AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00007
Edition Number	1
Date	22 July 2010

An Open-label, Single-Centre, 3-way Single Dose Crossover Study to Assess the Relative Bioavailability After Oral Administration of a Tablet Variant of AZD9668 compared to AZD9668 Tablets and to Further Investigate the Safety and Tolerability of AZD9668 in Healthy Subjects

Study dates: First subject enrolled: 16 November 2009
Last subject last visit: 30 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

The first healthy volunteer signed informed consent for the study on 16 November 2009, and the last healthy volunteer completed the study on 30 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 a tablet variant of AZD9668 compared to AZD9668 tablets	Relative bioavailability of AZD9668 (F_{rel}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from zero to infinity (AUC), area under the plasma concentration-time curve from zero to last quantifiable concentration (AUC_{0-t}), smallest disposition rate constant (λ_z), terminal half-life ($t_{1/2\lambda z}$), oral plasma clearance (CL/F), oral volume of distribution during terminal phase (V_z/F) of AZD9668	Pharmacokinetics
Secondary	**Secondary**	
To further investigate the safety and tolerability of AZD9668	Adverse events, vital signs, 12-lead ECG, haematology, clinical chemistry and urinalysis	Safety and tolerability
Exploratory[a]	**Exploratory**	
To collect pharmacogenetic samples for possible retrospective exploratory analysis to investigate the influence of genotype on drug response (where response is considered to encompass safety, tolerability, pharmacokinetic and pharmacodynamic response where appropriate)	Pharmacogenetics (planned analysis)	Pharmacogenetics

a Exploratory pharmacogenetic data are not reported in the CSR or in the CSR synopsis.

Study design

The clinical study was an open-label, randomised, 3-way crossover single-dose study to investigate the relative bioavailability of AZD9668, administered by different tablets and to further evaluate the tolerability and safety of AZD9668 in healthy volunteers. Fifteen male and female volunteers received 60 mg AZD9668 (batch DLE 494), 60 mg AZD9668

(DLF 497) and 60 mg AZD9668 tablet Variant 1 in three treatment periods on three separate occasions.

Target subject population and sample size

A total of 15 healthy male and female volunteers aged 18 to 54 years inclusive were randomised to yield data from at least 12 healthy volunteers.

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

Table S2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD9668	30 mg tablet batch DLE 494[a], single oral dose of 60 mg	AstraZeneca	D0900131	09-004267AZ
AZD9668	30 mg tablet batch DLF 497[b], single oral dose of 60 mg	AstraZeneca	D0900131	09-005028AZ
AZD9668	30 mg tablet Variant 1[c], single oral dose of 60 mg	AstraZeneca	D0900452	09-006270AZ

a Treatment A
b Treatment B: this batch had the same composition as batch DLE 494 but had a slightly less rapid in vitro dissolution profile compared to batch DLE 494
c Treatment C (reference): this batch had a slower *in vitro* dissolution profile compared to both batches of AZD9668 tablets.

Duration of treatment

Each healthy volunteer received 3 single doses of AZD9668, each separated by a wash-out period of at least five days.

Statistical methods

Descriptive statistics were used for all parameters in the study.

No formal statistical hypothesis testing was performed in this study.

The pharmacokinetic analysis set was based on healthy volunteers with adequate sampling and compliance to the treatment. All healthy volunteers who received at least one dose of the investigational product and for whom any post-dose data were available were included in the safety population. Relative bioavailability between oral tablet formulations of AZD9668 was estimated using an analysis of variance model with healthy volunteer, formulation, and period as fixed factors in a multiplicative model for AUC. PK parameters after administration of AZD9668 were described with mean.

Subject population

The healthy male and female volunteers enrolled in this study were between the age of 20 and 54 years and were found eligible for this Phase I clinical pharmacology study according to all criteria defined in the CSP.

The healthy volunteers were well balanced in regards to demographic and baseline characteristics across the three sequence groups. However, it was not intended and not possible to balance the number of male and female healthy volunteers overall or between the sequence groups.

