Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00003
Edition Number	1
Date	18 March 2010

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of oral AZD2423 after Single Ascending Doses in Healthy Japanese Male and Non-Fertile Female Volunteers

Study dates: First subject enrolled: 25th August 2009
Last subject last visit: 26th November 2009

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 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of single ascending oral doses of AZD2423 in Japanese subjects.	Adverse events, vital signs, physical examinations, telemetry, dECGs, clinical chemistry and haematology labs, and urinalysis.	
Secondary	**Secondary**	
To characterise the pharmacokinetics (PK) of AZD2423 and assess the dose proportionality of the PK following administration of single ascending oral doses in Japanese subjects.	Plasma and urine concentrations of AZD2423. The PK parameters C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $t_{1/2}$, λ_Z, CL/F, V_z/F, A_e, f_e, CL_R.	
Exploratory		
To investigate levels of CCL2 in plasma.	CCL2 levels.	
To collect an optional blood sample for genotyping for future, possible exploratory genetic research related to AZD2423*.	Identifying / exploring genetic variations that may affect PK, PD and safety related to AZD2423.	
To collect serum/plasma samples to allow for possible post hoc analysis of antidiuretic hormone (ADH)*.	Analysis of ADH in case of adverse events.	

* With the exception of unexpected findings, the second and third exploratory objectives are not reported in this CSR.

Study design

This was a Phase I, double-blind, parallel group, placebo-controlled, randomised within each dose group, single ascending dose study, with the objective to assess the safety, tolerability and pharmacokinetic profile of AZD2423 in ascending doses.

Target subject population and sample size

Thirty-one healthy Japanese subjects aged ≥20 to ≤55 years were randomised in 4 cohorts. Eight subjects who were eligible to participate were included in Cohorts 1, 2, and 3 and seven subjects who were eligible to participate were included in the last cohort (Cohort 4) and received either AZD2423 or placebo, randomised 6:2.

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

Single oral doses of AZD2423 (10 mg, 30 mg, 90 mg and 300 mg) with a starting dose of 10 mg.

AZD2423 (1 mg/mL oral solution)

AZD2423 (10 mg/mL oral solution)

Placebo to match AZD2423 (oral solution)

Duration of treatment

Single oral dose.

Statistical methods

The analysis of safety, tolerability, PK and PD data was mainly descriptive with listings, summary statistics and graphs as appropriate.

Subject population

All subjects completed the study with 23 subjects receiving AZD2423 and 8 subjects receiving placebo. All 31 randomised subjects received one dose of study drug and were included in the safety analysis and PD sets. The PK analysis set included 23 subjects who received AZD2423. The subjects were aged between 21 and 35 years with a mean age of 25.74 years. Body Mass Index (BMI) values ranged from 18.75 to 26.40 kg/m^2 with a mean BMI of 21.07 kg/m^2. Overall, subjects in each of the cohorts were well balanced in terms of age, height, weight and BMI.

Summary of safety results

There were no clinically significant abnormalities in clinical laboratory assessments, vital signs and 12-lead dECGs. No serious adverse events were reported by any subject and there were no discontinuations from the study. Very few AEs were reported during the study which included upper respiratory tract infection and contact dermatitis. No AEs were reported with the 90 mg and 300 mg doses. These AEs were considered to be moderate (upper respiratory tract infection) and mild (contact dermatitis) in intensity (Table S2). The AEs were not considered to be dose related or causally related.

Table S2 Number (%) of subjects who had at least 1 AE by Preferred Term, arranged by System Organ Class (Safety analysis set)

	AZD2423					
	Placebo	**10 mg**	**30 mg**	**90 mg**	**300 mg**	**Total****
	n=8	**n=6**	**n=6**	**n=6**	**n=5**	**n=23**
System Organ Class/Preferred Term*						
Infections and infestations	0 (0%)	2 (33.3%)	0 (0%)	0 (0%)	0 (0%)	2 (8.7%)
Upper respiratory tract infection	0 (0%)	2 (33.3%)	0 (0%)	0 (0%)	0 (0%)	2 (8.7%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (4.3%)
Dermatitis contact	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (4.3%)

* Number of healthy subjects who reported at least 1 AE for a PT/SOC
** Total column includes only subjects on Active drug.
Pre-treatment Adverse Events are not included in summary table.
Source data: t110203.sas

