AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9742
Study Code	D2690C00002
Edition Number	2
Date	15 September 2011

A Phase I, Single Center, Double-blind Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Intravenous AZD9742 after Administration of Multiple Ascending Doses for 14 days in Healthy Male and Female Subjects

Study dates: First subject enrolled: 02 February 2010
Last subject last visit: 23 August 2010

Phase of development: Clinical pharmacology (I)

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

Study center(s)

The study was conducted at a single center:

Publications

None at the time of writing this report.

Objectives and criteria for evaluation (refer to Table S1)

Table S1 Primary and secondary objectives and outcome variables

Objective Priority	Type	Description	Variable Description
Primary	Safety	Assessment of safety and tolerability of AZD9742 following multiple-ascending intravenous doses	Adverse events, laboratory variables[a], physical examinations, ECGs (12-lead, digital, and telemetry), vital signs (blood pressure and pulse rate [supine and orthostatic], temperature, and body weight)
Secondary	PK	Characterization of the pharmacokinetics of AZD9742 following administration of multiple-ascending intravenous doses	Single dose (Day 1): C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-12)}$, $AUC_{(0-24)}$, λ_z, $t_{1/2\lambda z}$, CL, V_{ss}, $A_{e(0-t)}$, CL_R, and f_e. Multiple dose (Day 17): C_{max}, t_{max}, C_{min}, $C_{ss,avg}$, %Fluct, t_{min}, AUC_τ, CL, V_{ss}, $R_{ac(Cmax)}$, $R_{ac(AUC)}$, λ_z, $t_{1/2\lambda z}$, linearity factor, $A_{e(0-\tau)}$, CL_R, and f_e.
Exploratory[b]	PK	Collection of plasma and urine samples for identification and presence of AZD9742 metabolites	Not applicable.
	Safety/ PK/PD	Collection of blood samples for DNA extraction and storage for future possible exploratory research into genes that may influence response, ie, distribution, safety, tolerability, and efficacy of AZD9742 treatment	Not applicable.
	PG	Collection and storage of plasma and serum samples from healthy volunteers for possible biomarker analysis	Not Applicable.

DNA deoxyribonucleic acid; ECG electrocardiogram; PG pharmacogenetic; PK pharmacokinetic.

[a] Non-routine laboratory assessments included serum and urine bone markers, fecal occult blood, and fingerstick glucose.

[b] Reported separate from the CSR.

Study design

This was a Phase I randomized double-blind placebo-controlled single center study to assess the safety, tolerability, and pharmacokinetics of AZD9742 following multiple-ascending dose administration to healthy volunteers.

It was initially planned that 48 healthy volunteers aged 23 to 45 years participated in 4 cohorts. However, one reserve cohort was added to the study to better define the maximum tolerated human dose and exposure. Twelve volunteers were allocated to each dose level to receive either AZD9742 (n=9) or placebo (n=3).

Each volunteer received a single dose of AZD9742 or placebo on Day 1. After a 3-day washout, repeated dosing commenced on Day 4 with AZD9742 or placebo once or twice daily for 13 days (ie, to Day 16), followed by a final dose on the morning of Day 17. A total of 15 or 28 doses of AZD9742 were given to each volunteer receiving once or twice-daily doses, respectively. Frequent pharmacokinetic sampling was performed up to 72 hours after the first and the last doses of AZD9742. Urine samples for pharmacokinetic analysis were collected in the second and consecutive dose groups.

Target subject population and sample size

Healthy male and/or female (of nonchildbearing potential) volunteers aged 23 to 45 years; although females of nonchildbearing potential were eligible for enrollment, none were enrolled.

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

Investigational product, dosage, and mode of administration

The study medication was supplied by the Sponsor. The starting dose of multiple intravenous doses of AZD9742 was based on emerging data from the D2690C00001 single-ascending dose study. AZD9742 was administered via intravenous infusion (fixed rate) as shown in Table S2.

Table S2 Doses and treatment regimens administered

Cohort	Treatment[a]	Dosing frequency[b]	Infusion	Rate of investigational product delivery
1	1000 mg	qd	4 hour	250 mg/hour
2	750 mg	bid	1 hour	750 mg/hour
3	1000 mg	bid	1 hour	1000 mg/hour
4	500 mg	qd	0.5 hour	1000 mg/hour
5	1000 mg	bid	2 hour	500 mg/hour

qd once daily; bid twice daily.
[a] AZD9742 (N=9) or placebo (N=3).
[b] Single dose on Day 1, followed by multiple doses on Days 4 through 16 and a final morning dose on Day 17.

