AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2423
Study Code	D2600C00002
Edition Number	1
Date	17 November 2010

A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral AZD2423 Solution after Multiple Ascending Doses in Young and Elderly Healthy Volunteers

Study dates: First subject enrolled: 05 Oct 2009
Last subject last visit: 14 May 2010

Phase of development: Clinical Pharmacology (I)

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

Study centre

Early Phase Clinical Unit – London, PAREXEL International, Northwick Park Hospital, Harrow, Middlesex, United Kingdom.

Study period		Phase of development
First subject enrolled	05 Oct 2009	I
Last subject completed	14 May 2010	

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 AZD2423 in young and elderly subjects following administration of multiple ascending doses at steady state and, if possible, estimate the maximum tolerated dose (MTD) if within the predefined exposure limits (Part 1 and Part 2 only)	Adverse events, laboratory variables, vital signs (blood pressure, pulse, body temperature), electrocardiogram (ECG), telemetry	Safety and tolerability
Secondary	**Secondary**	
To characterise the multiple dose pharmacokinetics of AZD2423 and assess the time required to reach steady state, the degree of accumulation and the time dependency of the pharmacokinetics (Part 1 and Part 2 only)	$C_{max,ss}$, $t_{max,ss}$, $C_{ss,min}$, $t_{1/2\lambda z,ss}$, $AUC_{\tau,ss}$, CL_{ss}/F, R_{ac}, CL_R, $f_{e,ss}$, $A_{e,ss}$ Time dependency, R_{AUC}, of the pharmacokinetics by comparing $AUC_{\tau,ss}$ and AUC (Day 1) (ANCOVA) Dose proportionality of $C_{max,ss}$ and $AUC_{\tau,ss}$ (ANCOVA)	Pharmacokinetics
To characterise the single and multiple dose pharmacokinetics (PK) of AZD2423 in elderly subjects (Part 1 only)	AUC, AUC_{0-t}, AUC_{0-24}, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F, V_Z/F, CL_R, f_e, A_e $C_{max,ss}$, $t_{max,ss}$, $C_{ss,min}$, $t_{1/2\lambda z,ss}$, $AUC_{\tau,ss}$, CL_{ss}/F, R_{ac}, CL_R, $f_{e,ss}$, $A_{e,ss}$	Pharmacokinetics
To investigate concentration of AZD2423 in cerebrospinal fluid (CSF) (Part 2 only)	AZD2423 concentrations at 4 h (Day 8) and 24 hours after last dosing on Day 8 (Day 9)	Pharmacokinetics
To investigate the pharmacokinetics of the new tablet formulation compared to oral solution (Part 3 only)	AUC, AUC_{0-t}, t_{max}, $t_{1/2\lambda z}$, C_{max}, CL/F Relative bioavailability based on AUC and C_{max} (ANOVA)	Pharmacokinetics
To investigate the effect of food in comparison to fasting condition, on the extent and rate of absorption of AZD2423 given as tablet formulation (Part 3 only)	AUC, AUC_{0-t}, t_{max}, $t_{1/2\lambda z}$, C_{max}, CL/F Food effect based on AUC and C_{max} (ANOVA)	Pharmacokinetics

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To investigate the safety and tolerability of oral solution and tablet formulation of AZD2423 in young subjects following administration of single doses (Part 3 only)	Adverse events, laboratory variables, vital signs (blood pressure, pulse, body temperature), electrocardiogram (ECG), telemetry	Safety and tolerability
Exploratory endpoints		
To investigate levels of chemokine ligand 2 (CCL2) in plasma (Part 1 and Part 2 only)	Levels of CCL2 in plasma at pre-and post-dose (Parts 1 and 2) and at follow-up (Part 1 only)	Pharmacodynamics
To investigate levels of chemokine ligand 2 (CCL2) in CSF (Part 2 only)	Levels of CCL2 in CSF at 4 h (Day 8) and 24 h after last dosing on Day 8 (Day 9)	Pharmacodynamics
To investigate levels of additional potential effect markers, such as additional ligands for CCR2 (such as CCL7/8/11 and 13), cytokines, chemokines, other inflammatory mediators or patterns of inflammatory mediators (Part 1 only)*	Pre- and post-dose levels of additional potential effect markers, such as - additional ligands for CCR2 (such as CCL7/8/11 and 13) - cytokines (such as tumour necrosis factor [TNF]α and interleukin [IL]-6) - chemokines (such as IL-8) - other inflammatory mediators or patterns of inflammatory mediators	Pharmacodynamics
To collect serum/plasma samples to allow for possible post hoc analysis of immunoglobulins, gastrointestinal (GI) hormones and antidiuretic hormone (ADH), cytokines and chemokines and other inflammatory mediators and patterns of inflammatory mediators in case of adverse events (AEs) (Part 1 only)*	Serum/plasma samples were collected and stored appropriately to allow for possible post-hoc analysis in case of related adverse events of - immunoglobulins (IgG, IgA, IgE and IgG subclasses IgG1, IgG2, IgG3 and IgG4) - GI hormones, eg. vasoactive intestinal peptide, pancreatic polypeptide, gastrin, somatostatin - antidiuretic hormone (ADH) - pro-inflammatory and anti-inflammatory cytokines (such as TNFα and IL-6), chemokines (such as IL-8), and other inflammatory mediators and patterns of inflammatory mediators	Pharmacodynamics
To collect blood for possible AZD2423 metabolite identification (Part 1 and Part 2 only)*	Venous blood samples were collected and stored for possible assessments of AZD2423 metabolites.	Pharmacokinetics
To collect urine for possible AZD2423 metabolite identification (Part 1 only)*	Urine samples for possible explorative investigation of AZD2423 metabolites were taken from the total urine sample provided during each collection period.	Pharmacokinetics

