AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5213
Study Code	D3030C00002
Edition Number	1
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A Phase I, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral AZD5213 After Administration of Multiple Ascending Doses for 10 Days in Healthy Male and Non-fertile Female Volunteers

Study dates: First subject enrolled: 12 July 2010
Last subject last visit: 29 May 2011

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was conducted at 3 sites; 2 sites in Sweden and 1 site in the 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 AZD5213 at steady state following administration of multiple ascending doses in healthy young male, nonfertile female, and elderly volunteers	Adverse events, laboratory variables, vital signs, electrocardiograms, physical and neurological examinations, Columbia Suicide Severity Rating Scale, and sleep diaries	Safety
Secondary	**Secondary**	
To characterize single-dose and multiple-dose pharmacokinetics, dose proportionality, time to reach steady state, and degree of accumulation and time dependency of orally-administered AZD5213 in healthy young male, nonfertile female, and elderly volunteers	C_{max}, $C_{ss,max}$, $C_{ss,min}$, $C_{ss,avg}$, t_{max}, $t_{ss,max}$, λ_z, $\lambda_{ss,z}$, $t_{1/2\lambda z}$, $t_{1/2\lambda z,ss}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-24)ss}$, AUC, CL/F, CL_{ss}/F, V_z/F, Rac_{AUC}, Rac_{Cmax}, %_Fluctuation, time dependency, $Ae_{(0-24),ss}$, $f_{e,ss,po}$, and $CL_{R,ss}$	Pharmacokinetic
Exploratory[a]	**Exploratory**	
To collect a blood sample aimed at establishing a panel of deoxyribonucleic acid samples to enable exploratory genetic research and exploring the impact of genetic characteristics that may affect the pharmacokinetic and pharmacodynamic (including biomarkers), safety, and tolerability related to treatment with AZD5213.	Future exploratory genetic research	Pharmacogenetic
To obtain blood and urine samples for possible exploratory analysis to investigate the presence and/or identity of drug metabolites of AZD5213	Future metabolite research	Pharmacokinetic

[a] Results of exploratory analyses are not included in the clinical study report.

Study design

This was a Phase I randomized, double-blind, placebo-controlled, parallel-group, multi-center assessment of the safety, tolerability, and pharmacokinetics of AZD5213 following single and multiple ascending dose administration to healthy young (18 to 50 years of age, inclusive) and elderly (65 to 80 years of age, inclusive) male and nonfertile female volunteers. The study

design allowed a gradual escalation of dose between panels with safety monitoring to ensure the safety of the volunteers. The study was conducted at 3 sites; 2 sites in Sweden and 1 site in the United States.

The starting dose was determined from the results of the single ascending dose study (D3030C00001) and the doses given in this study were first evaluated and found to have acceptable safety and tolerability in the single ascending dose study. The starting dose for the current study was 1 mg and was expected to yield an exposure in the mid-range of the projected therapeutic exposure. Considering the short half-life of approximately 4 to 5 hours, steady-state exposure following multiple-dose administration was anticipated to be similar to that following the single 1 mg dose. The highest dose was chosen to give exposure at steady state (maximum concentration [$C_{ss,max}$] or area under the concentration-time curve [$AUC_{(0-24,ss)}$]), equivalent to that at the highest single-dose C_{max} or AUC in the single ascending dose study with acceptable safety and tolerability.

Up to 72 healthy young and elderly volunteers were planned for enrollment in up to 9 cohorts total for each of the 2 age groups (8 healthy volunteers per cohort; 6 active and 2 placebo). Each healthy volunteer received AZD5213 (or placebo) for a total of 11 daily doses (single dose on Day 1 and repeated daily doses on Days 3 to 12). The cohort with young volunteers was exposed before the elderly cohort at each dose level. Volunteers who withdrew from the study due to reasons other than an adverse event were permitted to be replaced at the discretion of the Sponsor and/or Investigator.