Summary of pharmacokinetic results

The results of the evaluation of relative bioavailability of AZD9668 60 mg between the three tablet formulations batch DLE 494, batch DLF 497 and reference Variant 1 by an ANOVA are shown in Table S3.

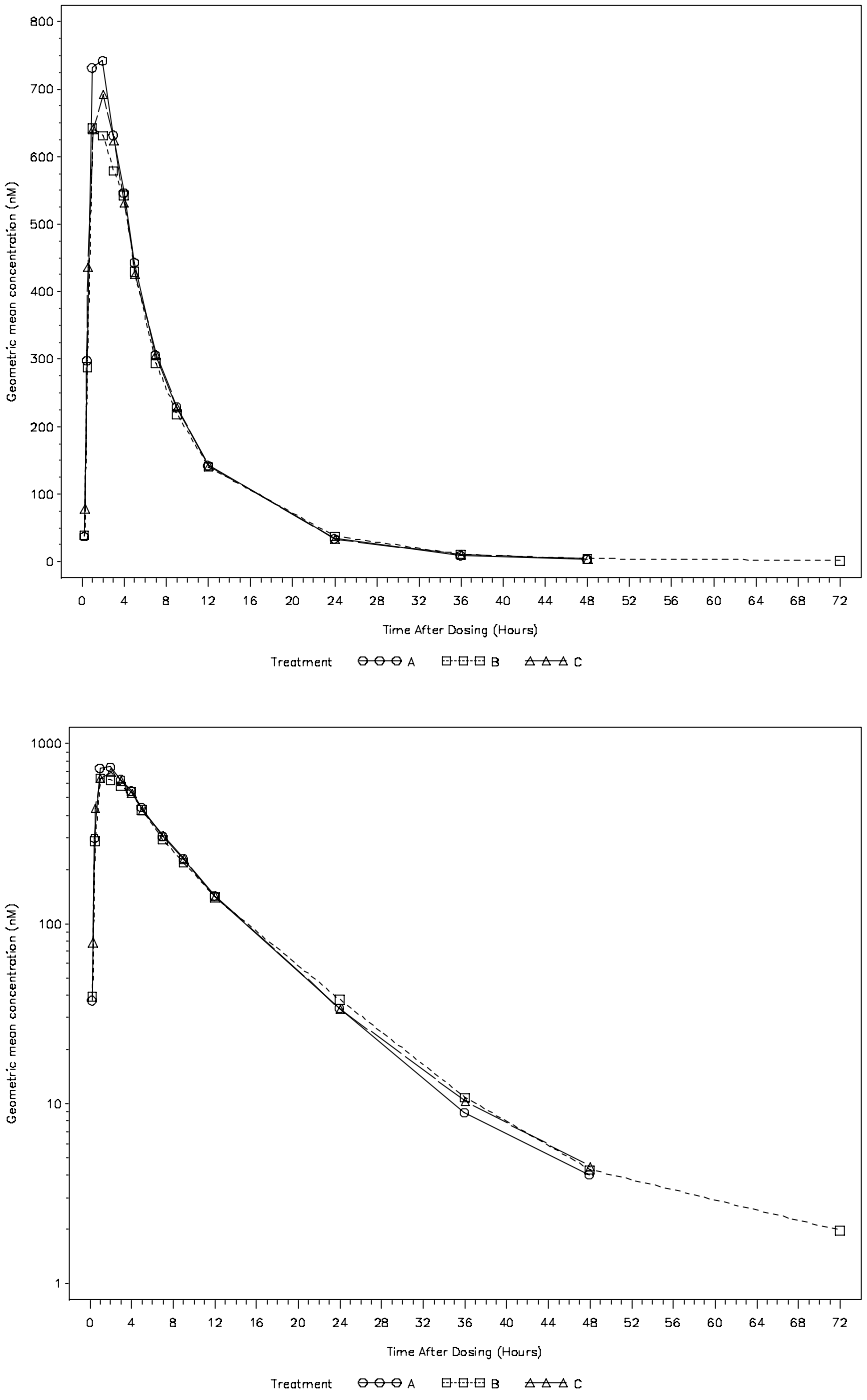
Table S3 Relative bioavailability (PK analysis set)

