Clinical Study Report Synopsis

Drug Substance	AZD9742
Study Code	D2690C00003
Edition Number	1
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A Phase I, Single Center, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses of Intravenous AZD9742 in Healthy Male and Female Japanese Subjects

Study dates: First subject enrolled: 26 APR 2010
Last subject last visit: 26 JUL 2010

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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 in the USA.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of single followed by multiple ascending intravenous (IV) doses of AZD9742 in healthy Japanese male and female (of non-childbearing potential) subjects.	Adverse events Chemistry, hematology and urinalysis laboratory variables including serum and urine bone markers Vital signs: Blood pressure, Pulse, Body temperature dECG/ECG: resting 12-lead ECG, real time telemetry Physical examinations
Secondary	PK	To characterize the PK of AZD9742 following administration of single and multiple ascending IV doses of AZD9742 in healthy Japanese subjects.	Single dose: PK outcome variables calculated for AZD9742 were: C_{max}, t_{max}, $AUC_{(0-t)}$, AUC_{tau}, AUC, λ_z, $t_{½}$, Vd_{ss}, CL, CL_R, f_e and $A_{e(0-t)}$ Multiple dose: PK outcome variables calculated for AZD9742 on Day 4 were: C_{max}, t_{max} and AUC_{tau} PK outcome variables calculated for AZD9742 on Day 10 were: C_{max}, t_{max}, C_{tau}, AUC_{tau}, V_{ss}, CL_{ss}, $Rac_{(Cmax)}$ and $Rac_{(AUC)}$), linearity factor, $t_{½}$, CL_R, $A_{e(0-t)}$ and f_e.
	Safety/ Efficacy	To investigate the influence of multiple IV doses of AZD9742 on intestinal bacterial flora in healthy Japanese subjects.	Stool samples for intestinal flora: aerobic and anaerobic bacteria including *Clostridium difficile*,

Study design

In this Phase I, randomized, double-blind, placebo-controlled, SAD/MAD study, the starting dose of AZD9742 was 500 mg. In each cohort, 10 healthy Japanese male subjects were randomized to active treatment (n=8) or placebo (n=2). Each subject participated in one dose cohort only.

Screening (Visit 1) was conducted within 28 days of admission to the Clinical Pharmacology Unit (CPU), which occurred on the day before dosing started (Day -1). Subjects remained in-house until all assessments/procedures were completed on Day 13. Subjects returned to the CPU approximately 5 to 9 days after discharge, on Day 18 to 22 for the follow-up assessments.

Subjects in Cohort 1 received 500 mg AZD9742 or placebo, Cohort 2 received 750 mg AZD9742 or placebo, and Cohort 3 received 1000 mg AZ9742 or placebo. Within a cohort, each subject received a single dose of AZD9742 or placebo on Day 1. After a 3-day washout, repeated dosing commenced (Day 4) with AZD9742 or placebo administration twice daily for 6 days (ie, to Day 9), followed by a final single dose on the 7th day (ie, Day 10). The single dose and multiple doses were administered as a 1 or 2-hour IV infusion per the specified dosing regimen for that cohort (500 and 750 mg infused over 1 hour, 1000 mg infused over 2 hours). A total of 14 doses of AZD9742 or placebo were given to each subject who completed the planned dosing regimen.

After each dose cohort, a Safety Review Committee (SRC) evaluated the safety, tolerability and the PK of AZD9742 and decided the next dose (proceeded with planned dose, increased or decreased dose, repeated dose or dose stopped).

Target subject population and sample size

Healthy Japanese male and female (of non-childbearing potential) subjects, 23 to 45 years of age (inclusive). Thirty healthy Japanese male subjects were enrolled.

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

Table S2 Details of investigational product

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Lot number/ Batch Number	Expiration
AZD9742	Sterile solution, 620 mg (20 mg/mL) in 50 mL vial with a fill volume of 31 mL	AstraZeneca R&D, Charnwood, UK	H 2112-01-01	10-002689AZ/ P8210	15 March 2011
				10-003174AZ/ P8210	15 March 2011
Placebo	Sterile solution of Dextrose 5% in water (D5W)	Baxter	Not applicable	C798017 / NA	June 2011
				C799874 / NA	July 2011

Duration of treatment

The duration of subject participation was approximately 52 days, including a 28 day screening period, 14 day confinement period and a follow-up visit approximately 5 to 9 days after discharge.

