AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9742
Study Code	D2690C00001
Edition Number	1
Date	28 September 2010

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

Study dates: First subject enrolled: 3 December 2009
Last subject last visit: 19 March 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)

The study was conducted at a single center:

Publications

There are 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 safety and tolerability of AZD9742 following administration of single ascending intravenous doses when given to healthy male volunteers and female volunteers of nonchildbearing potential	Adverse events, laboratory variables, physical examinations, electrocardiograms (12-lead, digital, and telemetry), and vital signs	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics of AZD9742 following administration of single ascending intravenous doses of AZD9742	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{½\lambda z}$, CL, Vd_{ss}, CL_R, f_e	PK

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 single ascending dose administration to healthy male and female volunteers of nonchildbearing potential.

The following AZD9742 doses were proposed: 50, 150, 450, 1000, 2000, and 3000 mg. Actual AZD9742 doses given were 50, 150, 450, 1000, 1500, and 1250 mg. The dose of 1500 mg AZD9742 was proposed after cohort 4 due to the expectation that in cohort 5, mean C_{max} might reach a level close to the stopping criteria of 25.1 µM. The expectation was based on the mean C_{max} value of 15.43 µM reported during the interim pharmacokinetic analysis in volunteers who received 1000 mg AZD9742 and linear pharmacokinetics of AZD9742 over the range of doses from 50 mg to 1000 mg. The dose of 1250 mg AZD9742 was proposed after cohort 5 as it would contribute new knowledge as to whether AZD9742 presents non-linear pharmacokinetics. With a dose of 1250 mg, it was expected that mean C_{max} would be below the stopping criteria of 25.1 µM. Volunteers participated in only one dose group.

Upon completion of each dose level, safety variables and AZD9742 pharmacokinetics were reviewed by the Safety Review Committee in order to determine the progression of dose

escalation. Volunteers were not enrolled in the next higher dose group until data obtained up to Day 6 were deemed safe and tolerable.

Target subject population and sample size

Healthy male volunteers, and female volunteers of nonchildbearing potential, aged 23 to 45 years.

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

Table 1 Details of investigational product

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD9742	Sterile solution, 620 mg (20 mg/mL) in 50 mL vial with a fill volume of 31 mL	AstraZeneca, Mölndal, Sweden	H2112-01-01-01
Placebo	Dextrose 5% injection	Baxter Health Care, Round Lake, IL, United States	C775973

AZD9742 was administered via intravenous infusion over 4 hours with a fixed infusion rate. The investigational product matching placebo was supplied by the Sponsor. Placebo was administered via intravenous infusion over 4 hours with a fixed infusion rate.

Duration of treatment

Each volunteer received a single intravenous dose of AZD9742 or placebo administered over 4 hours. The duration of volunteer participation was approximately 45 days, from the time of screening until study discharge.

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.

The following PK parameters were determined using actual sampling times: C_{max}, time to maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from zero to the time of the last measurable concentration [$AUC_{(0-t)}$], area under the plasma concentration-time curve from zero extrapolated to infinity (AUC), terminal elimination half-life ($t_{½\lambda z}$), total body clearance (CL), volume of distribution at steady-state (Vd_{ss}), renal clearance (CL_R), and fraction of dose excreted unchanged in the urine (f_e).

