AstraZeneca

Clinical Study Report Synopsis

Drug Substance AZD5213

Study Code D3030C00001

Edition Number 1

[redacted]

A Phase I Study of Orally-administered AZD5213 in Healthy Male and Non-fertile Female Subjects Including a Randomized, Double-blind, Placebo-controlled, Parallel-group Assessment of the Safety, Tolerability and Pharmacokinetics of Single Ascending Dose (Part 1) and an Open-label Assessment of the Effect of Food on the Pharmacokinetics (Part 2)

Study dates: First subject enrolled: 05 May 2010
Last subject last visit: 22 December 2010

Phase of development: Clinical pharmacology (I)

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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

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety and tolerability of single ascending oral doses of AZD5213, and to estimate the maximum tolerated dose, if within the predefined exposure and dose limits, in healthy male and non fertile female volunteers (Part 1)	Adverse events, laboratory variables, pulse, blood pressure (including orthostatic), body temperature, electrocardiograms, Columbia Suicide Severity Rating Scale, and sleep diary	Safety
Secondary	**Secondary**	
To investigate single-dose pharmacokinetics and dose proportionality of orally-administered AZD5213 in healthy male and non fertile female volunteers (Part 1)	AUC, C_{max}, t_{max}, $t_{1/2}\lambda z$, CL/F, VZ/F, CL_r , A_e , and fe_{po}	Pharmacokinetics
To investigate the potential effect of food on AZD5213 pharmacokinetics after administration of AZD5213 as an oral solution (Part 2)	AUC, C_{max}, t_{max}, $t_{1/2}\lambda z$, CL/F, VZ/F	Pharmacokinetics
Exploratory	**Exploratory**	
To collect and store DNA samples for future exploratory genetic research	Future exploratory genetic research	Pharmacogenetics

Results of the exploratory analysis are not included in this report.

Study design

The study consisted of 2 parts, a dose escalation part (Part 1) and a food interaction part (Part 2), with healthy male and female volunteers of nonchildbearing potential. In both parts, volunteers were admitted to the Clinical Pharmacology Unit on Day -1, following an up to 30 day screening period. A follow-up visit occurred 7 to 10 days after last dose of study medication. Each volunteer in the dose escalation part (10 dose cohorts of 8 volunteers each) received AZD5213 (or placebo) only once on Day 1. The doses of AZD5213 were 0.1, 0.3, 1.0, 2.0, 5, 10, 20, 30, 50, and-80 mg.

Volunteers in the food interaction part (8 volunteers) received a single AZD5213 dose of 10-mg on 2 different occasions. Under Treatment A (fed), volunteers received AZD5213 30-minutes after a high-fat, high-calorie breakfast; under Treatment B (fasted), volunteers received AZD5213 after a 10-hour fast. Volunteers were assigned in a random manner to 1 of 2 sequences of dosing treatments (Sequence AB or Sequence BA).

Target subject population and sample size

The target population consisted of healthy male and female volunteers of nonchildbearing potential 18 to 50 years of age inclusive at the day of enrollment. Each volunteer met all of the inclusion criteria and none of the exclusion criteria at the time of randomization. The volunteer population was selected without bias.

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

AstraZeneca supplied the investigational product and placebo to the Investigator as an oral solution (0.1-mg/mL [batch 10-000896AZ] in 50 mL bulk bottle; 2-mg/mL [batch 10-000897AZ] in 50 mL bulk bottle; placebo [batch 09-001559AZ] in 100 mL bulk bottle). The Pharmacist at the clinical pharmacology unit dispensed AZD5213 or matching placebo oral solutions from study specific bulk bottles provided to the site.

Duration of treatment

Dose escalation:

Each volunteer received a single dose of AZD5213 or placebo. The duration of volunteer participation was approximately 40 days including a 30-day screening period, a 5-night/6-day residential period and a follow-up period 7 to 10-days after the last of investigational product was administered.

Food interaction:

Each volunteer received a single dose of AZD5213 on 2 different occasions (Period 1 and Period 2) in an open-label crossover fashion. The duration of volunteer participation was approximately 50 days including a 30-day screening period, a 5-night/6-day residential period, at least a 7-day washout period, a second 5-night/6-day residential period, and a follow-up period at 7 to 10 days after the last dose of IP was administered.

Statistical methods

In the dose escalation and food interaction parts, the safety, tolerability data were summarized using descriptive statistics. Dose proportionality in the dose escalation part was assessed graphically and analyzed by using the power model approach. Least-squares estimates and 95% confidence intervals for slope and intercept were presented.

For the food interaction part, the primary pharmacokinetic parameters were analyzed using an analysis of variance model on the log-transformed $AUC_{(0-\infty)}$ and C_{max} with fixed effects for

sequence, period, and treatment and volunteer nested within sequence as a random effect. Geometric means, ratios of geometric means (fed/fasted), and the associated 95% confidence intervals were presented.

