Clinical Study Report Synopsis

Drug Substance	AZD7624
Study Code	D2550C00001
Edition Number	1
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A Double-blind Placebo-controlled, Randomised, Single centre, First Time in Man Study to evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Ascending Inhaled Doses of AZD7624 in Healthy Subjects

Study dates:	First subject enrolled: 28 January 2013 Last subject last visit: 15 August 2013
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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD7624 following inhaled administration of single ascending doses and to estimate the maximum tolerated dose, if within the predefined exposure and dose limits.	Adverse events, electrocardiograms, blood pressure and pulse rate, physical examination, body temperature, haematology, serum biochemistry chemistry, urinalysis, and spirometry
Secondary	PK	To characterise the PK of AZD7624 following inhaled administration of single ascending doses of AZD7624.	C_{max}, t_{max}, $t_{½\lambda z}$, $AUC_{(0\text{-}last)}$, AUC/D, $AUC_{(0\text{-}last)}/D$, C_{max}/D, AUC, CL/F, V_z/F, $A_{e(t1\text{-}t2)}$, $A_{e(0\text{-}last)}$, $fe_{(0\text{-}last)\%}$, CL_R
Exploratory	PD	To obtain blood samples for the PD biomarker: ex-vivo LPS-induced TNF-α production in whole blood. Changes in plasma tumour TNF-α levels will be assessed predose, and at 5 and 15 minutes postdose	LPS-stimulated TNF-α concentration
	Metabolites	To collect and store plasma and urine for exploratory analysis of AZD7624 metabolites	-
	Pharmacogenetic	To obtain blood samples for possible genetic research (These data will not form part of the CSR and are aimed at identifying/exploring PD, biomarker, or genetic variations that may affect the PK, PD, safety and tolerability profile related to AZD7624 treatment.)	-

$A_{e(0\text{-}last)}$: cumulative amount of drug excreted unchanged into the urine at the last sampling interval; $A_{e(t1\text{-}t2)}$: amount of drug excreted unchanged into the urine from time t1 to t2; AUC: area under plasma concentration-time curve from time zero extrapolated to infinity; $AUC_{(0\text{-}last)}$: area under the plasma concentration-time curve from time zero to the last measurable concentration; AUC/D: AUC divided by delivered dose; $AUC_{(0\text{-}last)}/D$: $AUC_{(0\text{-}last)}$ divided by delivered dose; CL/F: apparent clearance for parent drug estimated as dose divided by AUC; CL_R: renal clearance; C_{max}: observed maximum plasma concentration; C_{max}/D: C_{max} divided by delivered dose; $fe_{(0\text{-}last)\%}$: percentage of dose excreted unchanged into the urine from time zero to the last measured time point; LPS: lipopolysaccharide; PD: pharmacodynamic; PK: pharmacokinetic; $t_{½\lambda z}$: terminal half-life; t_{max}: time to reach maximum plasma concentration; TNF-α : tumour necrosis factor alpha; V_z/F: oral volume of distribution (apparent) during terminal (λz) phase; and observed and %change-from-baseline

([postdose – predose]/predose*100) for LPS-stimulated TNF-α release concentration at predose and 5 and 15 minutes postdose.

Study design

This was to be a phase I, first time in human, randomised, double-blind, placebo-controlled, single ascending dose study in healthy male subjects and female subjects of non childbearing potential.

Up to 5 dose levels of AZD7624 was to be investigated, with an option to add 4 additional cohorts, after implementation of Amendment 2. Within each cohort of 8 subjects, 6 subjects were randomised to receive AZD7624 and 2 subjects randomised to receive placebo. Six cohorts were ultimately randomised in this study.

The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects. Each subject was only included in 1 cohort.

Administration of the investigational product in each ascending dose cohort was preceded with 2 subjects in a sentinel cohort, such that 1 subject was randomised to receive placebo and 1 subject was randomised to receive AZD7624.

The safety data (adverse event [AE] profile, vital signs, body temperature, electrocardiogram (ECG), spirometry, and clinical laboratory safety tests) from the sentinel subjects up to at least 24 hours postdose, and implementation of Amendment 2, additional myoglobin and creatine kinase assessment at 48 hours postdose was reviewed by the Principal Investigator before the investigational product was administered to the 6 remaining subjects in the cohort.

Following completion of each dose level, the Safety Review Committee reviewed the available safety (up to 48 hours postdose) and available pharmacokinetic (PK) data (up to 24 hours postdose) to determine the next dose level.

Target subject population and sample size

Up to 72 healthy subjects aged 18 to 55 years (inclusive) were to be randomized to the study.

Planned:	Up to 72 subjects
Randomised:	48 subjects
Treated:	48 subjects
Completed:	48 subjects

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

Table S2 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Packaging Lot No. / Lot ID
AZD7624	Powder for nebuliser solution (20 mg)	AstraZeneca	13-000009AZ / 12-003254AZ
AZD7624	Powder for nebuliser solution (50 mg)	AstraZeneca	13-000010AZ / 12-003255AZ
Solvent for constitution and Placebo	Solution	AstraZeneca	13-000006AZ / 12-003256AZ

The following dose levels were administered in the study:

Table S3 Dose escalation

Planned	Actual lung deposited dose	Delivered dose
30 µg	29 µg	51 µg
100 µg	101 µg	174 µg
300 µg	336 µg	580 µg
600 µg	631 µg	1088 µg
1200 µg	1177 µg	2030 µg

Duration of treatment

Single dose on Day 1.