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
An optional blood sample for genotyping will be collected for future, possible exploratory genetic research aimed at identifying/ exploring genetic variations that may affect PK and pharmacodynamic (PD), safety and tolerability related to AZD2423*	Blood sample for genetic research was obtained at Visit 2 after randomisation.	Pharmacogenetics

$C_{max,ss}$ = maximum plasma concentration at steady state, $t_{max,ss}$ = time to $C_{max,ss}$, $C_{ss,min}$ = minimum plasma concentration at steady state, $t_{1/2\lambda z,ss}$ = terminal half-life at steady state, $AUC_{\tau,ss}$ = area under the plasma concentration-time curve from zero to the end of the dosing interval, CL_{ss}/F = oral systemic clearance at steady state, where 'F' denotes the unknown amount of systemically available drug, R_{ac} = extent of accumulation on multiple dosing, $CL_{R,ss}$ = renal clearance at steady state, $f_{e,ss}$ = fraction of drug excreted into urine at steady state, $A_{e,ss}$ = amount of drug excreted unchanged at steady state, R_{AUC} = time dependency

C_{max} = maximum plasma concentration, t_{max} = time to C_{max}, $t_{1/2\lambda z}$ = terminal half-life, AUC_{0-t} = area under the plasma concentration-time curve from zero to the time of the last measurable concentration, AUC = area under the plasma concentration-time curve from zero to infinity, AUC_{0-24} = area under the plasma concentration-time curve from zero to 24 hours post-dose, CL/F = oral systemic clearance, V_z/F = oral volume of distribution (apparent) during terminal (λ_Z) phase, CL_R = renal clearance, f_e = fraction of drug excreted into urine, A_e = amount of drug excreted unchanged.

PG_x = pharmacogenetics

* The data on this exploratory objective are not reported in this CSR.

Study design

This Phase I study was divided in three parts: Part 1, Part 2, and Part 3.

Part 1 was a multiple ascending dose (MAD) study part, in which the starting dose was determined from the global single ascending dose (GSAD) study D2600C00001. The starting dose of AZD2423 was 8 mg and dose escalation was to continue until the MTD and/or the predefined maximum exposure level was reached with respect to AZD2423 C_{max} and/or AUC. In each cohort, 8 healthy volunteers were randomised to active treatment or placebo. After each dose cohort (8, 24, 72, 150 and 300 mg), a Safety Review Committee (SRC) evaluated the safety, tolerability and the PK of AZD2423 and determined the next dose (planned dose, increased or decreased dose, repeated dose or dose stopped).

Part 2 was an open, non-randomised part to study CSF levels of AZD2423 in steady state after multiple dosing of an AZD2423 oral solution. Healthy young volunteers, aged ≥20 to ≤55 years (6 active, no placebo) were administered multiple doses of 100 mg (2 volunteers) or 300 mg (4 volunteers) AZD2423, based on data from earlier cohorts in this study, Part 1, and the GSAD study.

Part 3 was an open-label, partially randomised, three-way cross-over part of the study to investigate the safety, tolerability and pharmacokinetics of a AZD2423 tablet formulation compared to an oral solution and the effect of food on pharmacokinetics of AZD2423, when given as a tablet. Twelve healthy volunteers (all active, no placebo) were randomised to one of two treatment sequences where one single dose of 40 mg AZD2423 was administered as an

oral tablet formulation and one single dose of 40 mg AZD2423 as oral solution in a cross-over fashion, with a washout period of at least 7 days in between administrations. In addition, all 12 healthy volunteers were administered an oral tablet formulation of 40 mg AZD2423 together with food with a washout period of at least 7 days in between administrations.

Target subject population and sample size

Healthy young male and non-fertile female subjects aged ≥20 to ≤55 years and healthy elderly male and female subjects aged ≥65 to ≤80 years. In Part 1, 8 subjects participated in each cohort and received either AZD2423 or placebo, randomised 6:2. In Part 2, 6 young subjects, aged ≥20 to ≤55 years, received AZD2423. In Part 3, 12 young subjects, aged ≥20 to ≤55 years, received AZD2423.

Investigational product and comparators: dosage, mode of administration and batch numbers

- AZD2423, oral solution, strength: 1 mg, 10 mg, and 20 mg, single and multiple doses, starting with 8 mg, batch numbers: 1 mg/mL solution: 09-006534AZ, 09-006546AZ, 09-006626AZ, 09-006628AZ, 09-007977AZ, 09-006630AZ, and 09-006632AZ; 10 mg/mL solution: 10-000872AZ, 09-008939AZ, 09-009004AZ, and 09-006681AZ

- AZD2423, oral tablet, strength: 20 mg, single doses, batch number: 10-000035AZ

- Placebo, oral solution, batch numbers: 09-006680AZ and 09-009007AZ

Duration of treatment

Part 1: An initial single dose followed by a washout period of 72 hours was given at the beginning of each dose-panel. Thereafter, subjects were dosed daily from Day 4 to Day 14.

Part 2: Subjects were dosed once daily for 8 consecutive days.

Part 3: All subjects received three single doses of 40 mg AZD2423 each followed by a wash-out period of 7 days.

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability, pharmacokinetic and pharmacodynamic data were summarised descriptively including tables, listings and graphs, as appropriate.

