AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9742
Study Code	D2690C00008
Edition Number	1
Date	29 November 2010

A Phase I, Single Center, Open Label, 2-consecutive-group, 2-period, 1-sequence Crossover Study to Assess the Effect of Diltiazem (Cardizem®), a Moderate CYP3A4 Inhibitor, or Ketoconazole, a Potent CYP3A4 Inhibitor, on the Pharmacokinetics of a Single Intravenous Dose of 100 mg AZD9742 Administered as a 2-hour Infusion in Healthy Young Male and Female Volunteers

Study dates: First subject enrolled: 28 May 2010
Last subject last visit: 02 August 2010

Phase of development: Clinical pharmacology (I)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

The study was conducted at a single center:

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**	
The primary objective was to examine the effect of coadministration of CYP3A inhibitors (diltiazem or ketoconazole) on the pharmacokinetics of AZD9742.	C_{max}, t_{max}, AUC, $AUC_{(0\text{-}t)}$, $t_{½\lambda z}$, V_{ss}, CL, CL_R, f_e of AZD9742 $C_{(3h)}$ and $C_{(2h)}$ of diltiazem and ketoconazole, respectively.	Pharmacokinetic
Secondary	**Secondary**	
The secondary objective was to assess the safety and tolerability of AZD9742 when coadministered with diltiazem or ketoconazole.	Adverse events, supine and standing blood pressure and pulse rate, respiratory rate, weight, oral temperature, electrocardiogram variables, telemetry, physical examination, clinical laboratory variables, and fingerstick blood glucose	Safety
Exploratory	**Exploratory**	
Collect blood samples for deoxyribonucleic acid extraction and storage for future possible exploratory research into genes that may influence response ie, distribution, safety, tolerability, and efficacy of AZD9742 treatment.	Deoxyribonucleic acid exploratory research	Pharmacogenetic
Collect and store plasma serum samples from healthy young volunteers for possible exploratory biomarker analysis.	Biomarker exploratory research	Pharmacodynamic
Collect plasma and urine samples to allow possible investigation of whether AZD9742 metabolites present are different in the presence and absence of CYP3A inhibitors.	Metabolite exploratory research	Metabolites

Study design

This drug-drug interaction study was conducted as a single center, open-label, 2-group, 2-period, 1-sequence crossover study to examine the effect of coadministration of diltiazem or ketoconazole on the pharmacokinetics of AZD9742. Approximately 28 healthy volunteers

were assigned to 1 of 2 treatment groups; each consisted of 14 volunteers to ensure completion of at least 12 volunteers per group.

Volunteers from both Group 1 and Group 2 received a single dose of 100 mg AZD9742 via 2-hour intravenous infusion on Day 1, followed by a 72-hour washout period.

In Group 1, diltiazem 240 mg was administered orally with approximately 240 mL of water once daily starting on Day 4 for 14 consecutive days. Only on Day 11, a single 100 mg 2-hour intravenous infusion dose of AZD9742 was coadministered after diltiazem administration.

In Group 2, ketoconazole 200 mg was administered orally with approximately 240 mL of water every 12 hours starting on Day 4 for 10 consecutive days in which on Day 13, only the morning dose was administered. Only on Day 7, a single 100 mg 2-hour intravenous infusion dose of AZD9742 was coadministered after the morning dose of ketoconazole.

Target subject population and sample size

The target population was healthy male and female volunteers (of nonchildbearing potential), as judged by the Investigator, aged 23 to 45 years inclusive, with a body mass index between 18 and less than 30.5 kg/m^2. No female volunteers participated in this study.

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

AZD9742 100 mg (20 mg/mL, diluted for intravenous infusion), administered as a 2-hour infusion once daily, Lot Number 10-002864AZ.

Ketoconazole 200 mg tablet (00378-0261-01), administered orally twice daily, Lot Number 3016461.

Diltiazem 240 mg tablet (Cardizem® LA, 00074-3062-90), administered orally once daily, Lot Number 09M005P.

