AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9742
Study Code	D2690C00007
Edition Number	1
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A Phase I, Double-blind, Randomized, Placebo-controlled Study to Assess the Safety and Tolerability, and Pharmacokinetics of a Single Intravenous Dose of 750-mg AZD9742 Administered as a 1-hour Infusion in Healthy Elderly Male and Female Volunteers

Study dates: First subject enrolled: 22 June 2010
Last subject last visit: 22 July 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)

This was a single center study

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**	
To assess the safety and tolerability of AZD9742 following intravenous administration of a single 750-mg dose infused over 1 hour when given to healthy elderly volunteers (65 years of age or more)	Adverse events, clinical laboratory results, vital signs, electrocardiograms, and physical examinations	Safety
Secondary	**Secondary**	
To evaluate the pharmacokinetics of a single intravenous dose of 750-mg AZD9742 administered as a 1-hour infusion in healthy elderly volunteers	C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $t_{½\lambda z}$, V_{ss}, CL, amount of AZD9742 and fraction of dose excreted in urine at each collection interval, cumulatively [$Ae_{(0-t)}$ and $fe_{(0-t)}$] and overall, and CL_R of AZD9742	Pharmacokinetic
Exploratory[a]	**Exploratory**	
To 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
To compare pharmacokinetics of AZD9742 in healthy elderly volunteers with pharmacokinetics of AZD9742 in nonelderly volunteers (data for nonelderly volunteers to come from the single ascending dose or multiple ascending dose studies)	Pharmacokinetic	Pharmacokinetic
To collect and store plasma and serum samples from healthy elderly volunteers for possible exploratory biomarker analysis	Biomarker exploratory research	Biomarker research

[a] Any data generated from the exploratory objectives were reported separately from the clinical study report.

Study design

This was a Phase I, double-blind, randomized, placebo-controlled study designed to assess the safety and tolerability and pharmacokinetics of a single intravenous dose of 750 mg AZD9742 administered as a 1-hour infusion versus placebo in healthy elderly male and female

volunteers. Twelve healthy elderly volunteers who were at least 65 years of age were enrolled into the study and randomized (in a 9:3 ratio) to receive AZD9742 or placebo. The study consisted of a total of 3 visits of which one (Visit 2) was residential (4 nights). Serial blood and urine samples for pharmacokinetic assessments and safety measurements were taken prior to and over 72 hours after the start of infusion.

Target subject population and sample size

The target population was healthy elderly male and postmenopausal female volunteers, as judged by the Investigator, aged 65 years or older, with a body mass index between 18 and no more than 30 kg/m^2.

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

Investigational product, dosage, and mode of administration: Nine (9) of the 12 healthy elderly volunteers received a single dose of 750 mg AZD9742 administered as a 1-hour infusion on Day 1. The dose of AZD9742 and infusion duration were determined based on current clinical data from the multiple ascending dose study. The dose and infusion rate/time were selected such that the average maximum AZD9742 plasma concentration was likely less than 25.1 μM. Batch number: 10-003076AZ.

Comparator, dosage, and mode of administration: The investigational product-matching placebo was supplied by Bio-Kinetic Clinical Applications, LLC. Placebo was supplied as a sterile 5% dextrose solution and was administered via intravenous infusion at the same rate as that of AZD9742. Batch number: C800839.

Duration of treatment

The duration of each healthy elderly volunteer's participation in the study was approximately 43 days, including a screening period of 28 days, one residential period of 5 days, and a follow-up visit 5 to 10 days after discharge. Each volunteer received a single intravenous dose of study medication. The duration of the study was 1 month from screening until the last follow-up evaluation.

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 healthy elderly volunteers as possible to study medication and procedures.

The safety, tolerability, and pharmacokinetic data were summarized using descriptive statistics or frequency counts in tables, listings, and graphs, as appropriate.

Plasma concentrations and pharmacokinetic parameters were summarized using appropriate descriptive statistics, including 95% confidence intervals. Amounts of AZD9742 and fractions of the dose recovered in the urine were reported for each collection interval,

cumulatively, and overall. Figures of geometric mean concentration-time data were presented on both a linear and semi-logarithmic scale. Concentration-time data were also graphically presented on linear and semi-logarithmic scales for each healthy elderly volunteer.

