AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00017
Edition Number	1
Date	16 July 2010

A Phase I Open-label, Single-Centre, Single Dose, Two Cohort Crossover Study to Assess the Relative Bioavailability after Oral Administration of AZD9668 Free Base Dosed as a Suspension Compared to AZD9668 Tosylate Salt Dosed as a Tablet

Study dates: First subject enrolled: 16 November 2009
Last subject last visit: 22 December 2009

Phase of development: Clinical pharmacology (I)

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

Study period		Phase of development
First subject enrolled	16 November 2009	I
Last subject completed	22 December 2009	

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 relative systemic bioavailability after oral administration of the free base of AZD9668 dosed as a suspension compared to the tosylate salt of AZD9668 dosed as a tablet formulation at two dose levels	F_{rel} of AZD9668, C_{max}, t_{max}, AUC, AUC_{0-t}, λ_z, $t_{1/2\lambda z}$, CL/F, V_z/F	Pharmacokinetics
Secondary	**Secondary**	
To further investigate safety and tolerability of AZD9668	Adverse events, blood pressure, pulse, 12-lead ECG, haematology, clinical chemistry, and urinalysis	Safety
Exploratory	**Exploratory**	
To collect pharmacogenetic samples for possible retrospective exploratory analysis, to investigate the influence of genotype on drug response (where response was considered to encompass safety, tolerability, PK and pharmacodynamic [PD] response where appropriate).	DNA sequence	Pharmacogenetics

AUC= area under the plasma concentration-time curve from zero to infinity; AUC_{0-t}= area under the plasma concentration-time curve from zero to last quantifiable concentration; CL/F= oral plasma clearance; C_{max}= maximum plasma concentration; ECG= electrocardiogram; F_{rel}= Relative bioavailability; λ_z = smallest disposition rate constant; $t_{1/2\lambda z}$ = terminal half-life; t_{max}= time to C_{max}; V_z/F= oral volume of distribution during terminal phase.
These results of the exploratory analysis do not form part of the CSR or synopsis.

Study design

This was an open-label, single-centre, single-dose, two cohort crossover study to investigate the relative bioavailability of AZD9668 free base, administered via an oral suspension compared to AZD9668 tosylate salt, administered via tablet, and to further evaluate the tolerability and safety of AZD9668 in healthy volunteers. Cohort 1 was dosed with 20 mg of the free base of AZD9668, dosed as a suspension, and 20 mg of the tosylate salt of AZD9668, dosed as a tablet, in a randomised crossover manner; Cohort 2 was dosed with 60 mg of the free base of AZD9668, dosed as a suspension, and 60 mg of the tosylate salt of AZD9668, dosed as a tablet, in a randomised crossover manner.

Target subject population and sample size

A total of 28 healthy, male and female volunteers of non-childbearing potential aged 18 to 55 years inclusive.

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

Table S2 Investigational product

Drug	Formulation	Route of administration	Strength	Dose	Batch number
AZD9668 free base	suspension	oral	2 mg/g	20 mg (Treatment A), 60 mg (Treatment C)	09-006160AZ
AZD9668 tosylate salt	tablet	oral	10 and 30 mg	20 mg (Treatment B), 60 mg (Treatment D)	09-006289AZ (10 mg), 09-005028AZ (30 mg)

The indication of the amount of AZD9668 administered, given as free base or the tosylate salt, referred to the base form, ie similar amounts of the active compound of AZD9668 were given via the tablets or the suspension at both dose strengths.

Duration of treatment

Each healthy volunteer received two single doses of AZD9668 in two treatment periods separated by a wash-out period of at least five days.

Statistical methods

The pharmacokinetic analysis set was based on healthy volunteers with adequate sampling and compliance to treatment. All healthy volunteers who received at least one dose of investigational product and for whom any post-dose data were available were included in the safety population.

Descriptive statistics were used for all parameters in the study. No formal statistical hypothesis testing was performed in this study.