The pharmacokinetic parameters determined as appropriate in plasma and urine included AUC, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$, C_{max}, t_{max}, $t_{1/2\lambda z}$, CL/F, V_Z/F, CL_R, f_e, and A_e after single dosing and $C_{max,ss}$, $t_{max,ss}$, $C_{ss,min}$, $t_{1/2\lambda z,ss}$, $AUC_{\tau,ss}$, CL_{ss}/F, R_{ac}, CL_R, $f_{e,ss}$, $A_{e,ss}$ after multiple dosing. The pharmacokinetic analysis included the explorative analysis of the dose-proportionality of $C_{max,ss}$ and $AUC_{\tau,ss}$ using a power model (ANCOVA). Time dependency of the pharmacokinetics was investigated by comparing $AUC_{\tau,ss}$ and $AUC_{0\text{-}24}$ (Day 1) by ANCOVA. In Part 3, the log-transformed variables AUC and C_{max} were analyzed using a mixed model

ANOVA with fixed effects for sequence, period and treatment (tablet fasted, solution fasted) and a random effect for subject within sequence to assess relative bioavailability between a new tablet formulation and solution of AZD2423 in the fasted state. To investigate the effect of food in comparison to fasting condition, on the extent and rate of absorption of the new tablet formulation, the log-transformed variables AUC and C_{max} were analyzed using a mixed model ANOVA with fixed effects for sequence, period and treatment (tablet fasted, tablet fed) and a random effect for subject within sequence.

Subject population

Overall, 74 young and elderly healthy volunteers were included in this study.

In Part 1, 40 young (all men) and 16 elderly (10 men, 6 women) healthy volunteers were randomised into 5 and 2 cohorts, respectively. All healthy volunteers in Part 1 received single and multiple administrations of AZD2423 or placebo during the treatment visits as planned. All healthy volunteers randomised to treatment completed Part 1 of the study as planned, except for 2 young healthy volunteers (one each in Cohorts 1 and 2), who terminated the study prematurely due to AEs. The safety and the PD analysis sets each included all 56 volunteers randomised in Part 1. The PK analysis set comprised 42 healthy volunteers (30 young and 12 elderly), ie including all those healthy volunteers receiving AZD2423 and excluding all those who received placebo. Overall, the treatment groups in Part 1 were well balanced with regards to demographic and baseline characteristics.

In Part 2, 6 young healthy volunteers (all men) were included in the study. Four of the 6 healthy volunteers received multiple administrations of 300 mg AZD2423, while 2 subjects received multiple administrations of a lower dose (100 mg) during the treatment visits. Five young healthy volunteers completed the study as planned, whereas 1 volunteer was terminated prematurely due to adverse events (E0001230). All 6 healthy volunteers in Part 2 were included in the safety, the PK and the PD analysis sets. The CSF analysis set comprised 5 healthy volunteers; 1 healthy volunteer (E0001230) was excluded from the CSF analysis set due to incomplete CSF sampling.

In Part 3, 12 young healthy volunteers (all men) were randomised to one of two treatment sequences ABC or BAC, where A denotes the solution formulation (fasted), B denotes the tablet formulation (fasted) and C denotes the tablet formulation (fed). All young healthy volunteers in Part 3 received three single doses of 40 mg AZD2423, two single doses as tablets, once in fasted state and once in fed state, and one single dose of oral solution in the fasted state. All young healthy volunteers completed the study. All 12 healthy volunteers randomised in Part 3 were included in the safety and the PK analysis sets.

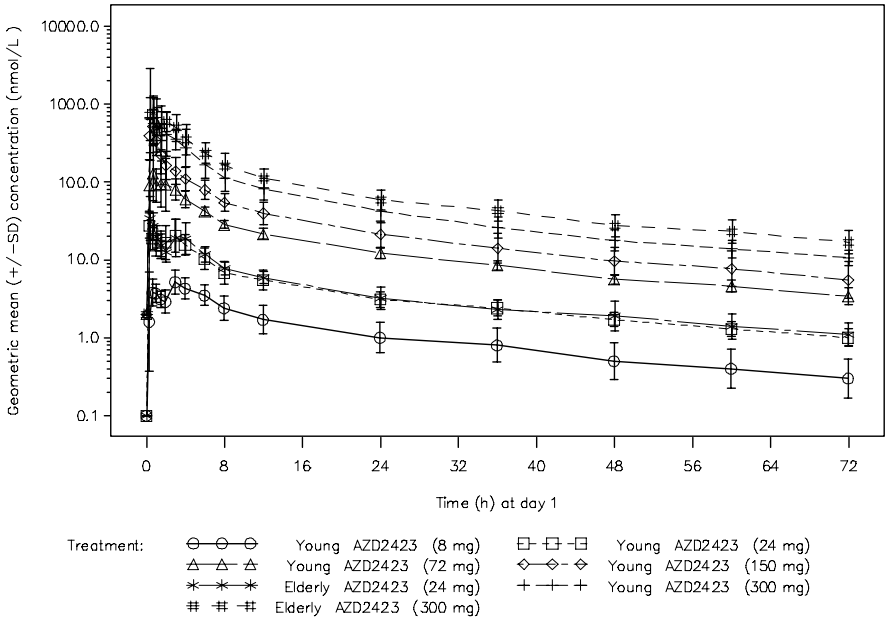
Summary of pharmacokinetic results

Part 1

The geometric mean AZD2423 plasma concentration-time profiles following single and multiple dose administration of 8 to 300 mg are displayed in Figure S1 (Day 1 and Day 14

profiles) and Figure S2 (Day 1 to Day 14). The corresponding main PK parameters of AZD2423 are shown in Table S2 to Table S5.

