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A Phase I, Single Centre, Double-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD5213 after Oral Administration of Single and Multiple Ascending Doses in Healthy Young and Elderly Japanese Subjects

Study dates:

Phase of development:

First volunteer enrolled: 16 April 2011
Last volunteer last visit: 13 October 2011
Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at one centre in Japan.

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**	
The primary objective of this study was to investigate the safety and tolerability of AZD5213 following single and multiple oral doses of AZD5213 in healthy young and elderly Japanese volunteers.	Adverse events, vital signs (body temperature, blood pressure and pulse rate), weight, temporal and quality aspects of sleep, physical examination, clinical chemistry, haematology, urine analysis, evaluation of 12-lead digital electrocardiogram (dECG) (QT/QTc interval, rhythm, rate, morphology), 12-lead paper ECG (pECG), telemetry, ophthalmological findings (fundoscopy and near/distant visual acuity) and Columbia-Suicide Severity Rating Scale (C-SSRS)	Safety
Secondary	**Secondary**	
The secondary objective of this study was to characterise single-dose and multiple-dose pharmacokinetics (PK) of orally administered AZD5213 in healthy young and elderly Japanese volunteers.	Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{\frac{1}{2}\lambda z}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F), apparent volume of distribution during terminal phase (V_z/F), renal clearance (CL_R), cumulative amount of drug excreted unchanged in urine (A_e) and fraction of orally administered drug excreted unchanged in urine ($f_{e,po}$).	Pharmaco kinetics
	Maximum plasma concentration at steady state ($C_{ss,max}$), time to steady state C_{max} ($t_{ss,max}$), minimum plasma concentration at steady state ($C_{ss,min}$), average plasma concentration at steady state ($C_{ss,avg}$), terminal half-life at steady state ($t_{\frac{1}{2}\lambda z,ss}$), area under the plasma concentration-time curve from zero to 24 hours at steady state ($AUC_{(0-24),ss}$), apparent plasma clearance at steady state (CL_{ss}/F), extent of accumulation on multiple dosing (Rac_{AUC} and Rac_{Cmax}), renal clearance at steady state ($CL_{R,ss}$), cumulative amount of drug excreted unchanged in urine over the dosing interval at steady state ($A_{e,ss}$), fraction of orally administered excreted unchanged in urine at steady state ($f_{e,ss,po}$), time dependency of the pharmacokinetics, dose proportionality.	
Exploratory		

Objectives	Outcome variables	Type
To identify/explore genetic variations that may affect the PK, safety and/or tolerability related to AZD5213 treatment or the target (histamine receptor H3) in DNA samples taken from consenting volunteers. An optional blood sample for genotyping will be collected and stored for this future, possible exploratory genetic research.	Future exploratory genetic research	Pharmaco genetics
To obtain blood and urine samples for possible exploratory analysis and investigate the presence and/or identity of drug metabolites of AZD5213.	Future metabolite research	Pharmaco kinetics

Study design

This was a Phase I, single centre, double-blind, randomised, placebo-controlled, parallel-group, single and multiple ascending oral dose study in healthy young male and elderly male and non-fertile female Japanese volunteers. This study consisted of two parts: one with a young volunteers group and another with an elderly volunteers group. Four dose levels were planned for young volunteers and two dose levels for the elderly volunteers.

Target subject population and sample size

Healthy Japanese young male volunteers aged 20 to 45 years and elderly male and female volunteers aged 65 - 80 years.

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

This study consisted of two part of young volunteers group and elderly volunteers group.

A single and multiple doses of AZD5213/placebo were given as an oral solution. Volunteers received a single dose on Day 1 (SAD). No dose was given on Day 2. Volunteers then received multiple dose once daily from Day 3 to 12 for 10 days (MAD).

Young volunteers received 1, 3, 6 and 10 mg of AZD5213/placebo for SAD, and same dose levels of AZD5213/placebo once daily for MAD.

After completion of the young volunteers group, elderly volunteers received 6 and 10 mg of AZD5213/placebo for SAD, and same dose levels of AZD5213/placebo once daily for MAD.

The doses were changed if needed, as decided by the Safety Review Committee (SRC).

Comparator, dosage and mode of administration

Placebo solution to match AZD5213.

Duration of treatment

Each volunteer received a single dose of AZD5213 or placebo on Day 1. Repeated dosing commenced on Day 3 with AZD5213 or placebo once daily for 10 days (Day 3 - 12). The volunteers were discharged after confirming volunteer's safety which is available at 48 hours after the last dosing (Day 14).

Statistical methods

No formal statistical hypothesis testing was performed. Safety, tolerability and pharmacokinetic data were summarised descriptively including tables, listings and graphs, as appropriate. Dose proportionality of PK variables was evaluated using a power model.

Subject population

In total, 32 Japanese young (aged 20 to 45) male volunteers (6 each in the 1, 3, 6 and 10 mg AZD5213 group and 8 in the placebo group), and 16 elderly male and female volunteers (6 each in the 6 and 10 mg AZD5213 group and 4 in the placebo group) were randomised into the study at 1 study site, each received 1 administration of study drug during the planned treatment visit. All 48 volunteers randomised to treatment completed the study. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety analysis included all randomised volunteers.