Relative bioavailability (F_{rel}) between oral tablet and suspension formulations of AZD9668 was estimated using an analysis of variance (ANOVA) model with healthy volunteer, formulation, and period as fixed factors in a multiplicative model for AUC or C_{max}. A separate ANOVA model was fitted for each cohort. Relative bioavailability of AZD9668 was estimated for each cohort as the ratio of geometric least squares means (suspension/tablet) from the ANOVA model, ie Treatment A / Treatment B and Treatment C / Treatment D.

Subject population

A total of 28 healthy male volunteers between the age of 29 and 54 years were enrolled and randomised into the study. All healthy volunteers except one received each 2 single doses of the investigational products (IP) during the planned treatment periods and these healthy volunteers completed the study according to the CSP. One healthy volunteer was prematurely discontinued from treatment after administration of Treatment D (60 mg AZD9668 tosylate salt) due to non-compliance, thus he did not receive Treatment C (60 mg AZD9668 free base).

All randomised 28 healthy volunteers were included in the Safety analysis set, while overall 27 healthy volunteers were included in the PK analysis sets.

All healthy volunteers included were well suited for the purpose of this study and were well balanced across all treatment groups in regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

The results of the evaluation of relative systemic bioavailability between AZD9668 free base and tosylate salt following single administration of 20 and 60 mg AZD9668 by an ANOVA are shown Table S3.

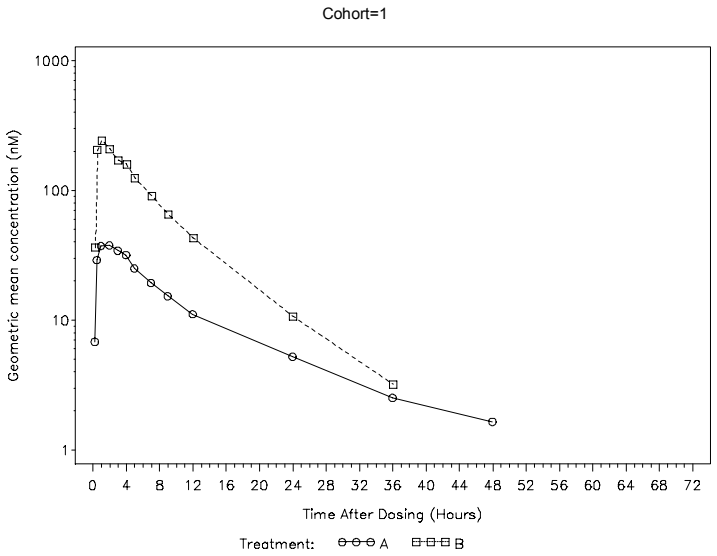
Table S3 Summary of relative bioavailability of AZD9668 free base suspension versus tosylate salt tablet at AZD9668 doses of 20 mg (Treatment A versus B) and 60 mg (Treatment C versus D). (PK analysis set)

Parameter	Unit	Treatments	AZD9668 free base suspension			AZD9668 tosylate salt tablet			90% CI		
			N	Geo. mean	CV (%)	N	Geo. mean	CV (%)	Ratio	Lower	Upper
AUC	(nM*h)	A vs. B	14	485	27.2	14	1829	23.3	0.265	0.224	0.314
		C vs. D	13	643	40.0	13	5039	25.7	0.128	0.102	0.160
C_{max}	(nM)	A vs. B	14	44.7	21.6	14	270	30.0	0.166	0.139	0.197
		C vs. D	13	50.7	33.1	13	650	37.1	0.078	0.061	0.099

Cohort 1: Treatment A (20 mg AZD9668 free base as suspension) and Treatment B (20 mg AZD9668 tosylate salt as tablets). Cohort 2: Treatment C (60 mg AZD9668 free base as suspension) and Treatment D (60 mg AZD9668 tosylate salt as tablets).
AUC= area under the plasma concentration-time curve from zero to infinity; C_{max}= maximum plasma concentration; CI= confidence interval; CV%= coefficient of variation in %; Geo. mean= geometric mean, N= number of healthy volunteers.