Batch or lot numbers of AZD9742 (sterile solution, 620 mg [20 mg/mL] in 50 mL vial with a fill volume of 31 mL): Lot No. 10-000409AZ, Lot No. 10-001061AZ, Lot No. 10-001660AZ,

Batch No. 10-000565AZ, and Batch No. P8210. For placebo to match AZD9742 intravenous infusion, 5% dextrose in water was used and was provided by the Clinical Pharmacology Unit.

Duration of treatment

The duration of volunteer participation was approximately 55 days, from the time of screening until study follow-up visit, including 20 days of confinement in the Clinical Pharmacology Unit. In addition, subjects returned to the Clinical Pharmacology Unit for a follow-up visit approximately 5 to 10 days from the last dose of the study medication.

Statistical methods

No formal power calculations were performed. The sample size was based on the desire to obtain adequate safety, tolerability, and pharmacokinetic data to achieve the objectives of the study while exposing as few volunteers as possible to study medication and procedures. The analyses of safety, tolerability, and pharmacokinetic data were summarized using descriptive statistics or frequency counts in tables, listings, and graphs, as appropriate.

Dose proportionality was analysed using the power model on the logarithm of AUC and $AUC_{(0\text{-}t)}$ following dosing on Day 1 and AUC_{τ} for Day 17 as the dependent variable and the logarithm of the dose as the independent variable. The intercept α and the slope β (in $[AUC]=\alpha*dose^{\beta}$) together with confidence intervals (2-sided 90%) were estimated and presented for both parameters. Due to different infusion rates, the parameters $C_{(0.5h)}$ and $C_{(1h)}$ were analyzed on log scale using a similar power model with infusion rate as the independent variable. The intercept and slope along with 2-sided 90% confidence intervals were estimated. Since these analyses are of an exploratory nature, no formal conclusions were drawn.

Figures of 0.5-hour $[C_{(0.5h)}]$ or 1-hour concentrations $[C_{(1h)}]$ versus infusion rates and AUC versus dose after single dose, and $C_{(0.5h)}$ or $C_{(1h)}$ versus infusion rates and AUC_{τ} versus dose on Day 17, showing the individual values, geometric mean and, where applicable, trend lines constructed from intercept and slope estimated from the statistical power model were presented. In addition, individual and geometric mean infusion-rate normalized concentrations or dose-normalized total exposure after single and multiple doses were plotted against infusion rates or dose to see if there were any obvious trends.

The time dependency of the pharmacokinetics was evaluated by comparing AUC_{τ} (Day 17) with AUC (Day 1). A mixed-effect analysis of variance model using the logarithm of AUC_{τ} (AUC) as the response variable and day as a fixed effect and subject nested within day as random effect. Transformed back from the logarithm scale, true geometric means were estimated and the ratios of true geometric means together with confidence intervals (2-sided 95%) AUC_{τ}/AUC were estimated and presented. Since these analyses were of an exploratory nature, no formal conclusions were drawn.

Subject population

In total, 60 male volunteers (39 White, 18 African American, 1 American Asian, 1 Native Hawaiian or other Pacific Islander, and 1 American Indian or Alaska Native) were randomized and received study drug according to the planned dosing schedule. Although females of nonchildbearing potential were eligible for enrollment in the study, none were enrolled. Of the 60 volunteers randomized to treatment, 51 (85.0%) completed the study. Of the 9 (15.0%) volunteers who did not complete the study, 6 of 9 volunteers (66.7%; Volunteers E0001027, E0001031, E0001061, E0001062, E0001075, and E0001140) were withdrawn due to AEs, 2 of 9 volunteers (22.2%; Volunteers E0001016 and E0001017) were lost to follow-up, and 1 of 9 volunteers (11.1%; Volunteer E0001074) discontinued due to volunteer decision. The safety analysis included all randomized volunteers. The pharmacokinetic analysis set included all volunteers who received AZD9742; volunteers who received placebo were not part of the pharmacokinetic analysis set.

Summary of pharmacokinetic results

Summary of AZD9742 plasma and urine pharmacokinetic parameters are presented in Table S3 and Table S4, respectively.

Following single and multiple doses of AZD9742, the geometric mean C_{max} and AUC or AUC_{τ} in all treatment groups remained below the exposure limits of 25.3 μM for C_{max} and 193.3 μM·h for AUC.

