AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9668
Study Code	D0520C00021
Edition Number	1
Date	2 March 2011

An Exploratory Study to Assess the Absolute Bioavailability of a Single Oral Dose of AZD9668 with Respect to an Intravenous Microdose of [^{14}C]AZD9668 in Healthy Male Subjects

Study dates: First subject enrolled: 1 June 2010
Last subject last visit: 21 June 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(s)

One clinical unit in the United Kingdom

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the absolute bioavailability and to evaluate the PK parameters of a single oral dose and a radiolabelled intravenous microdose of [^{14}C]AZD9668	PK parameters for oral AZD9668: AUC, AUC_{0-t}, C_{max}, $t_{1/2}$, t_{max}, λ_z, MRT and F	Pharmacokinetic
	PK parameters for intravenous [^{14}C]AZD9668: AUC, AUC_{0-t}, C_{max}, $t_{1/2}$, MRT, CL, λ_z, V_z, V_{ss} and F	Pharmacokinetic
Secondary	**Secondary**	
To investigate the safety and tolerability of AZD9668	Adverse events, clinical chemistry, haematology, urinalysis, vital signs, electrocardiogram, physical examination	Safety
Exploratory	**Exploratory**	
To collect blood/plasma samples for possible retrospective metabolism characterisation	NA	Pharmacogenetic
To collect pharmacogenetic samples for possible retrospective exploratory pharmacogenetic analysis to investigate the influence of genotype on drug response where response is considered to encompass safety, tolerability, PK and PD response, where appropriate	NA	Pharmacogenetic

Exploratory results are not reported in this Clinical study report.

λ_z: Apparent terminal rate constant; 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 the last measurable concentration; CL: Total body clearance; C_{max}: Maximum plasma concentration; F: Absolute bioavailability; MRT: Mean residence time; NA: Not applicable; PD: Pharmacodynamics; PK: Pharmacokinetics; $t_{1/2}$: Apparent terminal half-life; t_{max}: Time to reach maximum plasma concentration; V_{ss}: Volume of distribution at steady state; V_z: Volume of distribution.

Study design

This was an open-label study conducted at 1 clinical unit in 6 healthy male subjects. All subjects received a single 60 mg oral dose of AZD9668 (2 x 30 mg tablets) and a 60 μg intravenous microdose of [^{14}C]AZD9668, 1.25 hours later.

The study comprised 3 visits: Visit 1 (enrolment), at least 21 days before Visit 2; Visit 2 (1 treatment day and sample collection period from Days 2 to 4); and Visit 3 (follow-up), 5 to 7 days after the last sample collection.

Target subject population and sample size

Six healthy males aged 18 to 65 years (inclusive) with a body mass index of 18 to 30 kg/m^2 (inclusive) and a weight of 50 to 100 kg (inclusive) who had provided informed consent.

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

Table S2 Investigational products

Investigational product	Dosage form, strength and route of administration	Manufacturer	Batch number
AZD9668	Film-coated, oral tablet, 30 mg	AstraZeneca	09-004267AZ
[^{14}C]AZD9668	Tosylate drug substance	AstraZeneca	EN02961-62-03
[^{14}C]AZD9668	Intravenous solution	AstraZeneca	105329/C/01
[^{14}C]AZD9668	Intravenous subject syringes	AstraZeneca	105329/C/01-1 105329/C/01-2 105329/C/01-3 105329/C/01-4 105329/C/01-5 105329/C/01-6

Duration of treatment

Single oral dose

Single intravenous dose

Statistical methods

All data are presented by treatment, ie, oral and intravenous. Demography and baseline data were summarised and listed using appropriate summary statistics. All oral and intravenous pharmacokinetic (PK) data were listed and summarised using standard summary statistics. All safety data were summarised by descriptive statistics. The safety data address the secondary objective to assure the safety of all subjects by assessment of adverse events (AEs), laboratory measurements, vital signs and electrocardiogram (ECG).

All subjects who received AZD9668 and had at least 1 measured AZD9668 plasma concentration at a scheduled PK time point were included in the PK analysis set.

All subjects who received AZD9668 and for whom any post-dose data are available were included in the safety analysis set.