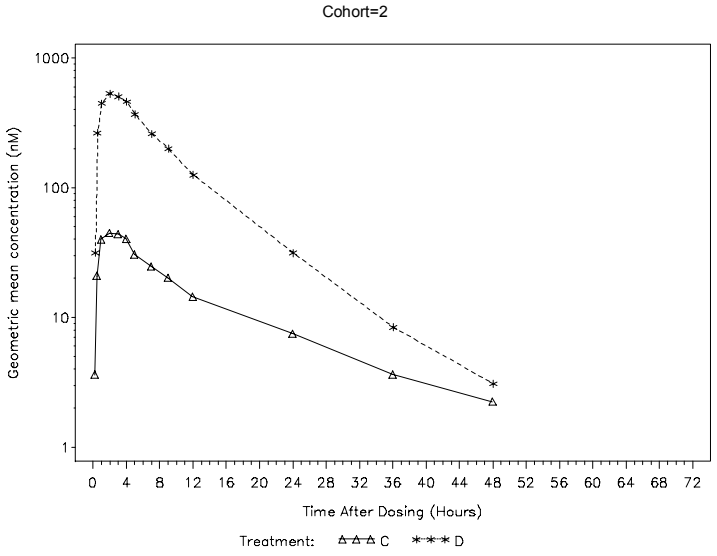
The geometric mean AZD9668 plasma concentration-time profiles (log-linear scale) after single oral dosing of 20 and 60 mg AZD9668 as free base or tosylate salt are presented in Figure S1 and Figure S2. A summary of the derived PK parameters of AZD9668 is shown in Table S4.

Figure S1 **Geometric mean AZD9668 plasma concentration (nM) versus time following 20 mg AZD9668 (Treatment A and B), log-linear scale. (PK analysis set)**



Cohort 1: Treatment A: 20 mg AZD9668 free base as suspension; Treatment B: 20 mg AZD9668 tosylate salt as tablets. The LLOQ (lower limit of quantification) was 1.00 nM

Figure S2 **Geometric mean AZD9668 plasma concentration (nM) versus time following 60 mg AZD9668 (Treatment C and D), log-linear scale. (PK analysis set)**



Cohort 2: Treatment C: 60 mg AZD9668 free base as suspension; Treatment D: 60 mg AZD9668 tosylate salt as tablets. The LLOQ (lower limit of quantification) was 1.00 nM.

Table S4 Summary of PK parameters of AZD9668. (PK analysis set)

