Clinical Study Report Synopsis

Drug Substance AZD7594

Study Code D3740C00001

Edition Number 1.0

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A Phase I, Single-center, Double-blind, Randomised, Placebo-controlled, Parallel-group, Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics After Single and Multiple Ascending Inhaled Doses of AZD7594 in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 25 September 2012
Last healthy volunteer last visit: 7 June 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 safety and tolerability of AZD7594 following inhaled administration of single ascending doses (Part A) and multiple ascending doses (Part B) and to estimate the maximum tolerated dose (MTD) if within the predefined exposure limits, in healthy male volunteers	Adverse events, electrocardiograms (ECGs), blood pressure and pulse rate, physical examination, body temperature, haematology, clinical chemistry, coagulation, urinalysis, and spirometry
Secondary	PK	To evaluate the PK of AZD7594 after single ascending (Part A) and multiple ascending inhaled doses (Part B)	Day 1 (Part A and Part B): C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, AUC, CL/F, V_z/F, MRT, C_{max}/D, AUC/D, and $AUC_{(0\text{-}24)}$/D Day 16 (Part B): C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, $AUC_{(0\text{-}last)}$, $AUC_{(0\text{-}24)}$, CL/F, C_{avg}, %fluctuation, C_{max}/D, $AUC_{(0\text{-}24)}$/D, Rac(C_{max}), Rac($AUC_{(0\text{-}24)}$), and $AUC_{(0\text{-}24)}$ on Day 16/AUC on Day 1
	PD	To evaluate the PD of AZD7594 after single ascending (Part A) and multiple ascending inhaled doses (Part B)	Part A: 24-hour plasma cortisol Part B: 24-hour plasma cortisol, plasma cortisol before and after ACTH stimulation, plasma DHEAS, plasma 4β-OH-cholesterol, glucocorticoid receptor biomarkers, and plasma osteocalcin
Exploratory[a]	PK	To collect and store plasma and urine samples for possible exploratory analysis of AZD7594 in urine and metabolites in plasma and urine and the plasma protein binding of AZD7594 (Part B only)	-

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Pharmaco-genetic	To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to inhaled AZD7594 (optional)	-
	Biomarker	To collect and store plasma samples for possible exploratory analysis of glucocorticoid-related biomarkers (other than the biomarkers included in the secondary objective), such as, but not limited to tumour necrosis factor (TNF)-α, interleukin (IL)-8, that may be influenced by inhaled AZD7594 (Part B only)	-

λ_z: terminal rate constant; ACTH: adrenocorticotropic hormone; AUC: area under the plasma concentration-time curve from zero extrapolated to infinity; $AUC_{(0-24)}$: area under the plasma concentration-time curve from zero to 24 hours postdose; $AUC_{(0-last)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; AUC/D: delivered dose-normalised AUC; $AUC_{(0-24)}$/D: delivered dose-normalised $AUC_{(0-24)}$; C_{avg}: average plasma concentration during a dosing interval; CL/F: apparent plasma clearance; C_{max}: maximum observed plasma concentration; C_{max}/D: delivered dose-normalised C_{max}; DHEAS: dehydroepiandrosterone sulphate; MRT: mean residence time; PD: pharmacodynamic(s); PK: pharmacokinetic(s); Rac: accumulation ratio; $t_{1/2\lambda z}$: terminal half-life; t_{max}: time to maximum observed plasma concentration; V_z/F: apparent volume of distribution during the terminal phase.

[a] If performed, these results will be reported separately from this Clinical Study Report.

Study design

This study was conducted in 2 parts: Part A and Part B.

Part A was a randomised, double-blind, placebo-controlled, parallel-group investigation of single ascending inhaled doses of AZD7594 or placebo in up to 9 sequential cohorts of 8 healthy male volunteers each. Within each cohort, 6 healthy volunteers were randomised to receive AZD7594 and 2 healthy volunteers to receive placebo. Six cohorts were ultimately randomised in this part of the study.

Part B only commenced investigational product administration following a satisfactory review of the safety, pharmacokinetic (PK) and pharmacodynamic (PD) data from at least 4 dose levels in Part A by a Safety Review Committee.

Part B was a randomised, double-blind, placebo-controlled, parallel-group investigation of multiple ascending inhaled doses of AZD7594 or placebo in 3 sequential cohorts of 9 healthy male volunteers each, with an option for an additional cohort of 9 healthy volunteers. Within each cohort, 6 healthy volunteers were randomised to receive AZD7594 and 3 healthy

volunteers to receive placebo. Three cohorts were ultimately randomised in this part of this study.

