AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8418
Study Code	D2590C00001
Edition Number	1
Date	01 September 2010

A Phase I, Single-center, Randomized, Double-blind, Placebo-controlled Single-ascending Dose, First Time Into Man Study to Assess the Safety, Tolerability, and Pharmacokinetics (Part A) and an Open-label Assessment of the Effect of Food on the Pharmacokinetics (Part B) of Orally Administered AZD8418 in Healthy Male and Female Subjects

Study dates:
Phase of development:

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: Quintiles Phase I Services, Overland Park, Kansas, United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the safety and tolerability of AZD8418 following the oral administration of single ascending doses and to estimate the maximum tolerated dose in healthy volunteers.	Adverse events, supine and standing blood pressure and pulse rate, respiratory rate, oral temperature, pulse oximetry, electrocardiogram variables, physical examination, clinical laboratory variables, Columbia Suicide Severity Rating Scale	Safety
Secondary	**Secondary**	
To characterize the pharmacokinetics of AZD8418 and its metabolites, AZ12606278 and AZ12818644, in plasma and urine, and provisionally assess the dose proportionality of the pharmacokinetics following administration of single ascending doses of AZD8418.	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, λ_z, MRT, $t_{1/2\ \lambda z}$, CL/F, V_{ss}, V_z/F, Ae, f_e, and CL_R of AZD8418	Pharmacokinetic
	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, λ_z, $t_{1/2\ \lambda z}$, Ael, and CL_R of AZ12606278 and AZ12818644	
To assess the effect of food on the safety and PK profile of AZD8418 and its metabolites.	Food interaction part of the study was not executed.	Pharmacokinetic
Exploratory	**Exploratory**	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD8418.	Genetic analysis	Pharmacogenetic

Study design

This was a randomized, double-blind, placebo-controlled parallel-group, single-center study. The study was to consist of 2 parts, a dose escalation part (Part A) and a food interaction part (Part B). Due to the trial being stopped early, the food interaction part (Part B) of the trial was not executed.

Part A of the study assessed the safety, tolerability, and pharmacokinetics of AZD8418 and its metabolites, AZ12606278 and AZ12818644, following single ascending dose administration of AZD8418 to healthy male and female volunteers. The study design for Part A allowed a

gradual escalation of dose with intensive safety monitoring to ensure the safety of the volunteers. In total, up to 40 healthy volunteers were exposed to single doses during the dose escalation.

Eight volunteers participated in each cohort. Volunteers were randomized such that 6 volunteers received AZD8418 and 2 volunteers received placebo. Each volunteer was only dosed once. The starting dose was 0.5 mg. Administration of the next and subsequent doses of AZD8418 was based on Safety Review Committee review of available safety, tolerability, and pharmacokinetic data from the previous doses. The provisional dose escalation was 0.5 mg, 1 mg, 2 mg, 4 mg, and 8 mg.

Target subject population and sample size

Approximately 40 healthy male and female (women of nonchildbearing potential or on an accepted method of contraception) volunteers within an age range of 18 to 45 years were to be enrolled.

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

AZD8418 powder for oral suspension, 20 mg (Lot numbers 09-007975AZ and 10-000980AZ) and 2000 mg (Lot number 09-007971AZ) (the Quintiles Phase I unit constituted to achieve stock suspensions of 0.2 mg/mL to 20 mg/mL). Doses administered to volunteers were 0.5, 1, 2, 4, and 8 mg.

Placebo was commercially available Ora-Plus® Oral Suspending Vehicle, NDC number 0574-0303-16 (Lot numbers 9328071 and 9297815). Placebo volumes were equivalent to the active dose for each study cohort.

Duration of treatment

For Part A, each volunteer received a single dose of AZD8418 or placebo. The duration of volunteer participation was approximately 45 days including a 30-day screening period, a 4-night/5-day confinement period and a follow-up period 5 to 10 days after discharge.

Part B of the study was not executed.

Statistical methods

Safety data were presented in individual listings. Tabular presentations of adverse events were presented.

Plasma concentrations, urine amounts and fractions excreted, and pharmacokinetic parameters for AZD8418 and its metabolites AZ12606278 and AZ12818644 were summarized by dose group using descriptive statistics and plotted as appropriate.

Preliminary dose proportionality for each analyte was assessed visually using plots of dose-normalized AUC, $AUC_{(0-t)}$, and C_{max} versus dose to conclude whether the data suggested dose proportionality. Subsequently, the PK analysis dataset was analyzed using an analysis of

covariance model with the logarithm of area under the curve as the dependent variable (Y) and the logarithm of the dose as the independent variable (X).

