multiple inhalations were similar to placebo, the 15 µg dose via a single inhalation and the 30 µg dose remained higher than placebo.

Summary of safety results

- No deaths, or DAEs, were reported in this study. An SAE (pelvic inflammatory disease) was reported by Subject E0001175 in Cohort 4 (5 µg)

- Overall, the percentage of subjects who reported AEs was similar for all AZD8848 dose levels combined and placebo

- The majority of AEs were considered mild in intensity and most of the AEs resolved. Three AEs were considered to be moderate in intensity: presyncope, reported by Subject E0001175 (Cohort 4[5 µg]) was a pre-treatment AE; dry mouth and dry eye, reported by Subject E0001407 (Cohort 7[15 µg]), were post-treatment AEs. An SAE (pelvic inflammatory disease) was reported by Subject E0001175 in Cohort 4 (5 µg) during the long term safety follow-up period and was considered to be not related to the investigational product by the Investigator

- Apart from the transient decrease in the lymphocyte count at 24 hours postdose, no trends were observed in haematology, biochemistry, and urinalysis parameters, for any subject during the study

- No clinically significant auto-antibodies were detected in any subject in this study

- No subjects showed any abnormal variations in QTcF values and no trends were evident in mean HR, QRS, QTcF, or PR intervals in the AZD8848 or placebo groups. Out of range 12-lead ECG readings were reported in the study, however none were considered to be clinically significant

- There were no clinically significant abnormal laboratory, vital signs, or physical examination results reported