Safety monitoring included assessment of adverse events, clinical laboratory evaluations, measurement of vital signs, recording of electrocardiograms, telemetry, and physical and neurological examinations. During the inpatient portion of the study, a sleep diary for self-assessment of quality and duration of sleep was completed. The Columbia-Suicide Severity Rating Scale was completed on Day -1, Day 14, and at the follow-up visit. Intensive blood sampling for pharmacokinetic analysis was conducted following dosing on Days 1 and 12; trough samples were collected on Days 5, 7, 10, and 11.

Target subject population and sample size

The target population consisted of healthy young male and nonfertile female volunteers aged 18 to 50 years, inclusive, and healthy elderly male and female volunteers aged 65 to 80 years, inclusive. Eight volunteers participated in each cohort and received either AZD5213 or placebo, randomized 6:2, for a total of 72 planned study participants.

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

AstraZeneca supplied the investigational product as an oral solution (0.1 mg/mL and 2 mg/mL in 50 mL bulk bottles). The Pharmacists dispensed AZD5213 oral solutions from study-specific bulk bottles provided to the sites. Doses administered in this study included (in the order of administration) 1, 3, 6, 18, 10, and 14 mg AZD5213 and placebo administered to young volunteers and 1, 6, and 10 mg AZD5213 and placebo administered to elderly volunteers.

Comparator, dosage, and mode of administration

The matching placebo oral solution was supplied by AstraZeneca in containers matching the AZD5213 product. Placebo volumes were equivalent to the active dose for each study cohort and were dispensed in matching specific bulk bottles provided to the site.

Duration of treatment

The study consisted of a screening visit (up to 30 days prior to study start), an inpatient treatment phase of 18 days (Days -1 to 17 with a single dose of investigational product on Day 1 and multiple daily doses from Days 3 to 12), and a follow-up visit 7 to 10 days after the last dose.

Statistical methods

Adverse events were summarized for each treatment group by system organ class and preferred term. Clinical laboratory, vital sign, and digital electrocardiogram results were summarized using descriptive statistics. The quality of sleep assessments from the self-reported sleep diary were summarized by the single worst event and for each night during the study. The self-reported and sleep log durations and awakenings of night-time (2000 to 1000) and day-time (1000 to 2000) sleep periods were summarized.

Pharmacokinetic concentrations and parameters for AZD5213 in plasma and urine were summarized using descriptive statistics and graphic displays as appropriate.

Single dose (Day 1) and multiple dose (steady state) dose proportionality of AZD5213 was assessed graphically and analyzed using the power model approach for pharmacokinetic parameters, AUC and C_{max}, on Day 1, and $AUC_{(0-24),ss}$ and $C_{ss,max}$ on Day 12. Age groups (young and elderly) were analyzed separately. Least-squares estimates and 95% confidence intervals for slope and intercept were presented.

An exploratory assessment of age effects on the dose-normalized AUC and C_{max} on Day 1, and $AUC_{(0-24),ss}$ and $C_{ss,max}$ on Day 12 was performed. A linear effects analysis of variance model was performed and geometric means together with confidence intervals (2-sided 95%) for AUC and C_{max} were estimated. Also, ratios of geometric means together with confidence intervals (2-sided 95%) were estimated for elderly versus young at each dose level.

The time dependency of the pharmacokinetics was evaluated by comparing $AUC_{(0-24),ss}$ (Day 12) with AUC (Day 1). For each dose level, a linear mixed-effect analysis of variance was performed and geometric means together with confidence intervals (2-sided 95%) were estimated and the ratios of geometric means together with confidence intervals (2-sided 95%) for $AUC_{(0-24),ss}$/AUC were estimated and presented. From this model, the ratios of accumulation $AUC_{(0-24),ss}$ (Day 12)/$AUC_{(0-24)}$ (Day 1), and $C_{ss,max}$ (Day 12)/C_{max} (Day 1) were also estimated by calculating ratios of the geometric least-squares means and presented with confidence intervals.