CL and V_{ss} were comparable across treatments. Renal clearance had a minor contribution to the overall clearance. On average, less than 8% of the dose was recovered as unchanged AZD9742 in the urine following both single and multiple-doses of AZD9742, and CL_R was in the range of 2 to 3 L/h. Urinary excretion of AZD9742 was independent of dose.

AZD9742 exposures appeared to increase proportionally with infusion rates (over the range of 250 mg/h to 1000 mg/h) and doses (over the range of 500 mg to 1000 mg). The slope estimates from the power model were approximately 1 for Day 1 $C_{(0.5h)}$ and $C_{(1h)}$ versus infusion rates and AUC versus dose relationships. On Day 17, for the once-daily regimens, the geometric mean $C_{(0.5h)}$ was comparable for the 250 mg/h and 1000 mg/h with geometric mean rate normalized concentrations of 0.0138 and 0.0151 μM/(mg/h). Likewise, for the twice-daily regimens, the geometric mean rate normalized concentrations were 0.0138 and 0.0147 μM/(mg/h) for $C_{(0.5h)}$ at 750 mg/h and 1000 mg/h, and from 0.0205 to 0.0209 μM/(mg/h) for $C_{(1h)}$ with infusion rates ranging from 500 mg/h to 1000 mg/h. The dose-normalized AUC_{τ} for a given dosing interval was similar across all 5 treatments irrespective of dosing frequency. The slope estimate from the power model for AUC_{τ} versus dose was also approximately 1.

With multiple-dose administration, visual assessments of predose AZD9742 versus study day from Day 6 to Day 17 suggest that AZD9742 concentrations appeared to reach steady-state after 2 days of dosings. Day 17 C_{max} did not show accumulation with the $R_{ac(Cmax)}$ of approximately 1. Geometric mean $R_{ac(AUC)}$ ranged from 1.03 to 1.15 for once-daily regimens and from 1.16 to 1.21 for twice-daily regimens indicating little accumulation of overall

exposure. The mean terminal elimination half-life ($t_{½\lambda z}$) was similar across treatments ranging from 15.3 hours to 21.4 hours on Day 1 and from 13.8 hours to 29.9 hours on Day 17. However, the effective half-life ($t_{1/2,effective}$) which is reflective of accumulation for a given dosage frequency was shorter and ranged from 6.69 to 8.10 hours in the once-daily treatments and from 3.92 hours to 5.21 hours in the twice-daily treatments.

The ratios of AUC_τ/AUC were close to unity with the Day 17 AUC_τ, approximately 2% to 14% higher than the Day 1 AUC. The CL and V_{ss} on Day 17 were also comparable to the Day 1 values. Therefore, considering the small sample size in the study, the overall trend suggests AZD9742 pharmacokinetics to be approximately time independent.

Table S3 Summary of plasma pharmacokinetic parameters of AZD9742 [geometric mean (CV%)] (pharmacokinetic analysis set)