Statistical methods

No formal sample size calculation was made for this study. A sample size of 10 subjects (8 AZD9742 and 2 placebo) per dose level was considered sufficient to characterize the PK characteristics and provide early safety and tolerability data in healthy Japanese subjects. A minimum of 7 subjects was required to complete each cohort.

To achieve the primary objective, safety and tolerability were evaluated via adverse event (AE) monitoring, vital sign assessments, physical examinations, electrocardiograms (ECGs) and clinical laboratory assessments. Data were presented by actual dose (not by cohort), and subjects receiving placebo were pooled across dose levels for the purpose of tabular and graphical safety summaries.

Adverse events were listed and summarized by system organ class, preferred term and dose. Vital signs (including orthostatic measurements), clinical laboratory measures, 12-lead ECG, and digital ECGs (dECGs) were summarized using descriptive statistics by protocol time and dose.

To achieve the secondary objectives, the PK profile of AZD9742 was evaluated by assessment of drug concentrations in plasma and urine. Subjects receiving placebo were not included in the summary and analysis of PK parameters. Individual PK parameters were calculated and summarized descriptively by dose level.

Given the exploratory nature, no formal statistical hypothesis testing was performed in this study. Since no planned formal statistical tests were performed in this study and the confidence intervals (CIs) were calculated for descriptive purposes only, no corrections for multiplicity were used. All available AZD9742 plasma concentrations and PK parameters were listed for the subjects. All PK parameters as well as AZD9742 plasma concentrations were summarized for the PK analysis population by dose and time point. Descriptive summary statistics included: number (n), arithmetic mean, standard deviation, geometric mean, coefficient of variation (CV%), minimum, median, and maximum; t_{max} was summarized by n, median, minimum, and maximum.

Where applicable, dose proportionality was demonstrated visually in an AUC vs. total daily dose plot, comparing the geometric means of AUC against a fitted linear line plotted through (0,0). The time dependency of the PK was evaluated by comparing the area under the curve from multi-dose sampling (Day 10) versus the area under the curve from single-dose sampling (Day 1). The accumulation ratio (Day10/Day1) and a 90% CI were calculated.

Subject population

In total, 30 Japanese male subjects were randomized into the study at a single study site. Subjects received a single dose of AZD9742 on Day 1 and twice daily doses on Day 4 through Day 9 with the last single dose given on Day 10. Twenty-eight subjects randomized to treatment completed the study; two subjects discontinued prematurely from the study. Subject 1012 (500 mg) withdrew due to personal reasons; he was last dosed on the morning of Day 9. Subject 1021 (1000 mg) withdrew due to personal reasons; he was last dosed on Day 1.

Demography and baseline characteristics were comparable for all active treatment groups and placebo for age, height, weight and BMI.

Summary of efficacy results

Not applicable to this study.

Summary of pharmacokinetic results

The predefined maximum mean exposure limit for AUC (193.3 µmol*h/L) was not reached during the study. The mean C_{max} exposure limit of 25.1 µmol/L was also not met during the study. However, individual subject C_{max} exceeded this limit for at least one subject in the 750 mg cohort (Days 4 and 10) and the 1000 mg cohort (Days 1, 4, and 10).

After a single IV dose, the geometric mean C_{max} was 12.3 µmol/L after the 500 mg dose infused over 1 h, 17.8 µmol/L after the 750 mg dose infused over 1 h, and 21.8 µmol/L after the 1000 mg dose infused over 2 hours. The median t_{max} was at the end of infusion for all dose levels (1 hour for 500 mg and 750 mg, 2 hours for 1000 mg).

Single dose geometric mean $AUC_{(0-t)}$ increased from 29.4 µmol*h/L (500 mg dose) to 65.7 µmol*h/L (1000 mg dose); AUC geometric mean values were very similar to $AUC_{(0-t)}$. AUC_{tau} geometric mean values were similar to $AUC_{(0-t)}$ and AUC, increasing from 28.3 µmol*h/L for the 500 mg dose to 63.3 µmol*h/L for the 1000 mg dose. The CV% for the single dose C_{max} and AUC parameters ranged from 8 to 29%.

Geometric mean $t_{½}$ was 27, 29 and 22 hours for the 500, 750 and 1000 mg dose levels, respectively; geometric mean CL and geometric mean Vd_{ss} were dose independent at 33 to 37 L/h and 97 to 119 L, respectively, after single dose.