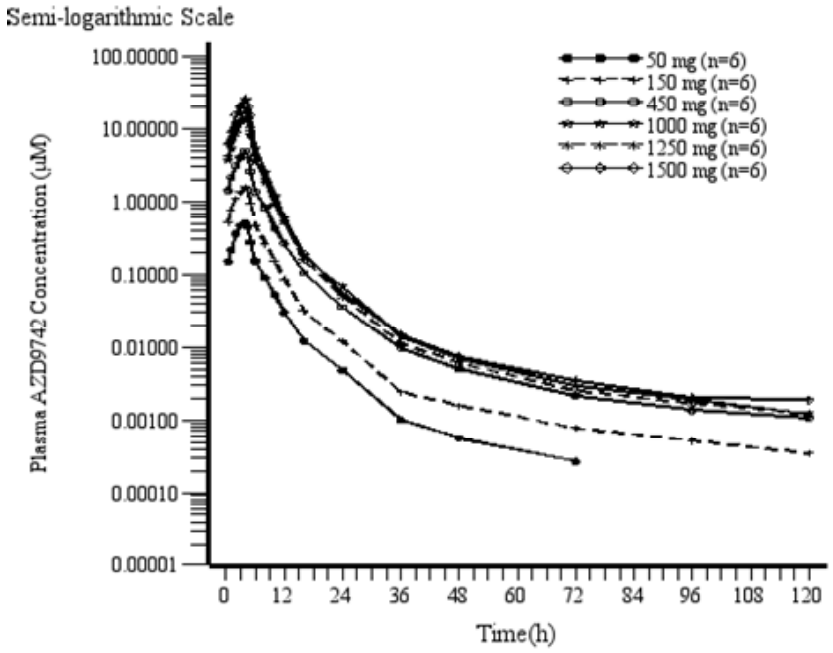
Subject population

In total, 48 male volunteers (30 white, 17 African American, and 1 American Indian or Alaska Native) were randomized and received study drug according to the planned dosing schedule. For each of the 6 treatment cohorts (50, 150, 450, 1000, 1500, or 1250 mg AZD9742, 6 volunteers received a single dose of study treatment and 2 volunteers received placebo. Of the 48 volunteers randomized to treatment, 46 completed the study. One volunteer each discontinued due to loss to follow-up (E00001068) and volunteer decision (E0001050). The safety analysis included all randomized volunteers. The 6 active-treated and 1 placebo groups were generally balanced in terms of demographics and baseline characteristics. The PK analysis set included all volunteers who received AZD9742; volunteers who received placebo were not part of the PK analysis set.

Summary of pharmacokinetic results

The plasma AZD9742 concentration-time profiles following administration of single ascending intravenous doses of AZD9742 were characterized by an increase in exposure with dose over the range of 50 to 1500 mg. Maximum plasma concentration was generally observed at the end of the 4-hour intravenous infusion. Plasma concentrations declined thereafter in a multi-exponential manner.

Figure 1 Geometric mean plasma concentrations of AZD9742 versus time curves (Pharmacokinetic analysis set)



AZD9742 exposure increased with dose in a slightly greater than proportional manner from 50 to 1500 mg, with a 30-fold increase in dose resulting in a 48.3- and 43.2-fold increase in C_{max} and AUC, respectively. However, the apparent deviation from dose proportionality may be

caused by variability in exposure (C_{max} and AUC), rather than non linear pharmacokinetics. The terminal elimination half-life ranged between 27.0 and 32.2 h and appeared to be independent of the administered dose between 150 and 1500 mg. Total clearance and Vd_{ss} were generally dose independent in the lower dose groups (50 to 450 mg), but decreased from 40.2 to 28.3 L/h and from 156 to 76.2 L, respectively, with increasing AZD9742 dose between 450 and 1500 mg. Renal clearance accounted for a small fraction of total clearance. Less than 10% of the administered dose of AZD9742 was recovered unchanged in the urine.

The predefined maximum exposure limit for C_{max} (25.1 µM) was reached, whereas AUC was well below the exposure limit (193 µM·h), at 1500 mg.

Table 2 Summary of pharmacokinetic parameters of AZD9742 [geometric mean (CV%)] (pharmacokinetic analysis set)

