Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00001
Edition Number	1
Date	12 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 Male and Female Volunteers without Childbearing Potential

Study dates: First subject enrolled: 17 July 2009
Last subject last visit: 03 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 AZD2423 following administration of single ascending doses and to estimate the maximum tolerated dose (MTD), if within the predefined exposure limits.	Adverse events, laboratory variables, vital signs (blood pressure, pulse, body temperature), ECG: resting 12-lead digital ECG and real time display (telemetry)	Safety
Secondary	**Secondary**	
To characterise the pharmacokinetics (PK) of AZD2423 and provisionally assess the dose proportionality of the PK following administration of single ascending doses of AZD2423.	AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{extrapolated}$, C_{max}, t_{max}, $t_{1/2\lambda Z}$, λ_z, CL/F, V_z/F, MRT, A_e, CL_R, f_e	PK
Exploratory	**Exploratory**	
To investigate levels of ligands (CCL2).	Plasma levels of CCL2 pre-and post-dose.	PD
The data from the remaining exploratory objectives are presented separately from this report.		

Study design

This was a single-ascending dose study, performed at a single centre as a first-time-in-man, randomised and placebo-controlled study with a starting dose of AZD2423 0.1 mg and dose escalation until the maximum tolerated dose (MTD) or the pre-defined exposure level (C_{max} of 2.2 µmol/L and/or $AUC_{(0-24)}$ of 13 µmol*h/L) was reached. In each panel 8 subjects were randomised to either AZD2423 or placebo.

Target subject population and sample size

Healthy male and non-fertile female volunteers aged 20 to 55 years (inclusive) with a Body Mass Index (BMI) between ≥18 and ≤30 kg/m^2 and a weight between ≥50 kg and ≤100 kg. Overall, 80 subjects distributed equally into 10 dose panels were evaluated.

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

- AZD2423; oral solution of 1 mg/ml (Batch number: 09-002871AZ) and 10 mg/mL (Batch number: 09-002935AZ); single dose administration: 0.1, 05, 2.5, 10, 30, 60, 90, 180, 300, and 600 mg.

- Placebo; oral solution (Batch number: 09-001559AZ).

Duration of treatment

Single dose

Statistical methods

The safety, pharmacokinetic (PK) and the pharmacodynamic (PD) data were summarised by means of descriptive statistics and listed.

The smoothed intervals QTcB, QTcF, QTcX and RR were analysed by an analysis of covariance (ANCOVA) model by target time point using *treatment* and *baseline* value as independent factors. The treatment effect was estimated together with its 95% two-sided CI.

Dose proportionality of AUC (and C_{max}) were analysed using a nonlinear regression analysis, an E_{max}-model, with dose normalised AUC (and C_{max}) as dependent and dose as independent variable. The model fitted was: y/dose = a + (b*dose)/(c+dose) where y represents the PK parameters AUC or C_{max}. Point estimates of a, b, c and the corresponding 2-sided 95% confidence intervals (CI) for AUC or C_{max} were calculated.

Subject population

In total, 80 healthy male and non-fertile female subjects were randomised into 10 cohorts, each subject received 1 administration of study drug (AZD2423 or placebo) during the planned treatment visit and all subjects completed the study in accordance with the amended CSP.

The safety and the PD analysis sets each included all 80 randomised subjects. The PK analysis set comprised 60 subjects, ie including all those subjects receiving AZD2423 and excluding all those who received placebo.

Overall, the treatment groups were well balanced with regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

The geometric mean AZD2423 plasma concentration-time profiles following single dose administration of 0.5 to 600 mg are displayed in Figure S1. The corresponding main PK parameters of AZD2423 are shown in Table S2 and Table S3.

Figure S1 **Geometric Mean (±SD) plasma concentrations (nmol/L) versus time profiles of AZD2423 following single ascending doses of AZD2423 from 0.5 mg to 600 mg (log-linear scale) – (PK analysis set)**