Parameter	Unit	Geometric means			F_{rel} (Test : Reference)			
		Treatments					90% CI	
		A	B	C	Ratio	Estimate	Lower	Upper
AUC	nM·h	6056	5793	5973	A : C	1.01	0.863	1.19
					B : C	0.970	0.825	1.14
					A : B	1.05	0.889	1.23
C_{max}	nM	891	745	813	A : C	1.10	0.890	1.35
					B : C	0.917	0.744	1.13
					A : B	1.20	0.971	1.47

Treatment A: 2x30 mg AZD9668 tablet batch DLE 494
Treatment B: 2x30 mg AZD9668 tablet batch DLF 497 (slightly less rapid in vitro dissolution)
Treatment C: 2x30 mg AZD9668 tablet Variant 1 (slower in vitro dissolution) used as reference
F_{rel} = relative bioavailability; CI = confidence interval; AUC = area under the plasma concentration-time curve from zero to infinity; C_{max}= observed peak or maximum plasma concentration

The geometric mean AZD9668 plasma concentration-time profiles in linear and log-linear scale are presented in Figure S1. A summary of the derived PK parameters of AZD9668 in plasma is presented in Table S4.

Figure S1 **Geometric mean plasma concentrations (nM) of AZD9668 against time, linear (top) and log-linear (bottom) scales (PK analysis set)**



Treatment A: 2x30 mg AZD9668 tablet batch DLE 494
Treatment B: 2x30 mg AZD9668 tablet batch DLF 497 (slightly less rapid in vitro dissolution)
Treatment C: 2x30 mg AZD9668 tablet Variant 1 (slower in vitro dissolution) used as reference
The LLOQ (lower limit of quantification) was 1.00 nM.

Table S4 Summary of PK parameters of AZD9668 in plasma (PK analysis set)

Treat-ment	Parameter		N	Geometric mean	CV (%)	Arithmetic mean	SD	Median	Min	Max
A	**C_{max}**	(nM)	15	891	31.0	930	282	844	576	1420
	t_{max}	(h)	15	NA	NA	NA	NA	1.02	0.500	2.00
	$AUC_{(0-t)}$	(nM·h)	15	6017	22.5	6158	1377	5768	4342	8528
	AUC	(nM·h)	15	6056	22.5	6198	1384	5792	4375	8590
	λ_z	(h^{-1})	15	0.0750	46.4	0.0817	0.0333	0.0894	0.0312	0.157
	$t_{1/2\lambda z}$	(h)	15	9.24	46.4	10.2	4.87	7.76	4.41	22.2
	V_z/F	(L)	15	242	47.0	268	140	234	120	652
	CL/F	(L/h)	15	18.2	22.5	18.6	4.06	19.0	12.8	25.1
B	**C_{max}**	(nM)	15	745	35.8	788	274	731	418	1390
	t_{max}	(h)	15	NA	NA	NA	NA	1.02	0.50	4.00
	$AUC_{(0-t)}$	(nM·h)	15	5748	28.0	5955	1661	5321	3859	9576
	AUC	(nM·h)	15	5793	28.0	6001	1668	5353	3877	9628
	λ_z	(h^{-1})	15	0.0702	46.9	0.0765	0.0311	0.0706	0.0254	0.123
	$t_{1/2\lambda z}$	(h)	15	9.87	46.9	10.9	5.58	9.82	5.65	27.3
	V_z/F	(L)	15	270	52.8	303	149	269	123	641
	CL/F	(L/h)	15	19.0	28.0	19.7	5.25	20.5	11.4	28.4
C	**C_{max}**	(nM)	15	813	37.7	864	318	744	370	1590
	t_{max}	(h)	15	NA	NA	NA	NA	1.02	0.500	2.98
	$AUC_{(0-t)}$	(nM·h)	15	5922	28.8	6148	1762	5818	3585	9646
	AUC	(nM·h)	15	5973	28.6	6197	1760	5872	3637	9666
	λ_z	(h^{-1})	15	0.0658	47.1	0.0716	0.0275	0.0790	0.0289	0.166
	$t_{1/2\lambda z}$	(h)	15	10.5	47.1	11.6	5.73	8.77	5.97	24.0
	V_z/F	(L)	15	280	58.2	325	200	224	155	745
	CL/F	(L/h)	15	18.4	28.6	19.1	5.29	18.7	11.4	30.2