Subject population

There were 12 volunteers who participated in the study and completed the study per protocol with 9 volunteers in the AZD9742 and 3 volunteers in the placebo groups. There were 6 (50.0%) men and 6 (50.0%) women and the race for all volunteers was white. The mean age at screening for all volunteers was 71.3 ±5.73 years and ranged from 64 to 85 years. All volunteers were at least 65 years of age at dosing. Demographics and baseline characteristics were well balanced between the treatment groups. All volunteers were considered healthy and there were no ongoing concomitant medications at study entry.

Summary of pharmacokinetic results

The summary of AZD9742 pharmacokinetic parameters is presented in Table S2.

Table S2 Summary pharmacokinetic parameters of AZD9742 in healthy elderly volunteers (pharmacokinetic analysis set)

Variable	Geometric mean (CV%) [n=9]
AUC (μM·h)	54.1 (30.3%)
AUC/Dose (μM·h/mg)	0.0721 (30.4%)
C_{max} (μM)	16.2 (36.9%)
C_{max}/Dose (μM/mg)	0.0216 (36.8%)
t_{max}[a] (h)	1.00 (1.00 – 1.00)
$t_{½λz}$ (h)	15.1 (20.9%)
CL (L/h)	30.0 (30.3%)
V_{ss} (L)	114 (33.3%)
$A_{e(0-72)}$ (mg)	45.2 (45.0%)
$f_{e(0-72)}$ (%)	6.03 (45.0%)
CL_R (L/h)	1.81 (32.7%)

[a] t_{max}: median (range) presented.

Following a single dose of 750 mg AZD9742 over a 1-hour infusion in healthy elderly volunteers, maximum concentrations were reached at the end of the infusion. After cessation of the infusion, concentrations fell rapidly in a multi-exponential manner with geometric mean concentrations at the 12-hour and 24-hour time points approximately 2.4% and 0.5%, respectively, of geometric mean C_{max}. However, a long terminal elimination phase with small residual concentrations was observed with $t_{½λz}$ between 11.7 hours to 22.6 hours.

Both the geometric mean C_{max} (16.2 µM) and AUC (54.1 µM·h) were below the exposure limits for C_{max} (25.1 µM) and AUC (193 µM·h) as defined in the single ascending dose (D2690C00001) and multiple ascending dose (D2690C00002) studies. Excretion of unchanged AZD9742 via the kidney is a minor elimination pathway with approximately 6% of the dose recovered in the urine and a geometric mean CL_R of 1.81 L compared to a geometric mean CL of 30.0 L.

A further stratification of the plasma PK data seemed to show a difference between the elderly male (n=4) and elderly female (n=5) subjects. The geometric mean (CV%) values in the females versus males were: 65.2 (18.4%) versus 42.8 (24.2%) µM·h for AUC, 20.6 (20.9%) versus 12.0 (25.9%) µM for C_{max}, 24.8 (18.4%) versus 37.9 (24.2%) L/h for CL, and 92.4 (12.5%) versus 148 (31.8%) L for V_{ss}, respectively. This difference in AZD9742 plasma PK between males and females will be further confirmed with more data.

A trend of higher urinary recoveries in the healthy female elderly volunteers compared to healthy male elderly volunteers was observed [geometric mean (CV%) $f_{e(0-72)}$ of 7.75% (41.6%) in females versus 4.41% (21.0%) in males] with no apparent differences the CL_R. Considering the small sample size and the high variability in the female subgroup, the difference in urinary recoveries is inconclusive. However, as excretion via the kidney has a minor contribution to the overall elimination, the observation is not anticipated to be clinically significant.

Summary of safety results

There were no deaths, serious adverse events, discontinuations due to adverse events, other significant adverse events, or adverse events of severe or moderate intensity during the study. There were a total of 4 adverse events reported in 3 volunteers including diarrhea (loose stools), pain (full body aches), and contact dermatitis (due to electrocardiogram patch irritation) in AZ9742-treated volunteers and muscle spasms (bilateral leg cramps) in a placebo volunteer. All of these events were assessed by the Investigator as mild in intensity and were resolved prior to study conclusion. The event of diarrhea was assessed by the Investigator as related to study drug; otherwise, all adverse events were considered not related.

There were no clinically relevant changes noted in mean, median, or individual clinical laboratory, vital sign, or digital electrocardiogram data following dosing. There were no symptoms observed (such as dizziness or nausea) indicative of orthostatic changes in vital signs.