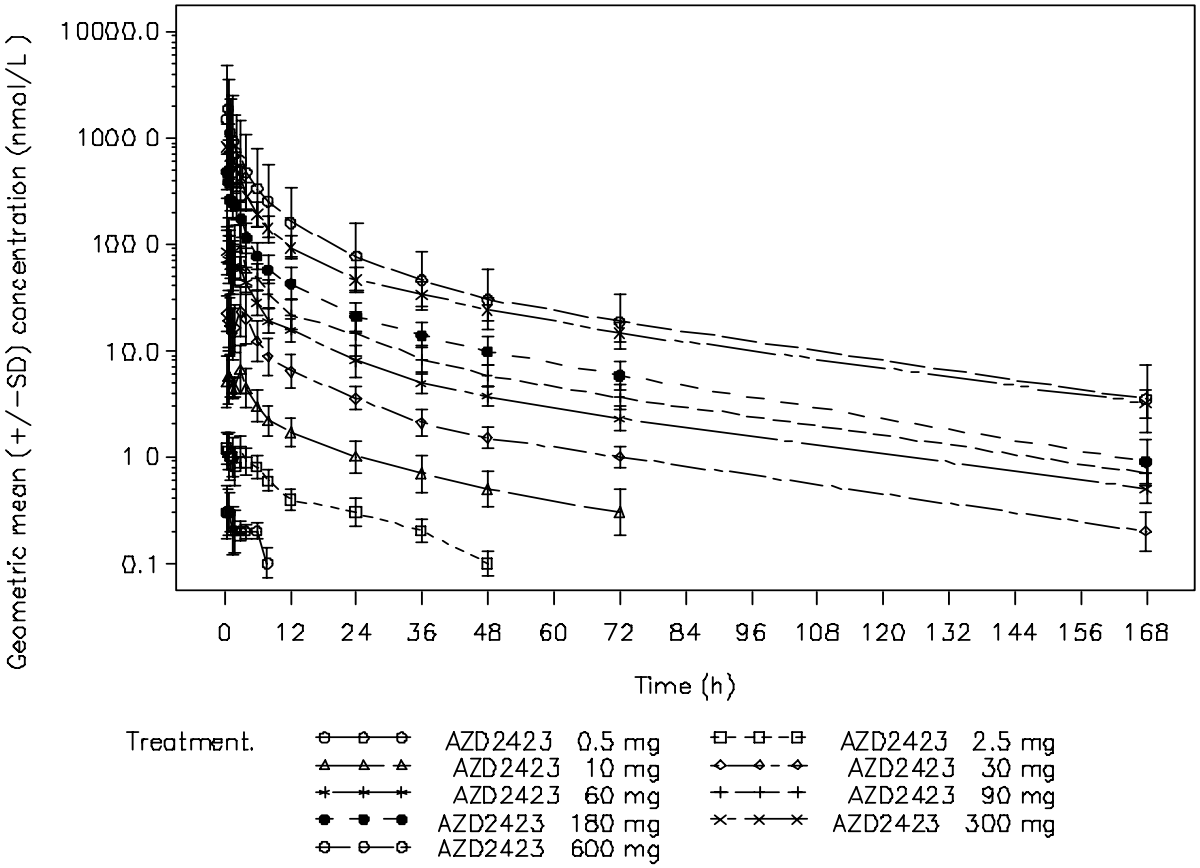

Table S2 Pharmacokinetic parameters of AZD2423; Part I – (PK analysis set)

Parameter	Statistic	Cohort 1 AZD2423 0.1 mg	Cohort 2 AZD2423 0.5 mg	Cohort 3 AZD2423 2.5 mg	Cohort 4 AZD2423 10 mg	Cohort 5 AZD2423 30 mg
		N= 6	N= 6	N= 6	N= 6	N= 6
AUC (h*nmol/L)	n	0	0	6	6	6
	Geomean	NQ	NC*	22.3	95.9	369
	CV%	NC	NC*	20.9	35.9	29.5
C_{max} (nmol/L)	n	0	6	6	6	6
	Geomean	NQ	0.345	1.50	9.67	29.2
	CV%	NC	32.6	27.5	27.6	37.4
t_{max} (h)	n	0	6	6	6	6
	Median	NQ	0.680	0.355	2.04	3.03
	Min-Max	NQ	0.35–3.03	0.34–3.02	0.35–3.05	1.0–4.05
$t_{1/2\lambda z}$ (h)	n	0	6	6	6	6
	Geomean	NQ	4.99	21.9	26.8	43.6
	CV%	NC	24.7	22.1	18.1	7.71
CL/F (L/h)	n	0	6	6	6	6
	Geomean	NQ	474	263	245	191
	CV%	NC	31.5	21.0	36.0	29.6
V_Z/F (L)	n	0	6	6	6	6
	Geomean	NQ	3410	8320	9460	12000
	CV%	NC	13.1	25.1	23.1	34.7
CL_R [L/h]	n	0	6	6	6	6
	Geomean	NQ	28.2	16.7	16.8	14.2
	CV%	NC	30.2	7.9	19.6	17.7
$f_{e(0-48)}$ [%]	n	6	6	6	6	6
	Geomean	5.40	5.95	6.34	6.85	7.47
	CV%	29.9	32.6	24.6	21.0	37.8

CV%= coefficient of variation; Geomean= geometric mean; NC=Not calculable; NQ= Not Quantifiable.