In addition to a graphical assessment of the steady state for AZD5213, a statistical evaluation of the steady state was also performed using the trough (predose) plasma concentrations

collected on Days 5 through 12 and Day 12, 24 hours (Day 13) by dose level. All valid concentrations on the natural-log scale were analyzed using a repeated measures analysis of variance model with treatment day as a fixed repeated effect and volunteer as a random effect. Dose levels and age groups (young and elderly) were analyzed separately.

Subject population

There were a total of 73 study participants at 3 study sites with 48 young volunteers (6 each in the 1, 3, 6, 10, 14, and 18 mg AZD5213 groups and 12 in the placebo group) and 25 elderly volunteers (6 each in the 1, 6, and 10 mg AZD5213 groups and 7 in the placebo group). There were 68 volunteers who completed all study procedures (44 young volunteers and 24 elderly volunteers). There were 4 volunteers in the 18 mg AZD5213 young group who were withdrawn from the study after Day 7 dosing for adverse events of sleep disorder. One volunteer in the elderly placebo group withdrew from the study at his discretion after dosing on Day 4 and an additional volunteer was enrolled at the discretion of the Sponsor.

Of the 73 study participants, there were 56 volunteers enrolled at Site 1 in the United States (all 48 young volunteers and 8 elderly volunteers) and 9 and 8 elderly volunteers at Site 2 and Site 3, respectively, in Sweden.

The mean age for all volunteers was 45 ±20 years (32 ±10 years [range: 19 to 50 years] for young volunteers and 71 ±4 years [range: 65 to 79 years] for elderly volunteers) and there were 64 (87.7%) men and 9 (12.3%) women. The race for 54 (74.0%) volunteers was white, for 15 (20.5%) volunteers was black, for 2 (2.7%) volunteers was Asian, and for 2 (2.7%) volunteers was American Indian/Alaskan native. The demographic characteristics for cohorts in young volunteers were generally well balanced. The 6 and 10 mg elderly groups had slightly more women (3 and 2, respectively) than the 1 mg (all male) group with slightly lower weight and body mass index as a result.

All study participants were healthy and without significant ongoing medical conditions and no previous medications were continued during study conduct. Five volunteers received 25 mg diphenhydramine orally for adverse events of sleep disorder: 1 volunteer from the 3 mg AZD5213 young group and 4 volunteers from the 18 mg AZD5213 young group. Two volunteers (1 each in the 10 mg AZD5213 young and 10 mg AZD5213 elderly groups) received paracetamol for adverse events of headache. There were 17 volunteers who were treated with topical hydrocortisone during the study for electrocardiogram patch irritation.

All 73 volunteers were part of the safety analysis set and all young and elderly volunteers who received AZD5213 (N= 54) were included in the pharmacokinetic analysis set.

Summary of pharmacokinetic results

Following single oral dose administration (Day 1) in young volunteers (1- to 18-mg dose range) and in elderly volunteers (1- to 10-mg dose range), the geometric mean AZD5213 plasma concentrations were above the limit of quantitation (greater than 0.1 nmol/L) for 36 hours after the 1-mg dose and up to 48 hours after the remaining doses. Following multiple oral dose administration (Day 12) in young volunteers (1- to 14-mg dose range) and

in elderly volunteers (1- to 10-mg dose range), the geometric mean AZD5213 plasma concentrations were above the limit of quantitation for 48 hours (last collection time point) after all doses, except the 1-mg dose in elderly which was quantifiable only up to 36 hours postdose.

In young and elderly volunteers, AZD5213 was rapidly absorbed following both single and multiple oral dosing with median t_{max} (0.67 to 1.79 hours) being independent of dose. Following t_{max}, the AZD5213 plasma concentrations declined in a mostly monophasic manner.