Figure S1 **Geometric mean (±SD) plasma concentrations (nmol/L) of AZD2423 on log scale versus time for all dose groups – single (top) and multiple (bottom) dose (PK analysis set) – Part 1**



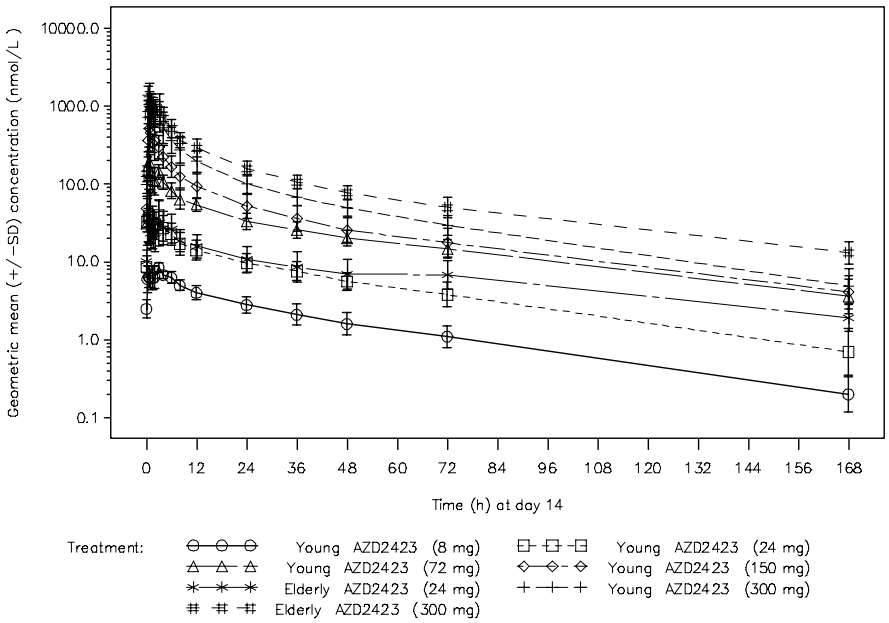


Figure S2 **Geometric mean (±SD) plasma concentrations (nmol/L) of AZD2423 on log scale versus time from Day 1 to Day 14 for all dose groups – single and multiple dose (PK analysis set) – Part 1**

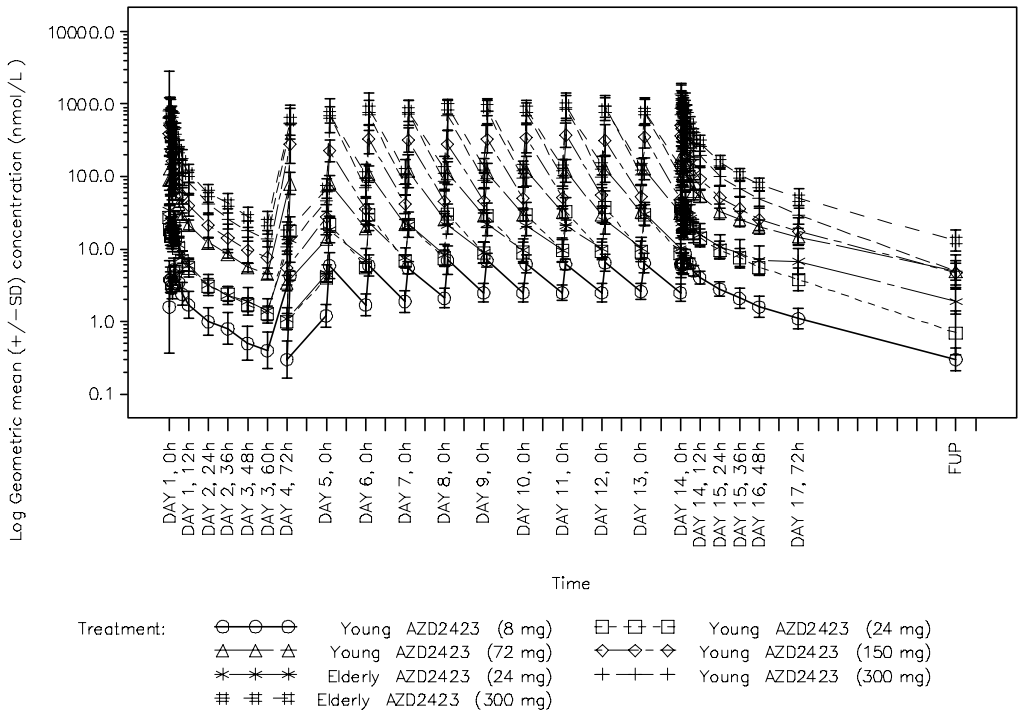


Table S2 **Summary of pharmacokinetic parameters of AZD2423 (young cohorts - single dose, Day 1) (PK analysis set) – Part 1**

Parameter	Statistics	Young AZD2423 (8 mg) N=6	Young AZD2423 (24 mg) N=6	Young AZD2423 (72 mg) N=6	Young AZD2423 (150 mg) N=6	Young AZD2423 (300 mg) N=6
AUC (h·nmol/L)	n	6	6	6	6	6
	Geom. Mean	95.4	327	1280	2590	5260
	CV(%)	39.9	26.2	18.7	35.8	29.5
$AUC_{extrapolated}$ (%)	n	6	6	6	6	6
	Geom. Mean	12.6	13.7	9.60	8.52	8.37
	CV(%)	55.3	27.8	15.0	61.0	37.0
C_{max} (nmol/L)	n	6	6	6	6	6
	Geom. Mean	6.05	29.1	181	590	1160
	CV(%)	26.4	35.4	59.1	44.3	28.6
t_{max} (h)	n	6	6	6	6	6

Table S2 **Summary of pharmacokinetic parameters of AZD2423 (young cohorts - single dose, Day 1) (PK analysis set) – Part 1**