After a single morning dose on Day 4, the geometric mean C_{max} was 12.5 µmol/L after the 500 mg dose infused over 1 h, 21.4 µmol/L after the 750 mg dose infused over 1 hour, and 24.9 µmol/L after the 1000 mg dose infused over 2 hours, which were similar to the Day 1 C_{max} values. Median t_{max} was at the end of infusion for all dose levels (1 hour for 500 and 750 mg, 2 hours for 1000 mg).

Geometric mean AUC_{tau} increased from 30.2 µmol*h/L (500 mg dose) to 74.7 µmol*h/L (1000 mg dose), also similar to the Day 1 AUC_{tau}. The CV% for Day 4 C_{max} and AUC parameters ranged from 13 to 26%.

After twice daily IV doses from Day 4 to Day 9 and a single dose on Day 10, the geometric mean C_{max} was 12.4 µmol/L after the 500 mg dose infused over 1 h, 21.7 µmol/L after the 750 mg dose infused over 1 hour, and 4.3 µmol/L after the 1000 mg dose infused over 2 hours. Median t_{max} was at the end of infusion for all dose levels (1 hour for 500 and 750 mg, 2 hours for 1000 mg).

Geometric mean AUC_{tau} increased from 34.4 µmol*h/L (500 mg dose) to 80.6 µmol*h/L (1000 mg dose). Geometric mean $AUC_{(0-t)}$ increased from 37.3 µmol*h/L (500 mg dose) to 85.6 µmol*h/L (1000 mg dose); AUC geometric mean values were very similar to $AUC_{(0-t)}$. The CV% for the C_{max} and AUC parameters ranged from 12 to 21%

After multiple IV doses, geometric mean $t_{½}$ was 25, 27 and 19 hours for the 500, 750 and 1000 mg dose levels, respectively; geometric mean CL_{ss} and geometric mean V_{ss} ranged from 25 to 29 L/h and 95 to 144 L, respectively.

The geometric mean ratios for the evaluation of the effect of time were 1.21, 1.30 and 1.17, respectively, for 500, 750, and 1000 mg dose levels. The 90% CIs surrounding the geometric mean ratios were 1.08 to 1.37 for 500 mg; 1.17 to 1.44 for 750 mg, and 0.99 to 1.39 for 1000 mg. Although these data may be interpreted with caution due to the small sample size, the data suggest single dose PK may not be entirely predictive of repeated dose PK when AZD9742 is administered twice daily as 1 or 2 hour infusions.

The geometric mean accumulation ratio (Rac) for C_{max} was 1.02, 1.21, and 1.08, respectively, for the 500, 750, and 1000 mg dose levels, suggesting little to no accumulation in peak AZD9742 exposure with multiple twice daily dosing. The 90% CIs surrounding the geometric mean ratios were 0.88 to 1.20 for 500 mg; 1.04 to 1.41 for 750 mg, and 0.90 to 1.30 for 1000 mg.

The geometric mean accumulation ratio (Rac) for AUC_{tau} was 1.25, 1.33, and 1.20, respectively, for the 500, 750, and 1000 mg dose levels, suggesting the accumulation in overall AZD9742 exposure with multiple twice daily dosing is not clinically significant. The 90% CIs surrounding the geometric mean ratios were 1.09 to 1.44 for 500 mg; 1.20 to 1.49 for 750 mg, and 1.00 to 1.43 for 1000 mg.

Geometric mean C_{max} values after single and multiple dose administration suggest that AZD9742 is approximately dose proportional across the 500 and 750 mg dose ranges infused over 1 hour. AUC and AUC_{tau} increased in a dose proportional manner over the dose levels of 500, 750, and 1000 mg for single dose data and multiple dose data. Data suggest that steady-state was attained after three days of twice daily dosing.

After a single IV dose, the mean amount of AZD9742 excreted in urine was 62, 111, and 94 µmol and the percent of unchanged drug excreted was 6, 7, and 4% for the 500, 750, and 1000 mg dose levels. Geometric mean renal clearance was 2.1, 2.5, and 1.3 L/h following a single IV dose of 500, 750, and 1000 mg AZD9742, respectively.

After multiple BID IV dosing, the mean amount of AZD9742 excreted in urine was 79, 107, and 128 µmol and the percent of unchanged drug excreted was 7, 7, and 6% for the 500, 750,

and 1000 mg dose levels. Geometric mean renal clearance after multiple IV dosing of 500, 750, and 1000 mg AZD9742 was 2.1, 1.7, and 1.5 L/h, respectively.