Statistical methods

The statistical analysis was performed using SAS® Version 9.2 by Quintiles according to Standard Operation Procedures and Work Instructions.

The analyses of safety, tolerability, PK, and pharmacodynamics (PD) were summarized descriptively including tables, listings, and graphs, as appropriate. Data are presented by lung deposited dose group, and subjects who received placebo were pooled across cohorts for the purposes of summarising the safety and PD results. Lung deposited dose of 336 µg (cohort 3) was repeated in cohort 4. Therefore, PK, PD, and safety data at 336 µg were presented as separate and in combination. This was as per agreement by the Sponsor.

Statistical analysis of dose proportionality was performed via power model and assessed graphically. Observed and change from baseline tumour necrosis factor alpha (TNF-α)

concentrations in plasma were summarised using descriptive statistics. A PK/PD plot was prepared by the Sponsor and has been included in the clinical study report.

The sample size was primarily based on experience from previous similar studies with other compounds, and it was determined without formal statistical considerations or formal power calculation.

Subject population

In total, 48 male subjects were randomised into the study (36 subjects to AZD7624 and 12 subjects to placebo). All subjects randomised to treatment completed the study. The cohorts and treatments were well balanced with regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

The mean predefined exposure stopping criteria were not met for the observed maximum plasma concentration (C_{max}) (24.2 nmol/L) or area under plasma concentration-time curve from time zero extrapolated to infinity (AUC) (157 nmol*h/L) at any cohort after the single inhalation dose in the 29 to 1177 µg AZD7624 lung deposited dose range. Exposure parameters increased by increasing dose within the 29 to 1177 µg dose range, with the exception of lower than expected value at the 631 µg dose (partly due to one subject with much lower systemic concentration). Based on the power model results, maximum exposure (C_{max}) showed reasonable dose proportionality within the entire dose range with slope being close to 1.0 and the 95% confidence interval encompassing value of unity. Total exposure (AUC) and area under the plasma concentration-time curve from time zero to the last measurable concentration ($AUC_{(0\text{-}last)}$) did not meet this criteria.

Geometric mean C_{max} and AUC were 23.2 nmol/L (ranged 15.3 to 31.0 nmol/L) and 41.0 nmol*h/L (ranged 29.3 to 49.3 nmol*h/L), respectively for the highest 1177 µg dose group.

The maximum AZD7624 plasma concentration occurred consistently at a median time to reach maximum plasma concentration (t_{max}) of 5 to 7 minutes following single inhalation dosing, and was independent of the dose.

On average, less than 8% of AZD7624 dose was excreted unchanged in the urine cumulatively over 48 hours for the 29 to 1177 µg doses. The renal clearance of AZD7624 (12 to 14 L/h) was low compared to the plasma clearance (101 to 118 L/h), indicating that renal excretion is not a primary route of drug elimination. Both renal clearance and systemic clearance appeared to be independent of the administered dose within the 336 to 1177 µg AZD7624 dose range.

Summary of pharmacodynamic results

There was no apparent inhibition of TNF-α release by AZD7624 at the 2 lowest dose levels (29 and 101 µg). Descriptive statistics of %change-from-baseline results indicated a consistent inhibition of ex-vivo lipopolysaccharide (LPS)-stimulated TNF-α release by

AZD7624 ranging from 35% (at 336 µg, cohort 3) to 76% (at 1177 µg, cohort 6). AZD7624 maximal inhibitory activity was observed at 5 minute postdose time point (end of inhalation dosing), coinciding with the drug's peak systemic concentration time at median t_{max} of 5 to 7 minutes.

Summary of pharmacokinetic/pharmacodynamic relationships

As plasma concentration of AZD7624 increased, there was a related increase in the %inhibition (measured as %change-from-baseline) of TNF-α release within the 336 µg (Cohorts 3 and 4) to 1177 µg (cohort 6) dose range. Maximal effect was observed at the top dose of 1177 µg. Data from the two lowest dose groups with no apparent %inhibition were excluded from the PK/PD plot.

Summary of safety results

No deaths or discontinuations from the study or from the investigational product due to AEs were reported. One serious AE was reported in the AZD 7624 336 µg cohort: severe myositis, considered to be not related to the investigational product. No subjects were prematurely withdrawn from the study due to AEs. At least 1 AE was reported for 6 subjects (16.7%) on AZD7624, 1 in each of the 6 cohorts (16.7%), and 2 subjects (16.7%) on placebo. All the AEs were considered to be mild in intensity and all resolved.

The most frequently reported AEs were back pain, reported for 2 subjects (AZD7624 101 µg and AZD7624 631 µg) and transaminases increased, also reported in 2 subjects (AZD7624 336 µg and AZD7624 1177 µg).

No clinically important values or changes were reported for laboratory measurements, vital signs, ECG, physical examination or spirometry.