Parameter	Statistics	Young AZD2423 (8 mg) N=6	Young AZD2423 (24 mg) N=6	Young AZD2423 (72 mg) N=6	Young AZD2423 (150 mg) N=6	Young AZD2423 (300 mg) N=6
	Minimum	0.710	0.330	0.350	0.360	0.290
	Median	3.11	0.920	0.665	0.670	0.680
	Maximum	4.08	4.05	3.01	1.51	1.49
$t_{1/2\lambda z}$ (h)	n	6	6	6	6	6
	Geom. Mean	28.8	30.9	25.0	27.6	28.8
	CV(%)	27.5	19.7	12.4	35.0	32.0
CL/F (L/h)	n	6	6	6	6	6
	Geom. Mean	197	172	132	136	134
	CV(%)	39.8	26.0	18.6	35.7	29.6
V_Z/F (L)	n	6	6	6	6	6
	Geom. Mean	8170	7660	4750	5420	5550
	CV(%)	42.8	22.3	22.5	22.4	58.8
CL_R (L/h)	n	6	6	4	6	6
	Geom. Mean	9.93	10.7	10.1	11.6	11.6
	CV(%)	22.6	27.3	22.5	52.4	21.3
A_e [0-24] (mg)	n	6	6	4	6	6
	Geom. Mean	0.403	1.49	5.54	12.9	26.0
	CV(%)	31.9	32.4	23.3	38.7	20.7
f_e [0-24] (%)	n	6	6	4	6	6
	Geom. Mean	5.03	6.19	7.68	8.58	8.68
	CV(%)	32.3	32.8	23.7	38.6	20.8

Geom. mean = geometric mean

For E0001082 and E0001088 (young 72 mg AZD2423) the urine PK parameters CL_R, A_e [0-24] and f_e [0-24] on Day 1 are not calculated due to error in collection of urine sample. At 24 hours post-dose (Day 1) Subject E0001082 voided into the container for Subject E0001088. As a result, the 12-24 hour urine collection for Day 1 for Subject E0001082 was incomplete and that for Subject E0001088 was contaminated.

Table S3 **Summary of pharmacokinetic parameters of AZD2423 (young cohorts - multiple dose, Day 14) (PK analysis set) – Part 1**

Parameter	Statistics	Young AZD2423 (8 mg) N=6	Young AZD2423 (24 mg) N=6	Young AZD2423 (72 mg) N=6	Young AZD2423 (150 mg) N=6	Young AZD2423 (300 mg) N=6
$AUC_{\tau,ss}$ (h·nmol/L)	n	5	5	6	6	6
	Geom. Mean	110	434	1630	3350	7550
	CV(%)	14.5	35.7	18.4	34.2	31.5
$C_{max,ss}$ (nmol/L)	n	5	5	6	6	6
	Geom. Mean	9.43	59.3	229	673	1490
	CV(%)	15.5	51.9	38.1	43.7	35.3
$t_{max,ss}$ (h)	n	5	5	6	6	6
	Minimum	0.330	0.650	0.290	0.660	0.330
	Median	3.03	1.02	0.500	0.845	0.505
	Maximum	4.05	3.03	3.03	2.04	0.700
$t_{1/2\lambda z,ss}$ (h)	n	5	5	6	6	6
	Geom. Mean	47.5	52.3	50.5	44.2	46.7
	CV(%)	9.70	13.3	21.5	14.3	14.8
R_{AUC} (1)	n	5	5	6	6	6
	Geom. Mean	1.30	1.26	1.27	1.29	1.44
	CV(%)	14.5	23.8	15.7	23.9	11.9
R_{ac} (AUC) (1)	n	5	5	6	6	6
	Geom. Mean	2.31	2.14	1.93	1.88	1.99
	CV(%)	12.7	24.1	17.5	21.5	12.0
R_{ac} (C_{max}) (1)	n	5	5	6	6	6
	Geom. Mean	1.63	2.05	1.27	1.14	1.29
	CV(%)	31.2	41.4	56.1	58.0	26.4
CL_{ss}/F (L/h)	n	5	5	6	6	6
	Geom. Mean	170	130	104	105	93.3
	CV(%)	14.5	35.7	18.5	34.2	31.5
$C_{avg,ss}$ (nmol/L)	n	5	5	6	6	6
	Geom. Mean	4.60	18.0	67.8	140	315
	CV(%)	14.6	35.6	18.4	34.1	31.4
$C_{min,ss}$ (nmol/L)	n	5	5	6	6	6

Table S3 **Summary of pharmacokinetic parameters of AZD2423 (young cohorts - multiple dose, Day 14) (PK analysis set) – Part 1**

Parameter	Statistics	Young AZD2423 (8 mg) N=6	Young AZD2423 (24 mg) N=6	Young AZD2423 (72 mg) N=6	Young AZD2423 (150 mg) N=6	Young AZD2423 (300 mg) N=6
	Geom. Mean	2.45	8.74	31.2	48.0	98.5
	CV(%)	28.7	32.1	25.7	38.0	26.8
$CL_{R,ss}$ (L/h)	n	5	5	6	6	6
	Geom. Mean	17.8	15.0	16.6	14.4	13.8
	CV(%)	15.3	28.3	42.2	34.4	14.0
$A_{e,ss}$ [0-24] (mg)	n	5	5	6	6	6
	Geom. Mean	0.837	2.76	11.5	20.5	44.5
	CV(%)	5.08	38.3	43.8	47.4	26.2
$f_{e,ss}$ [0-24] (%)	n	5	5	6	6	6
	Geom. Mean	10.4	11.5	15.9	13.6	14.8
	CV(%)	4.90	38.4	43.9	47.5	26.4

Geom. mean = geometric mean
R_{ac} (AUC) = $AUC_{\tau,ss}$ / AUC_{0-24}
R_{ac} (Cmax) = $C_{max,ss}$ / C_{max}
R_{AUC} = $AUC_{\tau,ss}$ / AUC (Time dependency)

Table S4 **Summary of pharmacokinetic parameters of AZD2423 (elderly cohorts - single dose, Day 1) (PK analysis set) – Part 1**

