AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5099
Study Code	D0910C00015
Edition Number	1
Date	18 June 2012

A Phase I, Single-center, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, and Pharmacokinetics of Intravenous AZD5099 Administered as Either a Single Infusion or Multiple Infusion in a 24 Hours Period to Healthy Male and Female Subjects

Study dates: First subject enrolled: 27 May 2011
Last subject last visit: 17 October 2011

Phase of development: Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD5099 following administration as either a single infusion or multiple infusions in a 24-hour period to healthy male and female (with nonchildbearing) volunteers	Incidence and severity of adverse events, abnormalities and time-matched comparison from Day -1 to 24 hours after the last infusion of the day of oral and core body temperature, vital sign assessments, electrocardiograms, telemetry, clinical laboratory assessments, and physical examinations.
Secondary	Pharmacokinetics	To characterize the pharmacokinetics of AZD5099 following administration as either a single infusion or multiple infusions in a 24-hour period to healthy male and female (with nonchildbearing potential) volunteers	C_{max}, t_{max}, λ_z, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $t_{1/2\lambda z}$, V_z, Vd_{ss}, CL, CL_R, $Ae_{(0-t)}$, $fe_{(0-t)}$
Exploratory	PK	To collect plasma and urine samples for possible detection and identification of AZD5099 metabolites	Presence of AZD5099 metabolites
	PG	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 AZD5099 treatment	Possible deoxyribonucleic acid genotyping analysis
	Biomarker	To collect and store plasma and serum samples from healthy volunteers for possible biomarker analysis	Possible biomarker analysis

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
		If there was clinically significant local infusion reaction, the volunteers were asked their permission to allow a skin punch biopsy for histopathological examination	Punch skin biopsy obtained per usual clinical procedures

Study design

This was a Phase I, first time in human, double-blind, randomized, placebo-controlled, parallel-group ascending dose study in healthy male and female (with nonchildbearing potential) volunteers conducted at a single center.

Although healthy male and female volunteers aged 18 to 55 years were allowed to participate in the study, only male volunteers were enrolled at study's end. Fifty-six male volunteers were enrolled in 7 different dose cohorts. For all cohorts, a staggered dosing schedule was used. Two volunteers (1 active and 1 placebo) were dosed on the first day and the remaining 6 volunteers (5 active and 1 placebo) were dosed on the third day, 48 hours after dosing of the initial volunteers.

Following a screening period of up to 28 days, volunteers who met eligibility criteria checked into the Clinical Pharmacology Unit (CPU) on Day -2 and underwent various safety and compliance checks. On Day -1, serial vital signs (under the same fasting condition as Day 1) were obtained throughout the day, corresponding to the measurement times on Day 1, to allow time-matched comparison of body temperature to be conducted, as hypothermia was hypothesized to contribute to rat lethality in preclinical studies.

Volunteers were randomly assigned to treatment on Day 1, and following dosing, underwent serial safety and PK assessments up to 120 hours postdose (ie, 5 days). Volunteers were discharged on Day 6 and a follow-up visit occurred 5 to 10 days after discharge.

Target subject population and sample size

Up to 80 healthy male and female (with nonchildbearing potential) volunteers aged 18 to 55 years, inclusive, may have been enrolled into the study. Fifty-six male volunteers aged 18 to 52 years were enrolled in the study and randomly assigned to treatment.

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

The study medication (20 mg/mL AZD5099 in 45 mL sterile solution; batch number P827) was supplied by the Sponsor. The investigational product-matching placebo was administered via intravenous infusion at the same rate as the investigational product. Cohorts 1 through 5

received the following respective doses of AZD5099 or placebo daily as a 2-hour intravenous infusion: 10, 25, 60, 180, and 300-mg. Cohort 6 was administered 500 mg AZD5099 or placebo daily as a 4-hour intravenous infusion. The dose for Cohort 7, 400 mg AZD5099 or placebo, was divided as 2 intravenous infusions of 2-hour duration each, given 12 hours apart relative to the start of the first infusion. No further increases in dosing were administered as it was predicted that higher doses would exceed the prespecified exposure limits.

Duration of treatment

The duration of volunteer participation was approximately 46 days, from the time of screening until study discharge, including 8 days of confinement in the clinical pharmacology unit.

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.

Adverse events were summarized for each treatment group by system organ class and preferred term. Tabulations and listings of data for vital signs, clinical laboratory tests, electrocardiograms, physical examination, and oral and core body temperature were presented as appropriate.

Pharmacokinetic concentrations and parameters of AZD5099 in plasma and urine were summarized using descriptive statistics and graphic displays as appropriate. Pharmacokinetic parameters such as area under plasma concentration-time curve, maximum concentration, etc. were shown graphically as appropriate, for preliminary dose proportionality analyses.

Subject population

Of the 56 volunteers enrolled in the study, all 56 (100%) were randomly assigned to treatment, received treatment and completed treatment at the 1 study site. Fifty-five (98.2%) of the 56 volunteers enrolled completed the study. One volunteer in Cohort 7 discontinued from the study due to volunteer decision on Day 5, 4 days after completing Day 1 treatment. All end-of-study assessments were completed for this volunteer on Day 5, prior to withdrawal. All volunteers were included in the safety and PK analysis sets.