Treatment A: 2x30 mg AZD9668 tablet batch DLE 494
Treatment B: 2x30 mg AZD9668 tablet batch DLF 497 (slightly less rapid in vitro dissolution)
Treatment C: 2x30 mg AZD9668 tablet Variant 1 (slower in vitro dissolution) used as reference
C_{max} = maximum plasma concentration; t_{max} = time to C_{max}; 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; λ_z = smallest disposition rate constant; $t_{1/2\lambda z}$ = terminal half-life; V_z/F = oral volume of distribution during terminal phase; CL/F = oral plasma clearance
NA = not applicable

The assessment of relative bioavailability between the three tablet formulations of AZD9668 indicated bioequivalence in terms of AUC as all estimated F_{rel} values for AUC were close to unity and the corresponding 90% CIs were all within the bioequivalence standard range (Table S3). The estimated F_{rel} values for C_{max} also indicated a comparable bioavailability of the three formulations, although the 90% CIs were slightly outside the bioequivalence standard range. However, confidence intervals for C_{max} were expected to be larger than those for AUC as the inter-individual variability of C_{max} values for batch DLE 494, batch DLF 497 and reference Variant 1 was higher than that of the corresponding AUC data.

The geometric mean plasma concentration-time profiles of AZD9668 following treatment with 60 mg AZD9668 of batch DLE 494, batch DLF 497 and reference Variant 1 were very similar (Figure S1).

Median t_{max} of AZD9668 was 1.02 hours after each of the three formulations, while individual t_{max} values ranged from 0.500 to 4.00 hours overall (Table S4).

The geometric mean AZD9668 C_{max} values ranged from 745 to 891 nM, while individual C_{max} values ranged from 370 to 1590 nM across the three tablet formulations of AZD9668 (Table S4). None of the healthy volunteers appeared to be an outlier with regard to AZD9668 C_{max} after any of the three tablet formulations.

The geometric mean $AUC_{(0\text{-}t)}$ ranged from 5748 to 6017 nM·h (individual values ranged from 3585 to 9646 nM·h) across the three AZD9668 tablet formulations. Geometric mean AUC values were only slightly higher than $AUC_{(0\text{-}t)}$ values thus indicating almost complete elimination of AZD9668 from plasma within the observation period. The CV (%) of AUC of 22.5% to 28.6% was lower than that of C_{max} (Table S4).

There were no apparent differences in the geometric mean apparent terminal half-life of the three AZD9668 formulations, $t_{1/2\lambda z}$, which ranged from 9.24 to 10.5 hours. The CV (%) of $t_{1/2\lambda z}$ was 46.4% to 47.1% (Table S4).

Geometric mean oral plasma clearance, CL/F, of AZD9668 was 18.2 to 19.0 L/h with individual values ranging from 11.4 to 30.2 L/h across the three tablet formulations of AZD9668 (Table S4).

There was also no notable difference in the apparent oral volume of distribution, V_Z/F, of the three AZD9668 tablet formulations, which ranged from 242 to 280 L. The CV (%) of V_Z/F was 47.0% to 58.2% (Table S4).

Summary of safety results

Overall, 11 treatment-emergent AEs were reported by 5 (33%) different healthy volunteers, most of mild and one of moderate intensity. A total of 5 AEs were considered by the Investigator to be related to AZD9668 including headache (4 AEs) and dizziness.

There was no remarkable difference in the frequency of healthy volunteers reporting AEs between the three oral tablet formulations of AZD9668, although this frequency was higher

after treatment with batch DLF 497 (Treatment B) relative to batch DLE 494 (Treatment A) and Variant 1 (Treatment C).

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.