AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9164
Study Code	D1882C00004
Edition Number	1
Date	11 February 2011

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of inhaled AZD9164 after Administration of Single and Multiple Ascending Doses for 13 days in Healthy Male and Female Japanese Subjects

Study dates: First subject enrolled: 16 April 2010
Last subject last visit:4 June 2010

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

The study was conducted at Richmond Pharmacology Ltd, St George's University of London, Cranmer Terrace, Tooting, London SW17 0RE, UK.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety and tolerability of single and multiple ascending doses of AZD9164	Adverse events, Laboratory variables, Vital signs: Blood pressure, Pulse, Body temperature, ECG: 12-lead ECG paper, 12-lead digital, spirometry and telemetry.	
Secondary	**Secondary**	
To characterise the pharmacokinetics (PK) of AZD9164 and assess the dose proportionality of the PK.	AUC, AUC(0-24), AUC(0-t), Cmax, tmax, λz, t½ λz, CL/F, Vλz/F, MRT, CLR, Ae (% dose), Cav, Rac	
To investigate pharmacodynamic (PD) effects of AZD9164	FEV_1, FVC, systolic blood pressure, diastolic blood pressure, heart rate, pulse, QTcF	
Exploratory	**Exploratory**	
To analyse AZD9164 metabolites in plasma and urine		
To collect an optional blood sample for genotyping for future, possible exploratory genetic research related to AZD9164	Identifying/exploring genetic variations that may affect PK, PD and safety related to AZD9164.	

The exploratory objectives are not reported in this CSR.

Study design

This was a Phase I, randomised, double-blind, parallel group, placebo-controlled, single and multiple ascending dose study in healthy male and female Japanese subjects conducted at a single centre. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects. Nine subjects participated in each cohort and received either AZD9164 or placebo, randomised as 6:3. Each subject was dosed in one cohort only. Subjects started with an initial single dose on Day 1 that was followed by a wash-out period of 72 hours to adequately define the single-dose PK. Thereafter the subjects were dosed once daily for 12 days from Day 4 (13 days of dosing in total, including the first single dose).

Target subject population and sample size

Up to 27 healthy subjects aged 20 to 45 years were to participate in a maximum of 3 cohorts. Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds.

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

The investigational product (IP) was supplied by Investigational Products, AstraZeneca R&D Lund/Mölndal as individual subject containers. AZD9164 Turbuhaler contained a powder mixture of AZD9164 tosylate and lactose monohydrate. 1 g of AZD9164 is equivalent to 1.368 g of AZD9164 tosylate. The placebo Turbuhaler contained lactose monohydrate powder. All Turbuhalers were supplied fully prepared and only required priming by designated staff.

Table S2 Details of IP and other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number	Expiry date
AZD9164 Turbuhaler®	200 µg (delivered dose)	AstraZeneca	09-007181AZ	02/09/2010
AZD9164 Turbuhaler®	500 µg (delivered dose)	AstraZeneca	09-007182AZ	02/09/2010
Placebo Turbuhaler®	Placebo Turbuhaler	AstraZeneca	09-002533AZ	02/09/2010
Labelled empty Turbuhaler® for practice		AstraZeneca	09-001441AZ	28/02/2012

Duration of treatment

Each subject received a single dose of AZD9164 or placebo on Day 1. Repeated dosing commenced on Day 4 with AZD9164 or placebo once daily for 12 days.

Statistical methods

The safety tolerability, pharmacokinetic and pharmacodynamic data were summarised descriptively including tables, listings and graphs, as appropriate. Comparisons of PD parameters (peak and average effects) was made using an analysis of variance technique. Placebo subjects from different dose levels were pooled for the comparisons.

Subject population

It had been planned to randomise a total of 27 healthy Japanese male and female subjects into three cohorts. The study was discontinued early as the development of the compound was halted following the findings of the parallel global MAD study (D1882C00002). Therefore, subjects were only enrolled and administered AZD9164 in two cohorts. Eighteen (18)

randomised subjects were enrolled and completed the study (12 subjects received AZD9164 and six subjects received placebo).

Each subject received 1 administration of study drug during the planned treatment visit. The first healthy volunteer entered the study on 16 April 2010 and the last healthy volunteer finished the study on 4 June 2010. All subjects enrolled and receiving treatment completed the study. Overall, the treatment groups were well balanced/comparable with regards to demographic characteristics.

Summary of safety results

No serious adverse events were reported by any subject and there were no discontinuations from the study. A total of twenty AEs were reported during the study of which rash was the most common (Table S3). There were no clinically significant abnormalities observed in laboratory variables, vital signs and ECG assessments.

A dose dependent initial decrease was observed in FEV_1 within five minutes following dosing with AZD9164 compared to pre-dose. This change was more marked on Day 1 compared with Day 15. Small initial decreases in FEV_1 were observed within 5 minutes following dosing with AZD9164 on Days 4, 5, 8 and 15. Generally, increases in FEV_1 past the individual baseline value were observed at 30 minutes and 2 hours post-dose for the 400 µg and 1000 µg dose level, respectively.