Coh.	Trt.	Parameter		N	Geometric mean	CV (%)	Arith. mean	SD	Median	Min	Max
1	A	C_{max}	(nM)	14	44.7	21.6	45.6	9.48	45.4	29.9	61.3
		t_{max}	(h)	14	–	–	–	–	1.00	0.50	4.00
		$AUC_{(0-t)}$	(nM*h)	14	449	28.8	465	124	471	271	724
		AUC	(nM*h)	14	485	27.2	501	127	508	287	753
		$t_{1/2,\lambda z}$	(h)	14	12.7	43.9	14.0	7.08	11.6	6.98	32.7
		V_z/F	(L)	14	1389	51.0	1590	1121	1253	768	5232
		CL/F	(L/h)	14	75.6	27.2	78.2	22.2	72.2	48.7	128
1	B	C_{max}	(nM)	14	270	30.0	280	79.4	270	143	443
		t_{max}	(h)	14	–	–	–	–	1.00	0.48	4.00
		$AUC_{(0-t)}$	(nM*h)	14	1812	23.2	1856	423	1756	1178	2512
		AUC	(nM*h)	14	1829	23.3	1874	428	1771	1185	2543
		$t_{1/2,\lambda z}$	(h)	14	6.33	18.4	6.43	1.21	6.45	4.74	8.71
		V_z/F	(L)	14	183	22.5	187	40.0	194	116	264
		CL/F	(L/h)	14	20.0	23.3	20.5	4.76	20.7	14.4	30.9
2	C	C_{max}	(nM)	13	50.5	33.1	52.9	16.9	53.4	30.3	82.2
		t_{max}	(h)	13	–	–	–	–	2.00	1.00	3.00
		$AUC_{(0-t)}$	(nM*h)	13	582	41.8	624	230	652	285	1001
		AUC	(nM*h)	13	639	40.0	681	235	719	321	1047
		$t_{1/2,\lambda z}$	(h)	13	13.8	55.1	16.1	12.0	12.5	8.24	53.2
		V_z/F	(L)	13	3420	61.3	3996	2551	3247	1373	10730
		CL/F	(L/h)	13	172	40.0	185	78.0	153	105	342
2	D	C_{max}	(nM)	13	654	37.1	697	289	610	415	1470
		t_{max}	(hr)	13	–	–	–	–	1.02	0.50	3.02
		$AUC_{(0-t)}$	(nM*h)	13	4995	25.7	5146	1324	5045	3501	7665
		AUC	(nM*h)	13	5028	25.7	5180	1333	5117	3519	7698
		$t_{1/2,\lambda z}$	(h)	13	6.71	16.9	6.80	1.12	6.48	4.77	8.66
		V_z/F	(L)	13	212	27.3	219	60.3	196	122	352
		CL/F	(L/h)	13	21.9	25.7	22.5	5.56	21.50	14.3	31.3

Cohort 1: Treatment A (20 mg AZD9668 free base as suspension) and Treatment B (20 mg AZD9668 tosylate salt as tablets). Cohort 2: Treatment C (60 mg AZD9668 free base as suspension) and Treatment D (60 mg AZD9668 tosylate salt as tablets).
Arith. mean= arithmetic mean; AUC= Area under plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$= Area under plasma concentration time curve from zero to the time of the last quantifiable concentration; CL/F= total apparent drug clearance; C_{max}= maximum plasma (peak) drug concentration; Coh.= cohort; CV= coefficient of variation; λ_z= terminal rate constant; Max= maximum; Min= minimum; SD= standard deviation;

$t_{1/2,\lambda z}$= terminal elimination half-life; t_{max}= time of the maximum plasma concentration; Trt.= treatment; Vz/F= apparent volume of distribution.

Relative bioavailability of AZD9668 administered as free base was significantly lower compared with administration as tosylate salt, both, at a dose strength of 20 mg and even more pronounced at 60 mg AZD9668. All corresponding 90% CIs were below the standard bioequivalence limits (80%, 125%). After administration of 20 and 60 mg AZD9668 free base the AUC of AZD9668 was 26.5% and 12.8%, respectively, and for C_{max} 16.6% and 7.8% of the systemic exposure observed after administration of AZD9668 tosylate salt.

Both, AZD9668 free base and tosylate salt were rapidly absorbed from the gastrointestinal tract and median t_{max} was reached after 1 or 2 hours. The apparent terminal half-life of AZD9668 was independent from dose about 6.5 hours following administration as tosylate salt and apparently about 13 hours following administration as free base. Apparently, absorption of AZD9668 free base is sustained and the absorption kinetics is the rate-determining step. Thus, the apparent terminal phase characterised by steady decline of AZD9668 plasma concentration is not a reflection of the terminal half-life of the compound but rather the absorption half-life ("flip-flop" kinetics).

The increase in systemic exposure (C_{max} and AUC) to AZD9668 following administration as free base was not proportional to the dose.

Summary of safety results

Overall, 7 treatment-emergent AEs were reported by 5 subjects, all of mild intensity, with 4 AEs considered by the Investigator to be related to AZD9668 (headache, maculo-papular rash, abdominal pain, nausea). There was no relevant difference in the frequency of subjects reporting AEs on AZD9668 either given the free base or the tosylate salt.

There were no deaths, other SAEs, AEs leading to withdrawal from the study, or other significant AEs.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG and physical examination.