Target subject population and sample size

Up to 72 healthy male volunteers in Part A and 36 healthy male volunteers in Part B, aged 18 to 45 years (inclusive) who signed informed consent were to be enrolled in this study.

Part A
Planned: Up to 72 healthy volunteers
Randomised: 47 healthy volunteers
Treated: 47 healthy volunteers
Completed: 47 healthy volunteers

Part B
Planned: Up to 36 healthy volunteers
Randomised: 26 healthy volunteers
Treated: 26 healthy volunteers
Completed: 25 healthy volunteers

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

Table S2 Details of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD7594	Suspension for nebulisation, 0.14 mg/g	AstraZeneca	12-002447AZ
AZD7594	Suspension for nebulisation, 0.8 mg/g	AstraZeneca	12-002448AZ
AZD7594	Suspension for nebulisation, 4.0 mg/g	AstraZeneca	12-002449AZ
Placebo	Placebo solution for nebulisation, 7.0 g	AstraZeneca	12-002451AZ

The following dose levels were administered in the study:

Part A
- Cohort 1: 4.7 µg lung deposited dose (7 µg delivered dose)
- Cohort 2: 24 µg lung deposited dose (38 µg delivered dose)
- Cohort 3: 119 µg lung deposited dose (187 µg delivered dose)
- Cohort 4: 399 µg lung deposited dose (624 µg delivered dose)
- Cohort 5: 799 µg lung deposited dose (1248 µg delivered dose)
- Cohort 6: 1198 µg lung deposited dose (1872 µg delivered dose)

Part B
- Cohort 1: 200 µg lung deposited dose (312 µg delivered dose)

- Cohort 2: 799 µg lung deposited dose (1248 µg delivered dose)
- Cohort 3: 1198 µg lung deposited dose (1872 µg delivered dose)

Duration of treatment

Part A: single dose on Day 1

Part B: single dose on Day 1 and multiple doses from Day 5 to Day 16 (1 dose per day).

Statistical methods

The data were summarised and presented for Part A and Part B separately by actual dose (not by cohort), unless otherwise indicated. Healthy volunteers who received placebo were pooled across cohorts in all analyses.

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarised for Part A and Part B separately using descriptive statistics (number, mean, standard deviation [SD], minimum, median, maximum) by treatment/dose group. Categorical variables were summarised for Part A and Part B separately in frequency tables (frequency and proportion) by treatment/dose group.

Dose proportionality of AZD7594 after single dose (Day 1) in Part A and Part B and multiple dose (Day 16) in Part B was assessed graphically and was analysed using the power model approach with the logarithm of PK parameters (area under the plasma concentration-time curve from zero extrapolated to infinity [AUC] and maximum observed plasma concentration [C_{max}] on Day 1) and (area under the plasma concentration-time curve from zero to 24 hours postdose [$AUC_{(0-24)}$] and C_{max} on Day 16) as the dependent variable and the logarithm of the dose as the independent variable.

For data collected in Part B, the time dependency of the PK was evaluated by comparing $AUC_{(0-24)}$ (Day 16) with AUC (Day 1) and accumulation was evaluated by comparing $AUC_{(0-24)}$ (Day 16) with $AUC_{(0-24)}$ (Day 1) and C_{max} (Day 16) with C_{max} (Day 1). A linear mixed-effect analysis of variance model using the logarithm of the above PK parameters as the response variable and treatment, day and treatment by day interaction as fixed effects. Day was treated as a repeated effect within subject.

For each PD variable, the different dose levels of AZD7594 were compared with placebo using an analysis of covariance model on log-transformed ratio-to-baseline PD variable values with fixed factor for treatment and the log-transformed baseline value as a covariate.

No correction for multiplicity was made.

Subject population

In total, 47 healthy male volunteers were randomised into Part A (35 healthy volunteers to AZD7594 and 12 healthy volunteers to placebo) and 26 healthy male volunteers were randomised into Part B (17 healthy volunteers to AZD7594 and 9 healthy volunteers to

placebo). The cohorts and treatments were well balanced with regards to demographic and baseline characteristics.

One healthy volunteer (3.8%) on 200 µg AZD7594 in Part B prematurely withdrew from the study due to personal reasons.