Subject population

There were 80 healthy adult male and female volunteers in the dose escalation part, with a mean age of 27 years. There were 8 healthy male volunteers (by chance, no females were enrolled) with a mean age of 31 years in the food interaction part. All volunteers were assigned in a random manner to study drug. The pharmacokinetic population included all volunteers who received at least 1 dose of AZD5213 and had 1 measured AZD5213 plasma concentration at a scheduled pharmacokinetic time point postdose. There were 6 volunteers per cohort who received the active treatment in the dose escalation part (total of 60 volunteers accross the 10 cohorts), and two volunteers receiving placebo per cohort (total of 20 volunteers across the 10 cohorts). There were 8 subjects who received the active treatment under the fasted and fed conditions in the food interaction part.

The safety population included all 88 volunteers (dose escalation and food interaction parts) enrolled in the study through last contact.

Summary of pharmacokinetic results

Dose escalation:

Following single oral dose administration in the 0.1 to 80-mg dose range, the geometric mean AZD5213 plasma concentrations were above the limits of quantitation for 12-hours (0.1-mg dose), 24-hours (0.3 to 1-mg dose), 36-hours (2.5-mg dose), or 48-hours (5 to 80-mg doses).

AZD5213 was rapidly absorbed following a single oral dose with median t_{max} being independent of dose. Following t_{max}, the AZD5213 plasma concentrations declined in a mostly monophasic manner. Elimination half-life, total body clearance, volume of distribution, and renal clearance of AZD5213 appeared to be independent of the administered dose. Urinary excretion of AZD5213 is a minor route of drug elimination (only 10% to 15% of dose).

Regression analysis indicated that both peak (maximum concentration) and total (area under the curve) AZD5213 plasma exposures are dose proportional in the 0.1 to 80-mg dose range.

Food interaction:

Following administration of 10-mg AZD5213 with a standardized high-fat breakfast, the mean AZD5213 plasma concentrations were quantifiable for 48-hours (last time point observed) following dosing in most subjects.

AZD5213 median t_{max} was slightly delayed when given with food (1.75-hours in fed versus 1.50-hours in fasted regimens). Exposure parameters appeared to be similar between the

fasted and fed treatments. The mean terminal elimination half-life of AZD5213 was similar in both the fasted and fed states.

Although C_{max} was 6% lower in the fed state, this was not considered clinically relevant. AUC was similar between fasted and fed treatments. Therefore, there was no significant food effect for AZD5213 exposure parameters.

Summary of safety results

There were no deaths, serious adverse events, adverse events leading to discontinuation, or other adverse events.

In the dose escalation part, there was a trend in the number of adverse events at the higher doses of AZD5213 (30 to 80-mg AZD5213), the most frequent adverse events being night sweats, nausea, sleep disturbance, and feeling hot.

In the food interaction part overall, there were 6 volunteers with adverse events reported during the fed period and 3 volunteers during the fasted period. The frequency of subjects with treatment-related AEs was similar across the 2 periods, fed (3 [37.5%] volunteers) and fasted (2 [25.0%] volunteers). Sleep disturbance and anxiety were the most frequent adverse events during the food interaction part.

There were no clinically relevant changes in hematology, blood chemistry, vital signs, electrocardiograms, urinalysis, or physical and neurological examination findings following dosing.

At doses of 10-mg or greater, the combined frequency of a single worst event per subject of self-assessed rating of either a "difficult night" or "very poor night" was more than twice (10 mg: n=3 or 50%; 20-mg: n=2 or 34%) that observed in the placebo group (n=2 or 10%). All volunteers receiving 50 and 80-mg AZD5213 rated their sleep as "fair," "difficult," or "very poor." At 50-mg, 5 out of 6 (83%) volunteers reported a "difficult" night; at 80-mg, 33% rated their sleep as "difficult" and 50% as "very poor." At doses of 20-mg or greater, at least 4 of 6 volunteers (67%) had a single category (1-point) shift (worsening) in their sleep quality compared to baseline; and at least 2 of the 4 volunteers (≥33%) had a shift of 2 categories or more. There was a trend in decreased nighttime sleep duration on Night 1 (post-dose) in more than half of all volunteers receiving 20-mg AZD5213 and in all volunteers who received 50 or 80-mg AZD5213, with an association to sleep-related AEs (sleep disturbance and night sweats). These trends were maintained on Night 2 in at least half of the volunteers receiving 50 and 80-mg AZD5213.

Based on the total number of AEs in the 80-mg cohort (total AEs = 28), and specifically those related to sleep (sleep disturbance and night sweats [n=10]), as well as decreased sleep duration and worsening in sleep quality, it was determined that this dose was not tolerated. The 50-mg dose was well tolerated in 5 out of 6 volunteers. There was an overall decrease in AEs (n =21), as well as a decrease of sleep-related AEs (n=7) in the 50-mg cohort.

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