Parameter	Statistics	Elderly AZD2423 (24 mg) N=6	Elderly AZD2423 (300 mg) N=6
AUC (h·nmol/L)	n	6	6
	Geometric Mean	355	7070
	CV(%)	23.9	29.4
$AUC_{extrapolated}$ (%)	n	6	6
	Geometric Mean	13.6	9.44
	CV(%)	24.1	19.2
C_{max} (nmol/L)	n	6	6
	Geometric Mean	43.7	1210
	CV(%)	29.6	63.3

Table S4 Summary of pharmacokinetic parameters of AZD2423 (elderly cohorts - single dose, Day 1) (PK analysis set) – Part 1

Parameter	Statistics	Elderly AZD2423 (24 mg) N=6	Elderly AZD2423 (300 mg) N=6
t_{max} (h)	n	6	6
	Minimum	0.320	0.350
	Median	0.515	0.685
	Maximum	4.05	3.03
$t_{1/2\lambda Z}$ (h)	n	6	6
	Geometric Mean	29.6	27.6
	CV(%)	32.0	12.1
CL/F (L/h)	n	6	6
	Geometric Mean	159	99.8
	CV(%)	23.7	29.5
V_z/F (L)	n	6	6
	Geometric Mean	6770	3970
	CV(%)	38.2	22.2
CL_R (L/h)	n	6	6
	Geometric Mean	6.54	6.91
	CV(%)	32.0	51.1
A_e [0-24] (mg)	n	6	6
	Geometric Mean	0.989	20.8
	CV(%)	18.2	31.4
f_e [0-24] (%)	n	6	6
	Geometric Mean	4.13	6.93
	CV(%)	18.2	31.7

Table S5 Summary of pharmacokinetic parameters of AZD2423 (elderly cohorts - multiple dose, Day 14) (PK analysis set) – Part 1

Parameter	Statistics	Elderly AZD2423 (24 mg) N=6	Elderly AZD2423 (300 mg) N=6
$AUC_{\tau,ss}$ (h·nmol/L)	n	6	6
	Geometric Mean	439	9560
	CV(%)	32.8	23.2
$C_{max,ss}$ (nmol/L)	n	6	6
	Geometric Mean	48.6	1340
	CV(%)	20.8	25.0
$t_{max,ss}$ (h)	n	6	6
	Minimum	0.340	0.350
	Median	3.04	1.02
	Maximum	6.05	3.07
$t_{1/2\lambda z,ss}$ (h)	n	6	6
	Geometric Mean	67.1	48.3
	CV(%)	19.2	9.03
R_{AUC} (1)	n	6	6
	Geometric Mean	1.24	1.35
	CV(%)	12.8	11.3
R_{ac} (AUC) (1)	n	6	6
	Geometric Mean	2.09	1.98
	CV(%)	17.6	8.67
R_{ac} (C_{max}) (1)	n	6	6
	Geometric Mean	1.11	1.11
	CV(%)	27.0	42.1
CL_{ss}/F (L/h)	n	6	6
	Geometric Mean	129	73.7
	CV(%)	33.0	23.2
$C_{avg,ss}$ (nmol/L)	n	6	6
	Geometric Mean	18.3	398
	CV(%)	33.0	23.2
$C_{min,ss}$ (nmol/L)	n	6	6

Table S5 Summary of pharmacokinetic parameters of AZD2423 (elderly cohorts - multiple dose, Day 14) (PK analysis set) – Part 1

Parameter	Statistics	Elderly AZD2423 (24 mg) N=6	Elderly AZD2423 (300 mg) N=6
	Geometric Mean	10.1	135
	CV(%)	33.9	23.4
$CL_{R,ss}$ (L/h)	n	6	6
	Geometric Mean	9.99	11.6
	CV(%)	26.6	27.9
$A_{e,ss}$ [0-24] (mg)	n	6	6
	Geometric Mean	1.87	47.0
	CV(%)	31.2	8.55
$f_{e,ss}$ [0-24] (%)	n	6	6
	Geometric Mean	7.80	15.7
	CV(%)	30.8	8.48

Geom. mean = geometric mean
R_{ac} (AUC) = $AUC_{\tau,ss}$ / AUC_{0-24}
R_{ac} (C_{max}) = $C_{max,ss}$ / C_{max}
R_{AUC} = $AUC_{\tau,ss}$ / AUC (Time dependency)

In general, AZD2423 was rapidly absorbed by young and elderly healthy volunteers after single and multiple dosing of 8 to 300 mg AZD2423. The median times for peak plasma concentration, t_{max} and $t_{max,ss}$, were generally within 0.5 to 1 hours for all dose levels except for the two lowest dose levels where median t_{max} values up to 3 hours were observed. The geometric mean apparent terminal half-life of AZD2423 after single dosing, $t_{1/2\lambda z}$, ranged from 25 to 31 hours, whereas that at steady state, $t_{1/2\lambda z,ss}$, was longer ranging from 44 to 52 hours in young and 48 to 67 hours in elderly healthy volunteers. The increase in $t_{1/2\lambda z,ss}$ on Day 14 may at least in part be considered to be the result of plasma concentrations being monitored for a longer period of time, revealing more of the true terminal elimination phase. A linear regression of the last three C_{trough} values at Days 12, 13 and 14 versus time point confirmed attainment of steady state in each dose group with young and elderly healthy volunteers.

Systemic exposure of single and multiple AZD2423 doses of 8 to 300 mg increased slightly more than dose-proportionally according to the fit of AUC and C_{max} values to a power model. The estimated deviation from dose-proportionality after multiple dosing was higher for C_{max} (point estimate: 1.36; 95% CI: 1.28 – 1.44) than that for AUC (1.18; 95% CI: 1.11 – 1.25). According to the estimated doubling factor $R=2^{\beta}$, doubling of multiple doses led to 2.57- and 2.27-fold increases in $C_{max,ss}$ and $AUC_{\tau,ss}$, respectively.