Table S3 Pharmacokinetic parameters of AZD2423; Part II – (PK analysis set)

Parameter	Statistic	Cohort 6 AZD2423 60 mg	Cohort 7 AZD2423 90 mg	Cohort 8 AZD2423 180 mg	Cohort 9 AZD2423 300 mg	Cohort 10 AZD2423 600 mg
		N= 6	N= 6	N= 6	N= 6	N= 6
AUC (h*nmol/L)	n	6	6	6	6	6
	Geomean	948	1450	2790	6480	10600
	CV%	19.2	25.1	21.5	24.3	71.2
C_{max} (nmol/L)	n	6	6	6	6	6
	Geomean	111	192	504	937	2710
	CV%	38.2	52.2	31.8	44.3	86.3
t_{max} (h)	n	6	6	6	6	6
	Median	0.695	1.36	0.375	0.360	0.535
	Min-Max	0.34–3.01	0.34–3.06	0.34–0.69	0.34–0.68	0.35–3.02
$t_{1/2\lambda z}$ (h)	n	6	6	6	6	6
	Geomean	48.6	44.0	46.0	43.3	43.6
	CV%	12.3	15.1	11.7	13.0	17.1
CL/F (L/h)	n	6	6	6	6	6
	Geomean	149	145	151	109	133
	CV%	19.2	25.3	21.5	24.4	71.3
V_Z/F (L)	n	6	6	6	6	6
	Geomean	10400	9230	10000	6790	8370
	CV%	24.6	33.1	28.1	28.9	89.6
CL_R [L/h]	n	6	6	6	6	6
	Geomean	13.0	13.3	14.5	10.9	13.8
	CV%	12.4	18.2	13.0	27.3	22.2
$f_{e(0-48)}$ [%]	n	6	6	6	6	6
	Geomean	8.76	9.17	9.59	10.0	10.4
	CV%	17.7	23.9	15.7	42.1	65.5

CV%= coefficient of variation; Geomean= geometric mean.

AZD2423 following single dose administration of 0.5 to 600 mg was rapidly absorbed, achieved peak plasma levels at a median t_{max} of 0.4 to 3.0 hours and elimination from plasma was characterized by a mean $t_{1/2\lambda z}$ of about 48 hours (range: 43 to 49 hours) following AZD2423 30 to 600 mg and shifted to shorter values at lower dose levels.

The evaluation of the dose-normalised AUC and C_{max} data suggested that systemic exposure to AZD2423 increased approximately proportional to dose from 60 to 600 mg AZD2423. Slightly more than dose-proportional increases in AUC and C_{max} were indicated at lower dose levels. The increase in AUC and C_{max} with ascending dose was well described by an E_{max}-model.

At 600 mg AZD2423, the pre-defined individual maximum exposure limit for C_{max} (2200 nmol/L) was exceeded, whereas individual $AUC_{(0-24)}$ were still below the exposure limit (13000 nmol*h/L).

The apparent volume of distribution (Vz/F) is high, clearly exceeding the physiological body space. The geometric mean CL/F was between 109 and 191 L/h following administration of 30 to 600 mg AZD2423, higher at lower doses, ie 474, 263 and 245 L/h after 0.5 mg, 2.5 mg and 10 mg AZD2423, respectively. Renal clearance was low and the fraction of AZD2423 excreted unchanged in urine within 48 hours did not exceed about 10% of the dose.

Summary of pharmacodynamic results

Becoming evident at 10 mg AZD2423, CCL2 plasma levels increased dose-dependently within 1 hour post-dose and reached peak levels between 6 to 24 hours after dosing. Maximum mean CCL2 levels in plasma achieved were: 313 pg/mL (10 mg), 464 pg/mL (30 mg), 569 pg/mL (60 mg), 648 pg/mL (90 mg), 603 pg/mL (180 mg), 989 pg/mL (300 mg) and 1270 pg/mL (600 mg), respectively, and 191 pg/mL after administration of placebo. Subsequently, geometric mean CCL2 levels declined slightly but remained more distinctively above baseline levels at 48 hours post-dose with ascending dose.

Summary of safety results

A total of 22 (36.7%) subjects receiving AZD2423 experienced 43 AEs and 6 (30.0%) subjects under placebo reported 9 AEs. Thirty (30) AEs reported by 13 (21.7%) subjects under AZD2423 and 7 AEs reported by 5 (25.0%) subjects under placebo were judged to be causally related to the IP by the investigator. The majority of AEs was of mild to moderate intensity. One subject receiving AZD2423 (30 mg) experienced an SAE (subacute appendicitis) of severe intensity which was judged by the investigator not to be related to AZD2423. There were no deaths, no discontinuations due to an AE or any other significant adverse event in the study.

AEs recorded following AZD2423 up to 300 mg did not reveal any apparent relation to treatment and were not noticeably different to those experienced following placebo.

Following a single dose of AZD2423 600 mg, 3 subjects experienced non-tolerable AEs, ie vomiting/nausea of moderate intensity judged to be related to AZD2423 by the investigator, by which stopping criteria for further dose escalation were met and the MTD determined. The most frequent SOC at AZD2423 600 mg was gastrointestinal disorders and most gastrointestinal AEs observed occurred around t_{max} of AZD2423.

No clinically important changes in laboratory safety variables, 12-lead ECG, vital signs and physical examination were observed.