Summary of pharmacodynamic results

Not applicable to this report.

Summary of safety results

There were no deaths, serious adverse events (SAEs), severe AEs, discontinuations of investigational product due to AEs, or any other significant adverse event (OAEs) in the study. All subjects (100%) administered AZD9742 reported AEs and 3 of 6 (50%) subjects administered placebo reported AEs.

AZD9742 given by IV infusion at 500 mg over 1 hour, 750 mg over 1 hour, and 1000 mg over 2 hours as a single dose, or multiple doses for 6.5 days, was well tolerated. A total of 92 AEs were reported by 24 of 24 subjects administered AZD9742 and 3 of 6 subjects administered placebo during the study. Twenty-nine of 92 (32%) AEs were reported after a single dose of IP on Day 1, and 63 of 92 (68%) AEs were reported during multiple dose IP administration Day 4 to 10.

All AEs were of mild intensity, with the exception of 6 AEs of moderate intensity including: 2 AEs of diarrhea for 750 mg; 1 AE of orthostatic hypotension for 750 mg; 1 AE of dizziness for 1000 mg; 1 AE of headache for 1000 mg, and 1 AE of hypotension for 1000 mg.

Eighty-two of the 92 AEs reported were assessed as possibly related to IP administration. The most commonly reported causally related AEs (reported by > 20% subjects overall on active) were postural orthostatic tachycardia syndrome, diarrhea, nausea, dizziness, and headache. The number of AEs (particularly, those related to vital sign measurements) for the 750 mg treatment was higher than the 500 and 1000 mg treatment groups. The treatment differences between the 750 and 1000 mg groups may be due to the faster 1 hour infusion time at the 750 mg dose level.

In addition, several subjects reported AEs at the site of treatment infusion. Injection site phlebitis was reported by 1 subject in the 500 and 750 mg treatment groups and by 2 subjects in the 1000 mg treatment group. Injection site thrombosis was reported by 1 subject in the 750 mg and placebo treatment groups and by 3 subjects in the 1000 mg treatment group. Peripheral edema was reported by 2 subjects in the 500 mg treatment group.

There were no AEs related to clinical laboratory values or ECG measurements. AEs related to vital signs (postural orthostatic tachycardia syndrome and orthostatic hypotension) were generally transient in nature and resolved spontaneously.

Mean supine and standing vital signs measurements (systolic and diastolic BP and heart rate) were within clinically acceptable limits at all times postdose for all treatments. Mean observed and change from baseline supine and standing vital signs were similar across treatments and over time.

Although mean vital signs measurements were clinically acceptable, there were several subjects in each treatment group that exhibited out of range measurements that were recorded as AEs (2 subjects for placebo; 1 subject for 500 mg; 7 subjects for 750 mg, and 2 subjects for 1000 mg). None of the study stopping criteria was met for vital signs measurements.

None of the subjects experienced clinically significant abnormalities in ECG data at any time point. There were no adverse events related to ECG measurements.

No adverse events were related to abnormal chemistry, hematology, urinalysis or bone marker laboratory values. Mean chemistry, hematology and urinalysis parameter values were generally within normal ranges for the study treatments at most time points. A summary of the shift in individual subjects from normal at baseline to lower or higher than normal at any time post treatment did not reveal any relevant trends.

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.

Fecal samples were analyzed for aerobic and anaerobic intestinal bacterial in order to determine if administration of AZD9742 had an effect on normal bacterial flora, as depletion of normal flora can lead to the overgrowth of bacterial known to cause gastrointestinal symptoms. Presence of Clostridium difficile, in particular, was evaluated. There was no correlation between AEs of diarrhea and the presence of C. difficile. There was no clear evidence of a relationship of intestinal bacterial flora to AEs reported.

Mean and change from baseline results for aerobic intestinal bacterial flora displayed no trends across active treatments and placebo. Review of mean and change from baseline results for anaerobic bacteria showed that by the end of treatment on Day 7, a slight decrease of normal flora was observed for the 1000 mg dose. The anaerobic bacterial flora results returned to pre-treatment levels by the end of study follow up visit.

Five subjects had abnormalities on post treatment physical examination that were not present at baseline. These were consistent with previously recorded AEs.