Exposure to AZD2423 appeared to be independent of time according to the point estimates and the 95% CIs for the ratio $R_{AUC} = AUC_{\tau,ss}/AUC$ (Day 1). The accumulation ratio based on AUC, R_{ac} (AUC) = $AUC_{\tau,ss}/AUC_{0-24}$ (Day 1) indicated an approximately 2-fold accumulation, whereas almost no accumulation can be assumed from the accumulation ratio based on C_{max}, R_{ac} (C_{max}) = $C_{max,ss}/C_{max}$ (Day 1).

Renal clearance accounted only for a small fraction of total clearance after single and multiple dosing. The geometric mean fraction of AZD2423 excreted unchanged in urine within 24 hours after multiple dosing was somewhat higher than the corresponding fraction after single dosing in healthy young and elderly volunteers.

Part 2

In Part 2, AZD2423 was rapidly absorbed by all healthy volunteers after multiple dosing of 100 and 300 mg AZD2423 as indicated by $t_{max,ss}$ values ranging from 0.33 to 1.5 hours. The geometric mean AZD2423 plasma concentration-time profiles after multiple dosing in Part 2 on Day 8 were similar to those obtained in Part 1 on Day 14. The geometric means of $AUC_{\tau,ss}$ and $C_{max,ss}$ after multiple dosing of 300 mg AZD2423 on Day 8 (6690 h·nmol/L and 1430 nmol/L, respectively) were similar to those obtained in Part 1 at the same dose level.

Part 3

The geometric mean AZD2423 plasma concentration-time profiles following single dosing of the tablet and the solution formulation of 40 mg AZD2423 in fasted state are displayed in Figure S3, while those of the tablet in fed and fasted state are shown in Figure S4.

Figure S3 **Plot of mean plasma concentrations (nmol/L) of AZD2423 on log scale versus time for the tablet and solution formulation in fasted state following a single dose administration (PK analysis set) – Part 3**

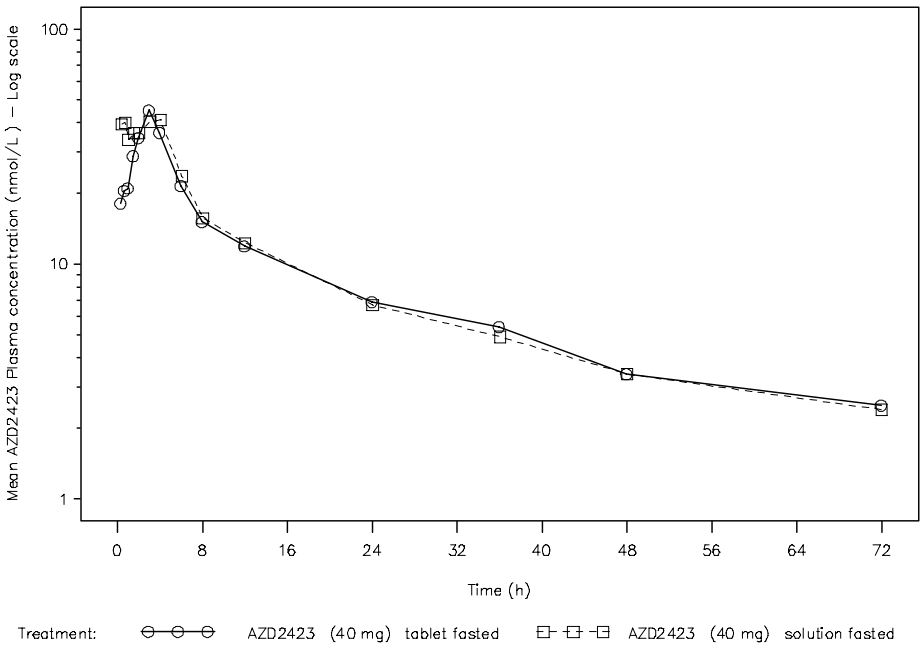
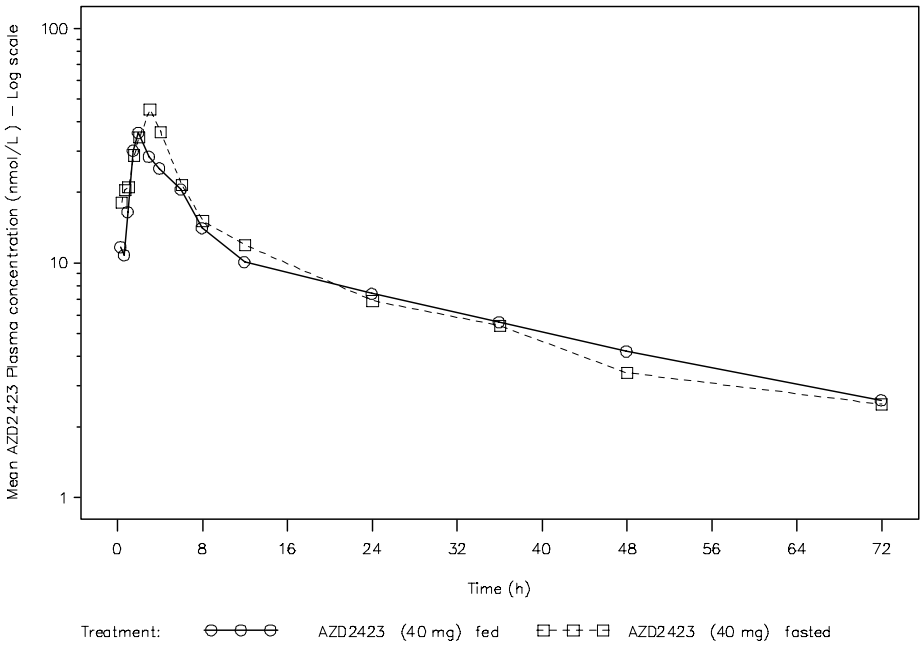


Figure S4 **Plot of mean plasma concentrations (nmol/L) of AZD2423 on log scale versus time for the tablet in fasted and fed state following a single dose administration (PK analysis set) – Part 3**



The shape of the plasma concentration-time curves in Part 3 was generally similar to that in Part 1, although the peak of the mean profile after administration of the tablet formulation in the fed state was somewhat lower than that after fasted administration.