	Parameters (unit)	Treatment 1 (1000 mg, 4 hour, qd) (N=9)	Treatment 2 (750 mg, 1 hour, bid) (N=9)	Treatment 3 (1000 mg, 1 hour, bid) (N=9)	Treatment 4 (500 mg, 0.5 hour, qd) (N=9)	Treatment 5 (1000 mg, 2 hour, bid) (N=9)
Day 1	AUC (μM·h)	51.2 (13.6%)	41.2 (17.4%)	61.3 (29.0%)	27.2 (16.8%)	47.8 (24.4%)
	C_{max} (μM)	10.2 (16.0%)	15.3 (16.0%)	24.4 (27.7%)	13.5 (31.1%)	15.2 (33.1%)
	t_{max} (h)[a]	4.00 (3.00 - 4.00)	1.00 (1.00 - 1.03)	1.00 (0.50 - 1.02)	0.50 (0.23 - 0.53)	2.00 (1.00 - 2.03)
	$t_{1/2,\lambda z}$ (h)	15.3 (36.4%)	21.4 (32.6%)	17.9 (26.4%)	18.7 (17.8%)	18.4 (27.1%)
	CL (L/h)	42.2 (13.6%)	39.3 (17.4%)	35.2 (29.1%)	39.7 (16.8%)	45.2 (24.4%)
	V_{ss} (L)	129 (12.8%)	126 (22.3%)	99.1 (28.6%)	114 (23.1%)	135 (29%)
Day 17	AUC_{τ} (μM·h)	57.2 (17.9%)	45.4 (13.2%)	66.2 (24.4%)	27.9 (22.1%)	52.0 (22.2%)
	$R_{ac(Cmax)}$	1.06 (9.7)	1.02 (13.5	0.914 (50.7)	1.03 (43.1)	1.05 (19.8)
	$R_{ac(AUC)}$	1.15 (12.0)	1.16 (10.0)	1.18 (21.9%)	1.03 (10.4)	1.21 (14.7)
	$C_{ss,max}$ (μM)	10.6 (15.9%)	15.6 (16.0%)	23.5 (42.2%)	13.8 (38%)	14.5 (24.4%)
	t_{max} (h)[a]	4.00 (4.00 - 4.03)	1.00 (1.00 - 1.08)	1.00 (1.00 - 1.50)	0.50 (0.48 - 0.52)	2.03 (2.00 - 2.12)
	$C_{ss,min}$ (μM)	0.0741 (44.3%)	0.419 (46.0%)	0.355 (20.7%)	0.0315 (35.7%)	0.499 (42.7%)
	t_{min} (h)[a]	24.00 (0.00 - 24.03)	12.00 (12.00 - 12.08)	12.00 (0.00 - 12.00)	0.00 (0.00 - 24.02)	12.00 (11.98 - 12.05)
	$C_{ss,av}$ (μM)	2.38 (17.9%)	3.78 (13.3%)	5.52 (24.5%)	1.16 (22.0%)	4.33 (22.1%)
	%Fluct	440 (8.0%)	401 (15.4%)	419 (23.7%)	1190 (20.6%)	323 (13.1%)
	$t_{1/2,\lambda z}$ (h)	23.9 (33.4%)	22.3 (25.6%)	13.8 (27.2%)	25.1 (43.7%)	29.9 (56.1%)
	$t_{1/2,effective}$ (h)	8.10 (34.7%)	3.92 (32.3%)	5.21 (39.2%)	6.69 (28.6%)	4.81 (36.9%)
	CL (L/h)	37.7 (17.9%)	35.7 (13.2%)	32.6 (24.5%)	38.7 (22.1%)	41.5 (22.3%)
	V_{ss} (L)	130 (16.2%)	137 (21.4%)	95.0 (47.8%)	136 (29.7%)	168 (24.9%)

CV% coefficient of variance; qd once daily, bid twice daily.
[a] Presented as median (range).

Table S4 Summary urine pharmacokinetic parameters of AZD9742 following single and multiple-dose administration [geometric mean (CV%)] (pharmacokinetic analysis set)

Study day	Parameters (unit)	Treatment 2 (750 mg, 1 hour, bid) (N=9)	Treatment 3 (1000 mg, 1 hour, bid) (N=9)	Treatment 4 (500 mg, 0.5 hour, qd) (N=9)	Treatment 5 (1000 mg, 2 hour, bid) (N=9)
Day 1	$Ae_{(0-72)}$ (mg)	30.2 (21.7%)	56.8 (21.3%)	27.1 (22.9%)	56.9 (26.1%)
	$fe_{(0-72)}$ (%)	4.03 (21.8%)	5.68 (21.3%)	5.41 (22.9%)	5.69 (26.1%)
	CL_R (L/h)	1.59 (19.3%)	2.00 (17.7%)	2.15 (30.6%)	2.58 (34.1%)
Day 17	$Ae_{(0-tau),ss}$ (mg)	51.2 (27.9%)	68.0 (22.4%)	30.6 (22.0%)	71.3 (25.4%)
	fe (%)	6.82 (27.8%)	6.80 (22.4%)	6.12 (21.9%)	7.13 (25.4%)
	CL_R (L/h)	2.43 (25.3%)	2.22 (39.7%)	2.37 (27.5%)	2.96 (26.9%)

CV% coefficient of variance; qd once daily, bid twice daily.
Notes: Urine samples were not collected in Treatment 1.

Summary of safety results

There were no deaths or serious adverse events reported during the study. Overall, the most frequently reported postdose adverse events were general disorders and administration site conditions (infusion site reaction: inflammation, extravasation, and pain), nervous system disorders (dysgeusia, postural dizziness, headache, and dizziness), and gastrointestinal disorders (nausea, diarrhea, and flatulence). Severe adverse events included 1 event each of increased blood creatine phosphokinase and abdominal pain.