Summary of pharmacokinetic results

Following single dose administration in Part A, the predefined maximum exposure limits for AUC (41.8 nM*h) and C_{max} (3.5 nM) were not reached at 1198 µg (lung deposited dose). Dose escalation in Part A was stopped because the maximum allowed lung deposited dose was 1200 µg.

Following single dose administration, systemic exposure of AZD7594 on Day 1 (Part A and Part B) increased in a dose proportional manner in the dose range 24 to 1198 µg (lung deposited doses). Following multiple dose administration, systemic exposure of AZD7594 on Day 16 increased in a dose proportional manner in the dose range 200 to 1198 µg (lung deposited doses.

In Part A, the median t_{max} occurred at 0.25 to 0.42 hours post single inhalation dosing. Mean values of $t_{1/2\lambda z}$ were similar (ranging from 21.9 to 28.1 hours) over the single lung deposited dose range of 119 to 1198 µg. Geometric mean CL/F increased from 131 to 178 L/h and V_z/F increased from 4080 to 6660 L over the lung deposited dose range of 119 to 1198 µg.

In Part B, the median t_{max} occurred at 0.08 to 0.39 hours postdose. Mean values of $t_{1/2\lambda z}$ were similar and ranged from 23.3 to 31.4 hours on Day 1 and Day 16 over the studied dose range. The ratio of Day 16 $AUC_{(0-24)}$ to Day 1 AUC was close to 100% (ranging from 83% to 93% across the 3 dose levels in Part B), indicating that the pharmacokinetic properties of AZD7594 are time-independent. Graphical examination indicates AZD7594 concentrations reached steady state following 4 days of once-daily dosing in Part B. The accumulation ratio of Day 16/Day 1 following once-daily dosing ranged from 1.08 to 1.34 based on C_{max} and from 1.59 to 1.98 based on $AUC_{(0-24)}$.

Summary of pharmacodynamic results

Following single and multiple dose administration of AZD7594, the active treatment/placebo ratio of $AUEC_{(0-24)}$ of plasma cortisol decreased with increasing dose. The estimated cortisol suppression after a single dose of 1198 µg (lung deposited dose) was 14% and 11% compared to placebo in Parts A and B, respectively. After multiple doses the estimated cortisol suppression was 23% compared to placebo. At the lower dose levels (4.7 to 799 µg lung deposited dose) the plasma cortisol suppression was comparable with placebo.

Following multiple dose administration of AZD7594 1198 µg (lung deposited dose), the increase in plasma cortisol after ACTH stimulation was 28% lower compared to placebo. At the lower dose levels (200 and 799 µg lung deposited dose) the effect of ACTH stimulation was comparable with placebo.

Following multiple dose administration of AZD7594 at 799 and 1198 µg (lung deposited dose) there was an estimated decrease in plasma osteocalcin of 23% and 47% compared to placebo, respectively. At the lower dose level (200 µg lung deposited dose) plasma osteocalcin levels were comparable with placebo.

Following multiple dose administration of AZD7594 plasma DHEAS and 4β-OH-cholesterol were comparable to placebo across all 3 dose levels in Part B.

Summary of safety results

Part A

In Part A, no deaths, serious adverse events (SAEs), or withdrawals from the study due to adverse events (AEs) were reported. At least 1 AE was reported for 10 healthy volunteers (21.3%): 7 healthy volunteers (20.0%) on AZD7594 and 3 healthy volunteers (25.0%) on placebo. At least 1 AE was reported for 1 healthy volunteer in each of the AZD7594 cohorts, with the exception of 2 healthy volunteers in the 799 µg cohort.

The most frequently reported AE was cough, reported for 3 healthy volunteers, all in AZD7594 cohorts (399 µg, 799 µg, and 1198 µg).

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

Part B

In Part B, no deaths or withdrawals from the study due to AEs were reported. One SAE was reported in the 1198 µg cohort during the follow-up period: severe abdominal pain, considered to be not related to the investigational product. Overall, at least 1 AE was reported for 13 healthy volunteers (50.0%): 7 healthy volunteers (41.2%) on AZD7594 and 6 healthy volunteers (66.7%) on placebo.

The most frequently reported AE was headache, reported for 5 healthy volunteers: 4 healthy volunteers (44.4%) on placebo and 1 healthy volunteer (5.9%) in the 1198 µg cohort. The percentage of healthy volunteers with at least 1 AE was higher on placebo than on AZD7594.

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