This study was discontinued prematurely because of the findings in the parallel D1882C00002 (Global MAD) study. Thus, in the COPD cohort of the study D1882C00002, AZD9164 was associated with initial and transient drops in FEV_1 that exceeded the predefined discontinuation criteria (fell below 30% in two subjects). Therefore only two cohorts were enrolled and administered AZD9164 in the current study in Japanese subjects. When analysing the findings from the current study, although the 1000 µg dose level also showed initial drops in FEV_1, the drops were not large enough to have warranted a halt to the study by themselves.

Overall, the findings of this study have demonstrated that single and multiple dose administration of AZD9164 was tolerated with no safety concerns identified in the studied dose range (400 µg and 1000 µg).

Table S3 Number (%) of subjects who had at least 1 AE by preferred term, arranged by system organ class (Safety analysis set)

		AZD9164		
	Placebo	400 µg	1000 µg	Total
System Organ Class/Preferred Term	n=6	n=6	n=6	n=18
Gastrointestinal Disorders				
Constipation	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Immune System Disorders				
Seasonal Allergy	0 (0%)	1 (16.7%)	0 (0%)	1 (5.6%)
Nervous System Disorders				
Headache	0 (0%)	1 (16.7%)	0 (0%)	1 (5.6%)
Paraesthesia	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Respiratory, Thoracia and Mediastinal Disorders				
Cough	0 (0%)	1 (16.7%)	1 (16.7%)	2 (11.1%)
Epistaxis	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Nasal Mucosal Disorder	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Respiratory Tract Irritiation	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Upper Repsiratory Tract Infection	0 (0%)	1 (16.7%)	0 (0%)	1 (5.6%)
Skin and Subcutaneous Tissue Disorders				
Contusion	0 (0%)	1 (16.7%)	0 (0%)	1 (5.6%)
Dermatitis Cotnact	0 (0%)	1 (16.7%)	0 (0%)	1 (5.6%)
Dry Skin	1 (16.7%)	0 (0%)	0 (0%)	1 (5.6%)
Folliculitis	0 (0%)	0 (0%)	1 (16.7%)	1 (5.6%)
Rash	2 (33.3%)	4 (66.7%)	0 (0%)	6 (33.3%)

Summary of pharmacokinetic results

Single and multiple doses of AZD9164 (400 µg and 1000 µg) were rapidly absorbed with a median t_{max} of 5 minutes (1000 µg) and 15 minutes (400 µg). Geometric mean $t_{½\lambda z}$ after the last dose was 107 hours (400 µg) and 130 hours (1000 µg). No firm conclusion regarding dose-proportionality could be drawn since only two dose levels were studied. Time-dependency was not evaluated since it was uncertain whether steady state had been reached. The exposure after single dose, as measured by AUC, was similar (400 µg) or slightly lower (1000 µg) than predicted from the D1882C00001 study. The slightly lower AUC in this study may be due to different formulations used in the studies; inhaled solution via nebulisation in the D1882C00001 study and inhaled dry powder by Turbuhaler in the present study. Additionally, the D1882C00001 study was performed in Caucasians and this study in Japanese subjects.

Summary of pharmacodynamic results

No significant effect on FEV_1 was seen on Day 1. AZD9164 improved average and peak FEV_1 compared to placebo over two weeks of treatment, despite the initial and transient drop in FEV_1 as described above (Summary of safety results) (Table S4). Although no significant effect on FEV_1 was seen on Day 1, AZD9164 improved average and peak FEV_1 compared to placebo over two weeks of treatment despite the initial and transient drop in FEV_1 described above (summary of safety). No systemic effects were detected with the exception of a statistically significant change in supine DBP with 1000 µg on Day 1 for both average and peak effect.

Table S4 ANOVA comparison between average and peak effect of FEV_1 and FVC over the first four hours of dosing (PD analysis set)

				Multiplicative model 95% CI		
Variable	**Parameter**	**Day**	**Comparison**	**Ratio**	**Lower**	**Upper**
Average effect over first 4 hours	FEV_1 (L)	1	400 µg Vs placebo	1.0114	0.9774	1.0466
			1000 µg Vs placebo	0.9777	0.9450	1.0114
		15	400 µg Vs placebo	1.0453	1.0070	1.0851
			1000 µg Vs placebo	1.0559	1.0175	1.0958
	FVC (L)	1	400 µg Vs placebo	0.9799	0.9507	1.0101
			1000 µg Vs placebo	0.9953	0.9652	1.0262
		15	400 µg Vs placebo	1.0324	0.9787	1.0889
			1000 µg Vs placebo	1.0344	0.9805	1.0912
Peak effect during the first 4 hours	FEV_1 (L)	1	400 µg Vs placebo	1.0105	0.9743	1.0481
			1000 µg Vs placebo	1.0068	0.9710	1.0440
		15	400 µg Vs placebo	1.0437	1.0040	1.0850
			1000 µg Vs placebo	1.0640	1.0238	1.1058
	FVC (L)	1	400 µg Vs placebo	0.9771	0.9543	1.0004
			1000 µg Vs placebo	0.9868	0.9636	1.0105
		15	400 µg Vs placebo	1.0322	0.9759	1.0918
			1000 µg Vs placebo	1.0352	0.9786	1.0951