Although this study allowed the enrollment of females of nonchildbearing potential, at the time of the study's end, only males were enrolled in this study. Otherwise, the volunteer's demographics and baseline values were well balanced across the 7 treatment cohorts. Of the 56 volunteers, 5 (8.9%) were Asian, 11 (19.6%) were black, 34 (60.7%) were white, and 6 (10.7%) were of other race. The mean age of all volunteers was 31±7 years (range from 18 to 52 years); mean height was 176±7 cm; mean weight was 78.1±10.1 kg; and mean body mass index was 25.2±2.8 kg/m^2. Medical histories were unremarkable and the use of concomitant medications overall were minimal.

Summary of pharmacokinetic results

The summary of key pharmacokinetic parameters of AZD5099 is presented in Table S2.

Table S2 Geometric mean (%CV) of key plasma pharmacokinetic parameters of AZD5099

	AZD5099 Dose (mg)						
Parameter (unit)	**10 mg QD (n = 6)**	**25 mg QD (n = 6)**	**60 mg QD (n = 6)**	**180 mg QD (n = 6)**	**300 mg QD (n = 6)**	**500 mg QD (n = 6)**	**200 mg BID (n = 6)**
AUC (ng·h /mL)	ND	3420 (23.9)	6750 (30.9)	27400 (38.5)	40100 (20.6)	93800 (54.9)	49200 (33.5)
$AUC_{(0-t)}$ (ng·h /mL)	747 (37.8)	2800 (30.3)	6660 (31.7)	27200 (38.2)	39800 (21.8)	93700 (55.0)	49100 (33.6)
$AUC_{(0-24)}$ (ng·h /mL)	746 (35.2)	2530 (27.4)	5900 (30.1)	23200 (33.7)	35900 (25.5)	84800 (56.2)	40900 (34.9)
C_{max} (ng/mL)	250 (29.6)	765 (18)	1850 (18.2)	6690 (25.2)	11200 (25.1)	18100 (54.4)	ND
C_{max1} (ng/mL)	ND	ND	ND	ND	ND	ND	7350 (23.2)
C_{max2} (ng/mL)	ND	ND	ND	ND	ND	ND	6480 (28.1)
t_{max} (h)	2 (2-2.05)	2 (2-2.17)	2.01 (2-2.1)	2 (1.85-2.03)	2 (2-2)	4.02 (4-4.13)	ND
t_{max1} (h)	ND	ND	ND	ND	ND	ND	2.03 (2-2.05)
t_{max2} (h)	ND	ND	ND	ND	ND	ND	14.03 (13.98-14.1)
$t_{1/2\,\lambda z}$ (h)	ND	16.2 (17)	14.4 (37.6)	17.8 (72.6)	10.6 (123)	10.6 (40.2)	12.4 (40.6)
CL (L/h)	ND	7.31 (23.9)	8.89 (30.9)	6.55 (38.4)	7.48 (20.6)	5.33 (54.8)	8.13 (33.5)
V_Z (L)	ND	171 (17.1)	184 (71.4)	168 (56.4)	114 (145.1)	81.4 (87)	145 (74.4)
V_{dss} (L)	ND	67.7 (27.1)	74.7 (37.8)	69 (34.4)	57 (76.6)	35.6 (67.2)	109 (42.5)

Note: ND: not determined; 500mg dose group: 4 hour intravenous infusion; other dose groups: 2 hour intravenous infusion; 200 mg dose group: C_{max1} and t_{max1} for morning dose and C_{max2} and t_{max2} for afternoon dose.

Plasma PK parameters, $t_{½\,\lambda z}$, CL, V_z, and V_{dss} in the 10 to 500 mg dose range, appared to be no trend of dose dependency.

Based on the visual observation of the exposure data, and estimates of slope, the peak and total exposure of AZD5099 appears to be dose proportional in the 10 to 500 mg dose range. This was supported by results of the power model which yielded 90% confidence intervals for the slope of 1.04 to 1.25 for AUC and 1.06 to 1.17 for C_{max}.

A very small fraction of the administered AZD5099 dose was excreted unchanged in the urine (fe<0.12%) and the excretion was not dose dependent.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Pharmacogenetics analysis was completed and is reported separately from this report.

Summary of safety results

There were no deaths, serious adverse events, adverse events of severe intensity, or adverse events that led to discontinuation reported during the study. The occurrence of adverse events was minimal, with 10 (23.8%) active-treated volunteers overall who reported at least one adverse event. Of these, 5 (11.9%) active-treated were assessed by the Investigator as related to study treatment. There were 7 (50%) placebo-treated volunteers who reported at least one adverse event. There were no dose-related trends observed in the reporting of adverse events, and all postdose adverse events were of mild intensity. The most frequently reported events overall were diarrhea, headache, and dizziness. There were no safety concerns identified in clinical laboratory test, vital signs, electrocardiograms, or physical examinations. There were no volunteers with clinical signs or symptoms of hypothermia or hyperthermia.