Variable	50 mg (N=6)	150 mg (N=6)	450 mg (N=6)	1000 mg (N=6)	1250 mg (N=6)	1500 mg (N=6)
AUC (µM·h)	2.63 (16.0%)	8.14 (26.5%)	24.1 (17.1%)	65.3 (20.8%)	78.7 (21.0%)	115 (19.0%)[b]
C_{max} (µM)	0.545 (12.9%)	1.67 (30.9%)	5.05 (17.5%)	14.9 (29.5%)	18.2 (23.9%)	26.3 (42.2%)
t_{max} [a] (h)	4.00 (3.00-4.50)	4.00 (4.00-4.50)	4.00 (4.00-4.50)	4.01 (3.00-4.50)	4.26 (3.00-4.50)	4.00 (3.00-4.00)
$t_{½λZ}$ (h)	13.4 (90.0%)	32.2 (13.7%)	28.8 (12.1%)	27.0 (27.5%)	28.7 (36.2%)	31.3 (25.0%)[b]
Vd_{ss} (L)	153 (16.8%)	153 (30.2%)	156 (20.6%)	103 (15.0%)	94.0 (19.8%)	76.2 (39.6%)[b]
CL (L/h)	41.1 (16.0%)	39.8 (26.6%)	40.2 (17.0%)	33.1 (20.9%)	34.3 (20.9%)	28.3 (18.9%)[b]
CL_R (L/h)	3.66 (19.5%)	2.78 (16.4%)	3.17 (14.7%)	2.77 (21.6%)	2.33 (25.4%)	2.00 (23.8%)
f_e (%)	8.90 (24.9%)	6.97 (21.7%)	7.83 (9.9%)	8.33 (18.7%)	6.79 (19.8%)	6.58 (21.0%)

[a] Presented as median (range).
[b] N=5.

Summary of safety results

There were no deaths, serious adverse events, discontinuations of AZD9742 due to adverse events, or any other significant adverse events in the study. A total of 60 adverse events (including 7 predose adverse events) were reported by 27 volunteers in the study. Volunteers in all treatment groups (50, 150, 450, 1000, 1250, 1500 mg AZD9742 and placebo) experienced adverse events; however, overall adverse events and treatment-related adverse events were most frequently reported by volunteers in the 1500-mg group. The most common adverse events during active treatment were headache and postural dizziness, each reported by 5 (13.9%) and 2 (16.7%) active-treated and placebo-treated volunteers, respectively. Overall, there were 21 treatment-emergent assessed as related to study drug reported in 12 volunteers. There were 10 (27.8%) active-treated volunteers who reported at least one adverse event assessed by the Investigator as related to study drug compared with 2 (16.7%) placebo-treated volunteers. Postural dizziness was the most commonly reported treatment-related adverse event (5/36 [13.9%] volunteers overall). Timing of onset correlated well with AZD9742 approaching peak concentration levels. Postdose postural dizziness was only observed in

placebo, 1000-mg, and 1500-mg treatment groups, and not by all subjects in those groups. It was not observed in the 50-mg, 150-mg, 450-mg, and 1250-mg treatment groups. There were 2 treatment-emergent adverse events of moderate intensity in active-treated volunteers, including testicular pain (150-mg AZD9742) and postural dizziness (1500-mg AZD9742) compared with 1 moderate event of joint sprain in a placebo-treated volunteer. All other adverse events were of mild intensity.

Volunteer E0001014 (50 mg) had a creatine kinase elevation peak of 1128 U/L (normal range 32 to 294 U/L) approximately 32 hours postdose. There were no associated symptoms with the increase and no clinically significant ECG findings. No pertinent medical history was reported and the Investigator was not able to find an alternative explanation for the increase. Dose escalation was not affected and the only action taken was to perform additional laboratory evaluations. Creatine Kinase MB and troponin were performed and all values were within normal limits.

There were no other clinically relevant treatment-related changes or trends in laboratory values during the study.

There were no clinically relevant treatment-related changes or trends in any vital sign, or electrocardiogram variables measured in volunteers exposed to AZD9742 during the study and no laboratory, vital sign, or electrocardiogram changes impacted dose escalation. No adverse events were reported for clinical laboratory or vital sign abnormalities. An adverse event was reported for Volunteer E0001054 (1000 mg) who experienced one episode of mild ventricular tachyarrhythmia approximately 16 hours postdose. The episode lasted for 1 to 2 seconds (4 beats) with a heart rate of 100 to 150 bpm; the volunteer was asymptomatic. As follow-up, a stress echocardiogram was performed and was normal. The adverse event was considered mild in severity and related to AZD9742; however, there was no impact on dose escalation.