Subject population

Enrolled: 6 subjects

Randomised: 6 subjects

Completed: 6 subjects

Summary of pharmacokinetic results

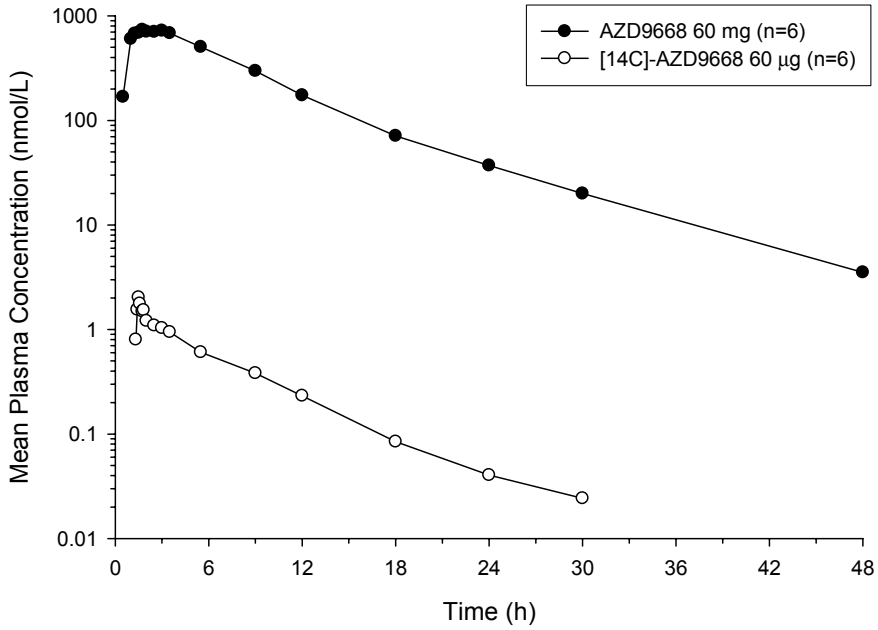
The patterns of the oral and intravenous concentration-time profiles were similar. In particular, the elimination portions of the concentration-time curves were nearly parallel for the two routes of administration. The 1000-fold difference in dose resulted in a similar difference in systemic exposure. AZD9668 and [^{14}C]AZD9668 plasma concentration data are summarized in Table S3 at selected time points through 24 hours. Geometric mean AZD9668 and [^{14}C]AZD9668 concentration-time profiles are shown in Figure S1.

Table S3 Summary of AZD9668 and [^{14}C]AZD9668 plasma concentration data at selected time points through 24 hours (nmol/L)

	Scheduled Time (h)								
	1.5	**1.75**	**2**	**3**	**5.5**	**9**	**12**	**18**	**24**
AZD9668 (60 mg oral)									
N	6	6	6	6	6	6	6	6	6
Mean	736	772	733	728	508	303	177	74.3	39.1
Minimum	404	397	454	604	441	241	133	47.3	21.7
Maximum	1100	1080	1040	889	594	393	226	115	59.4
Geo. Mean	690	735	707	723	505	298	174	71.2	37.1
Geo. CV%	42.3	37.0	30.5	13.5	11.2	19.6	20.8	31.8	37.2
[^{14}C]AZD9668 (60 µg IV)									
N	6	6	6	6	6	6	6	6	6
Mean	2.66	1.61	1.22	1.04	0.612	0.395	0.242	0.0892	0.0446
Minimum	0.245	0.589	1.05	0.812	0.472	0.241	0.131	0.0488	0.0156
Maximum	4.12	2.11	1.41	1.30	0.764	0.500	0.324	0.149	0.0713
Geo. Mean	2.03	1.49	1.21	1.03	0.606	0.383	0.232	0.0845	0.0404
Geo. CV%	141.9	50.0	11.4	16.9	15.7	29.4	34.7	37.3	56.5

Note: Scheduled times are relative to time of oral dose (end of infusion occurred at 1.5 hours).

Figure S1 Geometric mean AZD9668 and [^{14}C]AZD9668 plasma concentration-time profiles



Oral bioavailability of AZD9668 was approximately 80% with an average mean absorption time (MAT) following oral administration of about 2.4 hours. AZD9668 half-life was similar following oral and intravenous administration (~6 to 7 hours). Table S4 summarizes key AZD9668 PK parameters following both routes of administration.