Duration of treatment

The total duration of participation from screening to poststudy follow-up was approximately 57 days for each volunteer in Group 1 and 53 days for those in Group 2. Study time included a screening visit within 28 days prior to first dose (Visit 1), a confinement/residential period (Visit 2) of 19 days/18 nights and 15 days/14 nights for volunteers in Group 1 and Group 2, respectively, and a poststudy follow-up visit 5 to 10 days after discharge (Visit 3).

Statistical methods

Pharmacokinetic parameters were summarized using descriptive statistics. Amounts of AZD9742 and fractions of the dose recovered in the urine were reported for each collection interval and also cumulatively. For t_{max}, only n (number of observations), minimum, median, and maximum were reported.

Geometric mean and individual concentration-time AZD9742 profiles were presented both on linear and semi-logarithmic scale. Geometric mean figures were presented by group and day. Diltiazem and ketoconazole concentrations collected respectively at 3 hours and 2 hours postdose were plotted against study day. Figures of AZD9742 C_{max} and AUC on Day 1 (AZD9742 alone) and on Day 11 (coadministration with diltiazem) or on Day 7 (coadministration with ketoconazole) were presented.

Pharmacokinetic comparisons of test treatments (AZD9742 plus diltiazem and AZD9742 plus ketoconazole) to the corresponding reference treatment (AZD9742 alone) in each group were assessed separately. The AZD9742 pharmacokinetic parameters AUC and C_{max} for each of the interaction test treatments were compared with the pharmacokinetic parameters for the reference treatment. Comparisons between the test and reference treatments were made by using an analysis of variance model for each pharmacokinetic parameter (AUC and C_{max}) in each group. Parameters were analyzed on the natural log scale with terms for volunteer and treatment. The results of the analysis were presented in terms of geometric least-squares means, treatment effect (ratio of geometric least-squares means) and 90% confidence interval for the treatment effect. If the 90% confidence interval was completely contained within the limits (0.7, 1.43), then no interaction was concluded.

Pharmacodynamic evaluation was not planned. Any data generated from the biomarker analyses were reported separately.

Safety data were summarized using descriptive statistics.

Subject population

The first volunteer was enrolled on 28 May 2010 and the last volunteer completed on 02 August 2010. Twenty-eight volunteers (14 each in Groups 1 and 2) were enrolled and received study drug. Of the 28 volunteers, 27 volunteers completed the study. One volunteer completed all scheduled dosing, but was lost to follow-up and did not complete all end-of-study procedures. All 28 volunteers were included in the safety and pharmacokinetic analysis. Sixteen of the 28 volunteers consented to participate in the exploratory pharmacogenetic analysis.

The study population consisted of 28 healthy male volunteers with a mean age of 28.6 years and a mean body mass index of 25.89 kg/m^2.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Summary of AZD9742 pharmacokinetic parameters and results of statistical assessments of AZD9742 exposure parameters (AUC and C_{max}) are presented in Table S2 and Table S3, respectively.

Table S2 Summary of AZD9742 pharmacokinetic parameters [geometric mean (%CV)] (pharmacokinetic analysis set)

	Group 1		Group 2	
Parameters	**AZD9742 alone (Day 1) (n=14)**	**AZD9742 + diltiazem (Day 11) (n=14)**	**AZD9742 alone (Day 1) (n=14)**	**AZD9742 + ketoconazole (Day 7) (n=14)**
AUC (μM*h)	5.11 (17.0%)	8.05 (19.6%)	5.15 (21.8%)	19.4 (37.6%)
$AUC_{(0-t)}$ (μM*h)	5.10 (17.0%)	8.03 (19.5%)	5.14 (21.9%)	19.3 (37.8%)
C_{max} (μM)	1.35 (14.2%)	1.58 (19.2%)	1.44 (18.8%)	2.13 (31.3%)
t_{max} (h)[a]	2.00 (2.00-2.48)	2.00 (1.98-2.02)	2.00 (2.00-2.00)	2.50 (2.00-4.00)
$t_{½\lambda z}$ (h)	10.8 (78.2%)	40.7 (32.0%)	12.3 (91.2%)	29.0 (38.9%)
λ_z (1/h)	0.0640 (78.2%)	0.0170 (32.1%)	0.0563 (91.3%)	0.0239 (38.9%)
CL (L/h)	42.3 (17.0%)	26.8 (19.6%)	41.9 (21.9%)	11.2 (37.8%)
V_{ss} (L)	154 (18.7%)	176 (21.6%)	147 (24.3%)	142 (27.6%)
RAUC[b]		1.58 (15.3%)		3.76 (22.3%)
$RAUC_{(0-t)}$[b]		1.57 (15.4%)		3.75 (22.5%)
RC_{max}[b]		1.17 (12.7%)		1.48 (24.7%)
$Ae_{(0-t)}$ (mg)	8.82 (24.2%)	13.3 (19.4%)	7.30 (25.0%)	28.9 (24.1%)
$fe_{(0-t)}$ (%)	8.82 (24.2%)	13.3 (19.4%)	7.30 (25.0%)	28.9 (24.1%)
CL_R (L/h)	3.72 (20.7%)	3.57 (24.7 %)	3.06 (27.3%)	3.32 (25.9%)