Under fasted conditions, overall exposure to AZD2423 (AUC) for the tablet was comparable to that of the solution and 95% CIs were within the standard bioequivalence limits (0.80 to 1.25). A decrease in peak exposure (C_{max}) was seen for the tablet compared to the solution (19% decrease in mean ratio; lower limit of 95% CI was below the 0.80 to 1.25 range).

The overall exposure to AZD2423 (AUC) after administration of the tablet formulation in the fed state was comparable to that in the fasted state and 95% CIs were within the standard bioequivalence limits. A decrease in peak exposure (C_{max}) was seen for fed compared to fasted administration of the tablet (29% decrease in mean ratio; lower limit of 95% CI was below the 0.80 to 1.25 range).

Summary of pharmacodynamic results (Parts 1 and 2)

Increases from baseline in average plasma CCL2 levels were observed in all AZD2423 dose groups in young and elderly healthy volunteers up to 24 hours following single dosing on Day 1 and up to 168 hours following multiple dosing on Day 14. Geometric mean CCL2 plasma levels increased dose-dependently within 1 hour post-dose and reached peak levels at 6 or 24 hours following single and multiple AZD2423 dosing of 8 to 300 mg in young and elderly volunteers.

CCL2 plasma levels became correlated to AZD2423 plasma concentrations at 6 hours and even more pronounced at 24 hours after single dosing. At steady state, CCL2 plasma levels were correlated to the AZD2423 dose for the entire dose range from 0 to 48 hours post-dose on Day 14. There appears to be also a correlation between CCL2 plasma levels and AZD2423 plasma concentrations up to a dose level of 150 mg, whereas no correlation to AZD2423 plasma concentrations is apparent at a dose level of 300 mg.

Summary of pharmacokinetic/pharmacodynamic relationships (Part 2 only)

AZD2423 concentrations in CSF increased with increasing calculated free plasma concentrations. The geometric mean ratio of AZD2423 in CSF to calculated free plasma concentration was 0.16 at 4 hours post-dose after both 100 mg and 300 mg on Day 8. At 24 hours after the last dose on Day 8 (Day 9), the ratio was 0.41 at 100 mg and 0.43 in the 300 mg dose group.

There appeared to be a correlation between CCL2 levels in CSF and total AZD2423 concentrations in plasma at 4 hours post-dose on Day 8, whereas no correlation was observed at 24 hours after the last dose on Day 8 (Day 9).

Any correlation between CCL2 and AZD2423 concentrations in CSF is difficult to conclude, due to the variability and the limited number of volunteers.

Summary of safety results

No deaths or OAEs occurred in this study. Two young volunteers in Part 1 discontinued the study prematurely due to ventricular extrasystoles, one after receiving a single dose of 8 mg and the other after a single dose of 24 mg AZD2423. Both DAEs were judged by the Investigator as being mild in intensity and possibly causally related to study drug. In Part 2, two volunteers experienced post-dural puncture headache, which were reported as SAEs due to prolonged hospitalisation. These SAEs were judged by the Investigator as being not causally related to the administration of AZD2423, but related to the study procedure (sampling of CSF). Another volunteer in Part 3 discontinued the study prematurely due to frequent mild to moderate gastrointestinal AEs (abdominal pain and diarrhoea), considered by the Investigator to be causally related to study drug, after receiving 7 doses of 300 mg AZD2423.

In total, 150 AEs were reported in 37 of 60 healthy volunteers who were administered 8 to 300 mg AZD2423 in any part of the study, while 18 AEs were reported in 10 of 14 healthy volunteers who received placebo (Part 1 only). The majority of the 150 AEs after AZD2423 dosing in this study were considered by the Investigator to be mild in intensity, 26 AEs to be moderate (9 in Part 1 and 17 in Part 2) and none to be severe. With the exception of GI AEs, the number and incidence of AEs did not show an apparent relation to treatment, AZD2423 dose or age (Part 1).

Gastrointestinal AEs were reported with a higher frequency and severity following a dose of 300 mg AZD2423 compared with lower doses or placebo in both young healthy volunteers (Parts 1 and 2) and elderly healthy volunteers (Part 1 only). This increase in the number and severity of GI AEs at the 300 mg dose led to the conclusion to stop further dose escalation at this dose level, although the MTD was not determined. The most frequent GI AEs after AZD2423 dosing were nausea (25 AEs in 17 volunteers), diarrhoea (12 AEs in 7 volunteers) and vomiting (8 AEs in 4 volunteers), which occurred exclusively in Parts 1 and 2. The most frequent GI AE following placebo in Part 1 was diarrhoea (3 AEs in 3 volunteers). A relation of nausea and vomiting to AZD2423 dosing was evident by their onset time, which frequently coincided with the time of maximum concentrations following single or multiple dosing of AZD2423, and their duration, which was mostly less than 2 hours. There were some indications for the development of tolerance to GI AEs, as nausea and vomiting occurred most frequently after single dosing and was reported by only a few volunteers after more than one week of dosing.

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

Transient increases in ALT were observed in 3 volunteers after 72 and 300 mg AZD2423 and at the follow-up, while transient increases in CRP were observed in 6 volunteers at different AZD2423 dose levels and in 2 volunteers who received placebo.

An isolated decrease in blood pressure was observed in a volunteer on the day of CSF sampling in Part 2 and was associated with a syncope after CSF sampling.