Multiple adverse events associated with the infusion site were reported for the majority of volunteers. Infusion site adverse events were usually noted after several intravenous infusions at the same site. On clinical examination, many of these adverse events consisted of a combination of increased pain, swelling, warmth, and erythema. Vein irritation (ie, vein tenderness and swelling) was also noted for some volunteers. When given by peripheral intravenous infusion for a dosing period of 14 days, AZD9742 was not well tolerated with regards to soft tissue inflammation/vein irritation at the infusion site. These adverse events typically resolved in less than 5 days with line removal and by locally applying ice followed by heat, although some volunteers had residual vein firmness lasting for variable times afterwards. The AZD9742 dosage tolerated best in regards to infusion site adverse events was 500 mg qd at 1000 mg/hr (Treatment 4) and the AZD9742 dosage tolerated least was 1000 mg bid at 500 mg/hr (Treatment 5). Administration site AEs were not observed in the SAD (D2690C00001) study.

AZD9742 was not well tolerated with regards to postural dizziness. Postural dizziness events were typically associated with the initial AZD9742 administrations. As per study design, volunteers received a single initial dose on Day 1, followed by a 2-day washout period. Administration of the initial dose of the multiple-dose session was given on Day 4. Eighty-eight percent (21/24 episodes) occurred on either the initial single dose on Day 1 or within the first 3 doses of the multidose session. For the twice-daily regimens, postural dizziness was more commonly observed with the morning dosings. Similar to the SAD study, the onset was around the end of the infusion when t_{max} is expected. These episodes had increasing frequency which was dependent upon a combination of higher rate of administration and total dose administered. The AZD9742 dosage tolerated best in terms of postural dizziness was 1000 mg qd at 250 mg/hr (Treatment 1) and the AZD9742 dosage tolerated least was 1000 mg bid at 1000 mg/hr (Treatment 3).

AZD9742 was reasonably well tolerated regarding the incidence of gastrointestinal disorders. While several volunteers were categorized as having diarrhea, all but one actually had loose stools of short duration. The majority of nausea and vomiting observed was in response to orthostatic position change rather than being persistent during drug administration. It also appeared that they were dependent on administration rate. When administration rates were identical there was a higher incidence of symptoms with the larger total dose. The AZD9742 dosage tolerated best in this regard was 1000 mg qd at 250 mg/hr (Treatment 1) and the AZD9742 dosage tolerated the least was 1000 mg bid at 1000 mg/hr (Treatment 3).

Serum creatinine elevation was noted in several volunteers during dosing which returned to normal after dosing discontinuation. A mean creatinine elevation and a mean decrease in creatinine clearance were noted during dosing relative to placebo in all cohorts. It was most noted for Treatment 5 (1000 mg, 2 hour, bid) and least noted for Treatment 1 (1000 mg, 4 hour, qd). Other than creatinine elevation, there was no clinical, nor protocol-mandated laboratory evidence (ie, blood urea nitrogen, urinalysis, uric acid, and complete blood count) of nephrotoxicity.

No clinically significant changes were noted in supine vital signs. During the obtaining of orthostatic vital signs, an increase in pulse rate and/or a decrease in blood pressure was noted for some volunteers. Symptomatic volunteers who began to complain of lightheadedness or dizziness with a resulting inability to stand assumed a sitting or supine position in the vast majority of cases. As a result, standing vital signs were not able to be assessed in all volunteers. Slight increases from baseline were noted for all of the AZD9742 treatment groups in mean QTcF through 4 hours postdose on Days 1, 4, and 17. Mean QTcF for these groups decreased back to predose levels by approximately 6 hours to 12 hours postdose. Mean QTcF for the placebo group changed minimally following dosing on Days 1, 4, and 17. There were no clinically significant trends in telemetry. Other than those associated with the infusion sites, there were no significant changes in physical examinations during the study.

Mild creatine phosphokinase and Troponin I elevations were observed in one volunteer who was asymptomatic and demonstrated no interval change in electrocardiograms to suggest myocardial ischemia/inflammation. This was accompanied by an increase in sedimentation rate, C-reactive protein, and mild elevation of D-dimer. Computed tomography angiogram of the heart was without evidence of myocarditis, coronary artery disease, myocardial ischemia, CT evidence of pulmonary embolus, or aortic dissection. Upper extremity doppler was negative for deep vein thrombosis. A cardiac consultant felt that the volunteer had not experienced any ischemic event and further evaluation of the volunteer was not indicated.

Although AZD9742 is structurally and functionally distinct from quinolone antibiotics, which have been reported to cause tendonitis and tendon rupture in patients, the possibility that an effect on cartilage may be observed was evaluated during the study by monitoring of bone marker results. Monitoring in this study included measurement of bone specific alkaline phosphatase levels and other serum and urine bone markers. There were no trends of drug effects on bone markers, which indicate that AZD9742 does not have an effect on bone or cartilage.