Geometric mean elimination half-life (ranged from 4.9 to 7.1 hours), renal clearance (1.8 to 3.2 L/h), total oral clearance (21 to 28 L/h), and oral volume of distribution (161 to 226 L) appeared to be dose-independent in both young and elderly volunteers following single and multiple dosing. Overall, intersubject variability of key pharmacokinetic parameters were low as reflected by low geometric coefficient of variation for AUC (15% to 32%) and C_{max} (9% to 28%) in young and elderly volunteers after single and multiple dosing. Accumulation for exposure parameters between Days 1 and 12 was minimal in both young and elderly volunteers (ranged from 1.02- to 1.19-folds for $AUC_{(0-24)}$ and 0.95- to 1.37-folds for C_{max}). Pharmacokinetics of AZD5213 was time-independent in both young and elderly volunteers. Steady state was generally reached within 4 days of multiple dosing (on Day 7). Exploratory statistical comparison of dose-normalized key pharmacokinetic parameters revealed no relevant differences in exposure parameters between young and elderly volunteers on Days 1 and 12 ($C_{ss,max}$ was 9% higher in elderly volunteers). Urinary recovery of unchanged orally administered drug ranged from 10% to 14% in young and 9% to 11% in elderly, indicating urinary excretion of AZD5213 as unchanged drug is not the primary route of elimination.

Regression analysis of single and multiple dose data indicated that both peak (maximum concentration) and total (area under the curve) AZD5213 plasma exposures are dose proportional in the range of 1 to 14 mg in young (1 to 18 mg on Day 1) and 1 to 10 mg in elderly volunteers.

Summary of safety results

There were no deaths or serious adverse events reported during study conduct. Four volunteers from the 18 mg AZD5213 young group were withdrawn after Day 7 dosing (following 5 days of once-daily dosing) due to adverse events of sleep disorder. Adverse events of severe intensity were reported in 2 volunteers from the 18 mg AZD5213 young (sleep disorder) and 1 volunteer from the 10 mg AZD5213 elderly (nausea) groups.

In the young cohorts, 31 (86.1%) of AZD5213-treated and 7 (58.3%) placebo-treated volunteers reported at least 1 adverse event. In young volunteers, the most commonly-reported (3 or more AZD5213-treated volunteers) adverse events were sleep disorder, night sweats, application site irritation, feeling hot, headache, abnormal dreams, nausea, and contact dermatitis. Less commonly reported (1 volunteer each) adverse events related to sleep quality included initial insomnia, nightmare, and poor quality sleep. With the exception of abnormal dreams, the frequency of adverse events related to sleep disturbances and nausea suggested a trend with increasing dose.

In the elderly cohorts, 15 (83.3%) AZD5213-treated and 5 (71.4%) placebo-treated volunteers reported adverse events. In the elderly volunteers, the most frequently reported adverse events were headache, sleep disorder, insomnia, and nausea. Less commonly reported events that were related to sleep disturbances included abnormal dreams and nightmare.

No clinically relevant trends were noted in clinical laboratory variables and no adverse events were reported for abnormal laboratory findings. No clinically relevant trends were noted in vital sign findings in any position (supine, 2-minute standing, and 5-minute standing) and no clinically relevant orthostatic changes were noted in blood pressure or pulse following dosing. No clinically relevant trends were noted in electrocardiogram findings.

Quality of sleep assessments were similar across dose groups in young volunteers up to 10 mg AZD5213; at 14 mg and 18 mg, young volunteers reported diminished sleep quality. At 6 and 10 mg AZD5213, elderly volunteers reported diminished sleep quality.

No obvious change in sleep duration (self-reported or derived from sleep log) in young volunteers up to 10 mg AZD5213 was noted. A dose-dependent trend of decreasing sleep duration during the 14 and 18 mg AZD5213 treatments was observed and no development of dose tolerance was evident. There was no obvious change in self-reported sleep duration in elderly volunteers at 1 and 6 mg AZD5213, but self-reported sleep duration decreased following the 10 mg AZD5213 treatment. Sleep-log derived duration of sleep following 6 and 10 mg AZD5213 was shorter than for placebo volunteers.

No obvious treatment differences were noted in the frequency of night-time sleep periods/awakenings or day-time sleep periods in either population, with the exception of the night-time sleep in young volunteers receiving 18 mg AZD5213 once daily.