For Part B, no food-effect analysis was done since the food interaction part of the study was not executed.

Subject population

The first volunteer was enrolled on 23 November 2009 and the last volunteer completed the study on 31 March 2010. Forty male volunteers were enrolled and received investigational product. No females were randomized into the study. All 40 volunteers randomized to treatment completed the study. Six volunteers each received single doses of 0.5, 1, 2, 4, or 8 mg AZD8418 on one occasion. Single doses of placebo were received by 10 volunteers each.

The volunteer population consisted of 40 healthy males with a mean age of 26 years and a mean body mass index of 24.9 kg/m^2.

All 40 volunteers who were enrolled in the study were included in the safety and pharmacokinetic analyses.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

AZD8418 was rapidly absorbed across all doses (median t_{max} range: 0.50 to 1.00 hours), with mean plasma concentrations at doses up to 1 mg falling below limit of quantitation by 5 hours postdose. At doses greater than 1-mg AZD8418, plasma concentrations were quantifiable for up to 36 hours postdose. The first metabolite, AZ12606278 was formed rapidly (median t_{max} range: 1.25 to 3.00 hours) across all doses of AZ8418, with a second peak in plasma concentrations observed at 10 hours postdose. The second metabolite, AZ12818644, reached C_{max} between 5.00 and 10.02 hours postdose.

The geometric mean terminal half-life of AZD8418 at the highest dose (8 mg) was 9.4 hours. The geometric mean terminal half-life of AZ12606278 ranged from 12.6 to 15.9 hours across AZD8418 doses up to 4 mg, estimated at 30.9 hours at the 8 mg dose level. The geometric mean terminal half-life of AZ12818644 ranged from 14.2 to 18.1 hours across AZD8418 doses up to 4 mg, estimated at 29.8 hours at the 8 mg dose level.

After a single dose of AZD8418 at 8 mg dose level, the geometric mean C_{max} reached was 41.1, 60.0, 10.3 ng/mL, and the geometric mean AUC reached was 159, 1730, 565 ng*h/mL, for AZD8418, AZ12606278, AZ12818644, respectively.

With escalating doses of AZD8418, the Cmax of AZD8418 and the AUC of AZD8418, AZ12606278, and AZ12818644, tended to increase greater than in proportion to dose. While this preliminary analysis doesn't support a conclusion of dose proportionality for AZD8418,

AZ12606278, or AZ12818644, this study is exploratory in nature and was not designed to have sufficient sample size or statistical power to draw any definitive conclusions.

AZD8418 was only recovered in urine over the 0 to 6 hour interval at the 4 and 8 mg dose levels with a fraction of less than 0.2% excreted. AZ12818644 was only recovered in urine for up to 12 and 24 hours at the 4 and 8 mg dose levels with a fraction of less than 0.12% excreted. AZ12606278 was recovered in urine for up to 24 hours (2 mg and 4 mg) and 72 hours (8 mg) with a fraction of less than 0.12% excreted.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

AZD8418 at doses up to 8 mg was generally well tolerated when administered as a single dose and no dose-limiting toxicities were observed. There were no deaths, other serious adverse events, discontinuations of investigational product due to adverse events, or any other significant adverse events in the study. A total of 23 adverse events were reported by 19 volunteers in the study. Volunteers in all treatment groups (0.5, 1, 2, 4, 8 mg AZD8418 and placebo) experienced adverse events. The number of volunteers who experienced adverse events was comparable across active treatment groups, and was comparable between active treatment and placebo. The most common adverse events were application site dermatitis, upper respiratory tract infection, back pain, dizziness postural, and headache (all occurring in 1 placebo volunteer and 1 active-treated volunteer each). The only treatment-related adverse events were balance disorder (1 volunteer receiving 0.5 mg AZD8418), dizziness postural (1 volunteer receiving 4 mg AZD8418 and 1 volunteer receiving placebo), and migraine with aura (1 volunteer receiving 1 mg AZD8418).

There were no adverse events of severe intensity during study conduct. There were 3 treatment-emergent adverse events of moderate intensity in active-treated volunteers, including migraine with aura (1 mg AZD8418), muscle enzymes increased (1 mg AZD8418), and back pain (4 mg AZ8418). Of these, only migraine with aura was judged as related to study medication. All other treatment-emergent adverse events reported in active-treated and placebo volunteers were considered mild in intensity.

In general, changes in laboratory safety values, vital signs, ECG findings, physical examination findings, or Columbia Suicide Severity Rating Scale results were unremarkable and any changes of note were not considered significant enough to discontinue volunteers from the study due to the results.

Date of Report

01 Sept 10