Table S4 Summary of AZD9668 and [^{14}C]AZD9668 plasma pharmacokinetic parameters

	AUC (nmol·h/L)	C_{max} (nmol/L)	t_{max}[a] (h)	$t_{1/2}$ (h)	MRT[a] (h)	MAT[a] (h)	F (%)
AZD9668 (60 mg oral)							
N	6	6	6	6	6	5	6
Mean	6930	966	1.25	7.22	7.83	2.39	79.1
Minimum	5400	737	0.50	6.12	6.53	1.29	68.8
Maximum	8180	1380	3.00	9.03	10.51	3.12	89.8
Geo. Mean	6870	941	--	7.16	--	--	78.8
Geo. CV%	14.4	25.0	--	13.4	--	--	9.5
[^{14}C]AZD9668 (60 µg intravenous)							
N	6	6	6	6	6		
Mean	8.84	2.87	1.50	6.48	6.83		
Minimum	6.54	1.30	1.42	3.80	4.58		
Maximum	10.8	4.12	3.00	10.1	7.88		
Geo. Mean	8.72	2.71	--	6.23	--		
Geo. CV%	18.1	41.8	--	31.8	--		

a Median is presented for t_{max}, MRT and MAT. Sampling times for intravenous administration are relative to the oral dose. Time of maximum concentration for intravenous administration occurred at the end of infusion (1.5 hours after the oral dose).

MAT = MRToral-MRTiv,parent; F = [(AUCoral/AUCiv,parent) x (DOSEiv/DOSEoral)] x 100

Approximately 75% of the total plasma radioactivity was accounted for by the radiolabelled parent compound based on $AUC_{(0-24)}$ ratios. Both [^{14}C]-Total and [^{14}C]AZD9668 have a large volume of distribution, 162 L and 82 L, respectively, suggesting distribution outside the central compartment. The half-life for [^{14}C]-Total was approximately 3-fold longer than the radiolabelled parent compound. Table S5 summarizes key [^{14}C]-Total and [^{14}C]AZD9668 PK parameters following intravenous administration.

Table S5 Summary of [^{14}C]-Total and [^{14}C]AZD9668 plasma pharmacokinetic parameters following a 60 µg intravenous dose

	AUC (nmol·h/L)	$AUC_{(0-24)}$ (nmol·h/L)	C_{max} (nmol/L)	t_{max}[a] (h)	t1/2 (h)	CL (L/h)	Vss (L)	$AUC_{(0-24)}$[b] Ratio	C_{max}[b] Ratio
[14C] Total									
N	6	6	6	6	6	6	6	6	6
Mean	16.0	11.3	2.71	1.50	23.0	6.92	163	0.740	1.08
Minimum	14.6	9.96	1.07	1.42	14.7	5.89	142	0.598	0.815
Maximum	18.7	12.4	3.54	3.50	29.8	7.51	192	0.871	1.21
Geo. Mean	15.9	11.3	2.53	--	22.1	6.90	162	0.736	1.07
Geo. CV%	9.0	8.1	46.3	--	32.1	8.8	11.2	12.2	14.9
[14C]-AZD9668									
N	6	6	6	6	6	6	6		
Mean	8.84	8.38	2.87	1.50	6.48	12.8	82.6		
Minimum	6.54	6.46	1.30	1.42	3.80	10.2	75.6		
Maximum	10.8	10.1	4.12	3.00	10.1	16.8	88.1		
Geo. Mean	8.72	8.30	2.71	--	6.23	12.6	82.4		
Geo. CV%	18.1	15.9	41.8	--	31.8	17.9	6.8		

a Median is presented for t_{max}. Sampling times for intravenous administration are relative to the oral dose. Time of maximum concentration occurred at the end of infusion (1.5 hours after the oral dose).
b [^{14}C] AZD9668/Total [^{14}C] $AUC_{(0-24)}$ and C_{max} Ratio.

Summary of safety results

No deaths, serious adverse events (SAEs), discontinuation of the investigational product (IP) due to an AE (DAE) or severe AEs were reported. Ten treatment-emergent AEs (TEAEs) were reported for 5 subjects (83%) of which 3 TEAEs, reported for 2 subjects (33%), were considered to be causally related to the IP. Headache, in the System Organ Class Nervous system disorders, was the most frequently reported Preferred Term.

No relevant changes or values were observed in clinical chemistry, haematology or urinalysis variables, in vital signs measurements or in physical examination findings. No clinically significant ECG evaluations were reported.