[a] t_{max}: median (range) presented.
[b] Calculated as ratios of test (AZD9742+diltiazem)/reference (AZD9742 alone) in Group 1 and test (AZD9742+ketoconazole)/reference (AZD9742 alone) in Group 2.

Table S3 Statistical comparisons of AZD9742 exposure parameters (pharmacokinetic analysis set)

Groups	Parameters	Treatments	Geometric Least-squares Mean	Pairwise Comparisons (test/reference)[a]	
				Ratio (%)	90% confidence interval
Group 1 (n=14)	AUC (μM*h)	AZD9742 alone	5.111		
		AZD9742+diltiazem	8.053	157.57	(146.59, 169.38)
	C_{max} (μM)	AZD9742 alone	1.351		
		AZD9742+diltiazem	1.584	117.26	(110.37, 124.59)
Group 2 (n=14)	AUC (μM*h)	AZD9742 alone	5.152		
		AZD9742+ketoconazole	19.38	376.23	(338.99, 417.55)
	C_{max} (μM)	AZD9742 alone	1.438		
		AZD9742+ketoconazole	2.128	148.01	(131.93, 166.04)

Results are based on a linear mixed effects analysis of variance model with treatment fitted as a fixed effect and subject as a random effect.

[a] In Group 1, test=AZD9742 coadministered with diltiazem treatment and reference=AZD9742 alone treatment ; in Group 2, test=AZD9742 coadministered with ketoconazole treatment and reference=AZD9742 alone treatment.

In the AZD9742 alone treatments of both groups, the shape of the concentration-time profiles, as well as CL and V_{ss} values were comparable to those in the SAD (D2690C00001) study. Also similar to the SAD study, only a small fraction of the dose was renally cleared as unchanged drug; less than 10% of the dose was recovered in the urine as AZD9742.

Following AZD9742 with diltiazem coadministration on Day 11 (Group 1), decreased CL, significantly increased AUC, and increased overall $fe_{(0-t)}$ were observed. There was an approximately 37% decrease in CL. The CL_R did not change, although there was a 50% increase in the overall $fe_{(0-t)}$. The increase in AUC, although modest in magnitude (57.57%), was significant with the 90% confidence interval (CI) of the test/reference ratios completely above the protocol-specified limits of equivalence (0.7 to 1.43). For C_{max}, the 90% CI for the ratio of test/reference was contained within the protocol-specified limits of equivalence (0.7 to 1.43) indicating that there were no clinically significant changes to C_{max} observed due to drug-drug interaction. However, the lower limit of this confidence interval (110.37%) was above 100% and the p-value for this pairwise comparison was p=0.0005 indicating a statistically significant increase which was of the magnitude of approximately 17%.