Summary of pharmacokinetic results

The renal clearance of AZD2423 was low suggesting that the drug is not eliminated unchanged to any significant degree. After C_{max} was reached a steady elimination phase was observed until the end of the sampling period. The $t_{1/2}$ of about 30 hours was consistent between the cohorts and did not change when the dose was increased from 10 mg to 300 mg. Exposure was found to increase more than dose proportionally in terms of C_{max} and was dose proportional in terms of AUC. For all cohorts, the geometric mean of fraction excreted unchanged in the urine ranged from 6 % to 9 % and geometric mean of renal clearance ranged from 14.1 L/h to 15.1 L/h.

Table S3 Summary of pharmacokinetic parameters of AZD2423 (PK analysis set)

Parameter	**AZD2423**	**n**	**Arithmetic mean**	**SD**	**Geometric Mean**	**Geometric CV (%)**	**Median**	**Min**	**Max**
C_{max} (nmol/L)	10 mg	6	11.3	4.20	10.7	35.7	9.97	7.69	18.5
	30 mg	6	43.7	14.8	41.8	32.8	39.3	31.7	68.7
	90 mg	6	250	133	230	42.5	200	177	520
	300mg	5	1520	666	1390	50.2	1520	741	2380
t_{max} (h)	10 mg	6	2.49	1.13	2.26	53.2	2.58	1.08	4.10
	30 mg	6	1.70	1.55	1.14	134	1.12	0.370	4.08
	90 mg	6	1.55	0.975	1.25	90.2	1.53	0.370	3.08
	300mg	5	0.518	0.169	0.497	33.2	0.450	0.370	0.700
AUC (nmol*h/L)	10 mg	6	175	36.6	172	21.8	177	124	226
	30 mg	6	452	96.3	444	19.9	433	354	631
	90 mg	6	1610	340	1580	21.4	1600	1230	2080

Table S3 Summary of pharmacokinetic parameters of AZD2423 (PK analysis set)

Parameter	AZD2423	n	Arithmetic mean	SD	Geometric Mean	Geometric CV (%)	Median	Min	Max
	300mg	5	6530	883	6480	14.3	6740	5180	7450
$t_{1/2}$ (h)	10 mg	6	29.2	3.39	29.0	12.7	30.4	22.6	31.7
	30 mg	6	26.6	5.60	26.2	18.8	25.0	22.3	37.7
	90 mg	6	24.9	2.76	24.8	11.1	24.8	21.6	28.7
	300mg	5	33.1	17.0	29.9	53.3	21.8	18.9	54.7
CL/F (L/h)	10 mg	6	137	30.2	134	21.8	130	102	185
	30 mg	6	160	29.3	158	19.9	162	111	198
	90 mg	6	135	28.2	133	21.4	133	101	171
	300mg	5	109	16.2	108	14.3	104	93.9	135
V_Z/F (L)	10 mg	6	5680	1010	5600	18.5	5730	4190	7120
	30 mg	6	5990	602	5960	10.4	6050	4980	6740
	90 mg	6	4870	1220	4740	26.0	4840	3380	6610
	300mg	5	4950	2000	4650	41.0	3680	3260	7410
$f_{e\ (0\text{-}24)}$ (%)	10 mg	6	6.35	1.45	6.23	21.7	5.98	5.12	8.90
	30 mg	6	6.15	1.58	5.99	25.6	5.95	4.25	8.75
	90 mg	6	8.39	3.31	7.77	47.0	8.26	3.75	12.4
	300mg	5	10.2	3.69	9.45	49.3	10.4	4.26	14.1
CL_R (L/h)	10 mg	6	14.8	1.07	14.8	7.48	15.1	13.0	15.8
	30 mg	6	15.0	2.26	14.9	15.5	15.5	12.2	17.1
	90 mg	6	15.6	4.02	15.1	28.6	16.2	9.65	19.5
	300mg	5	15.2	5.49	14.1	50.6	15.7	6.20	20.0

Source data: t110302.sas

Summary of pharmacodynamic results

Mean CCL2 concentrations appeared to increase in a dose dependent manner. The highest concentrations were observed around 6 hours post-dose (10 mg, 30 mg, and 90 mg doses) and 24 hours post-dose (300 mg dose).