Following AZD9742 with ketoconazole coadministration on Day 7 of Group 2, decreased CL, significantly increased AUC and C_{max}, delayed t_{max}, and increased overall $fe_{(0-t)}$ were observed. The effects of ketoconazole on AZD9742 CL and total exposure were much greater than the diltiazem effects. In the presence of ketoconazole, CL was decreased to

approximately one-fourth of the CL in the AZD9742 alone treatment. Similar to Group 1, CL_R did not change while the overall $fe_{(0-t)}$ was approximately 300% higher. The increase in AUC was 276.23% with the 90% confidence interval of the test/reference ratios completely above the protocol-specified limits of equivalence (0.7, 1.43). There was a 48.01% increase in AZD9742 C_{max} with the upper bound of the 90% confidence interval outside the 1.43 limit.

Summary of safety results

In this population of healthy male volunteers, 100 mg AZD9742 as a 2-hour intravenous infusion, was well tolerated when administered alone and when coadministered with single-dose oral diltiazem (240 mg, qd) or ketoconazole (200 mg, bid). There were no deaths or serious adverse events reported during study conduct. No volunteers discontinued the study due to adverse events. One volunteer (E0001016) completed all scheduled dosing but was lost to follow-up and did not complete end-of-study procedures.

A total of 33 adverse events were reported in 19 volunteers during the study: 21 adverse events reported by 10 volunteers in Group 1 and 12 adverse events reported by 9 volunteers in Group 2. Of the 33 adverse events, there were 3 predose adverse events of nasal congestion, chlamydial urethritis, and dermatitis of the forearm.

Dysgeusia was the most frequently reported treatment-emergent adverse event in volunteers receiving AZD9742 alone (2 [14.3%] volunteers in Group 1 and 1 [7.1%] volunteer in Group 2).

Headache, memory impairment, and contact dermatitis were the most frequently reported treatment-emergent adverse events in Group 1 volunteers who received diltiazem alone (2 [14.3%] volunteers each). Tachycardia, upper abdominal pain, diarrhea, and malaise were the most frequently reported treatment-emergent adverse events in Group 1 volunteers who received AZD9742 plus diltiazem (1 [7.1%] volunteer each).

One event (1 [7.1%] volunteer) of contact dermatitis was the only treatment-emergent adverse event reported for volunteers in Group 2 who received ketoconazole alone. Chapped lips, catheter site pain, contact dermatitis, ecchymosis, and superficial thrombophlebitis were the most frequently reported treatment-emergent adverse events in Group 2 volunteers who received AZD9742 plus ketoconazole (1 [7.1%] volunteer each).

Overall, 4 volunteers reported adverse events that were considered related to study drug: 3 related adverse events reported by 3 (21.4%) volunteers in Group 1 (local infusion-induced cramp like pain and dysgeusia) and 1 related adverse event reported by 1 (7.1%) volunteer in Group 2 (increase flatulence).

Two adverse events of interest occurred during the study. Volunteer E0001027 experienced an adverse event of accelerated idioventricular rhythm (4-beat run, mild, and not related to study treatment) that began on Day 1 approximately 6 hours after receiving a dose of 100 mg AZD9742 alone. Three further episodes of accelerated idioventricular rhythm (3-, 4-, and 5-beat) were reported during additional telemetry performed on Day 2 through Day 6.

Additional clinical laboratory testing and a stress echocardiogram were normal. On Day 7, no further accelerated idioventricular rhythm was observed and dosing continued (200 mg ketoconazole alone).

Volunteer E0001018 (AZD9742+diltiazem) experienced an adverse event of orthostatic tachycardia (mild, intermittent, and not related to study treatment) that began predose on Day 12. The adverse event resolved the same day approximately 6 hours after onset. No further episodes of orthostatic tachycardia were observed.

There was 1 adverse event of constipation (AZD9742 alone; Study Day 4) assessed by the Investigator as moderate in intensity. The AE, which began on Day 4 intensified during diltiazem administration and was felt not to be related to the dose of AZD9742 which had been administered on Day 1. All other adverse events were assessed as mild in intensity.

There were no clinically relevant changes in clinical laboratory, vital sign, electrocardiogram, or physical examination findings during the study. In Group 2, 5 of 14 (35.7%) volunteers receiving AZD9742 plus ketoconazole had electrocardiogram QT values that met outlier criteria (change from baseline of 30 msec or more) compared to 1 of 14 (7.1%) volunteers receiving AZD9742 alone.