The mean age for all volunteers was 41.3±20 years and there were 39 (81.3%) men and 9 (18.8%) women. Overall, the demographic characteristics for treatments in each young and elderly volunteer group were generally well balanced.

Summary of pharmacokinetic results

Following single oral dose administration (Day 1) in young healthy volunteers (1 to 10 mg dose range) and in elderly healthy volunteers (6 and 10 mg), the median t_{max} was between 0.67 and 1.26 hours in young healthy volunteers and 0.67 hours in elderly healthy volunteers. In general, small inter-individual variability was seen in the C_{max} and AUC. In young healthy volunteers, the geometric means of AUC and C_{max} increased with ascending dose of 1 to 10 mg AZD5213 with AUC of 156 to 1420 h·nmol/L and C_{max} of 29.0 to 227 nmol/L, respectively. The AUC and C_{max} increased approximately dose proportionally. Elderly healthy volunteers showed geometric mean values of 1160 and 1780 h·nmol/L for AUC and 209 and 315 nmol/L for C_{max} after 6 and 10 mg AZD5213, respectively.

The geometric mean apparent terminals half-lives ($t_{\frac{1}{2}\lambda z}$) after single dosing were between 4.80 and 5.95 hours in young healthy volunteers, and were 6.18 and 5.80 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL/F were between 19.6 and 23.9 L/h in young healthy volunteers, and were 15.8 and 17.2 L/h in elderly healthy volunteers, respectively.

Urinary recovery of unchanged orally administered drug ranged from 13.0 to 13.9% in young and 12.1 to 12.8% in elderly healthy volunteers. The geometric mean renal clearance estimates were only 13 to 14% of the total body clearance in healthy young volunteers and 13

and 11% in elderly healthy volunteers, indicating urinary excretion of AZD5213 as unchanged drug is not the primary route of elimination.

Following once daily oral administration of AZD5213 starting on Day 3, steady state was generally reached within 4 days (Day 7), as supported by AZD5213 pre-dose plasma concentration values. The maximum exposure levels achieved by individual healthy volunteers following multiple dosing of 10 mg AZD5213 were below the predefined exposure limits of 2,000 nmol/L (C_{max}) and 20,000 h·nmol/L (AUC). The median $t_{ss,max}$ after multiple dosing on Day 12 (the last dosing day) was between 0.50 and 0.67 hours in young and elderly healthy volunteers.

In young healthy volunteers, the geometric means of $AUC_{(0-24),ss}$ and $C_{ss,max}$ on Day 12 increased with ascending dose of 1 to 10 mg AZD5213 with $AUC_{(0-24),ss}$ of 149 to 1410 h·nmol/L and $C_{ss,max}$ of 28.1 to 286 nmol/L, respectively. The $AUC_{(0-24),ss}$ and $C_{ss,max}$ increased dose proportionally. Elderly healthy volunteers showed geometric mean values of 1090 and 1530 h·nmol/L for $AUC_{(0-24),ss}$ and 221 and 333 nmol/L for $C_{ss,max}$ after 6 and 10 mg AZD5213, respectively. The steady-state exposure to AZD5213 in elderly healthy volunteers were approximately 40 to 50% higher compared with young healthy volunteers after 6 mg AZD5213, however the difference in the AZD5213 exposure between young and elderly healthy volunteers was less pronounced at the highest dose level of 10 mg.

Following multiple dosing, the geometric mean $t_{½λz,ss}$ ranged from 5.56 to 6.89 hours in young healthy volunteers, and was 6.91 and 6.78 hours in elderly healthy volunteers, respectively. The corresponding geometric mean CL_{ss}/F were between 20.5 and 25.8 L/h in young healthy volunteers, and was 16.8 and 19.9 L/h in elderly healthy volunteers, respectively.

The accumulation of AZD5213 in plasma over time was minimal in both young and elderly volunteers (ranged from 0.93 to 1.03 for $AUC_{(0-24)}$ and 0.97 to 1.26 for C_{max}). The exposures/PK of AZD5213 appeared to be time-independent after multiple oral dose administration for both young and elderly volunteers.

Summary of safety results

There were no deaths, serious adverse events (SAEs), discontinuation of study due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study. All the AEs were of mild intensity with the exception of 1 moderate AE (insomnia) observed in 1 elderly volunteer who received 10 mg AZD5213.

In the young cohorts, 5 (20.8%) of AZD5213-treated volunteers reported at least 1 AE. No AEs were reported in the placebo group. In young volunteers, insomnia was observed in 3 volunteers (1 volunteer in the 3 mg AZD5213 group and 2 volunteers in the 10 mg AZD5213 group). One volunteer in the 10 mg AZD5213 group experienced feeling hot and night sweats. All of these adverse events were of mild intensity. Orthostatic hypotension was reported from 1 volunteer in the 10 mg AZD5213 group. However, it was considered unrelated to the AZD5213 by the investigator (see Section 8.3).

In the elderly cohorts, 9 (75.0%) AZD5213 treated and 1 (25.0%) placebo-treated volunteers reported AEs. The most frequently reported AEs were feeling hot, insomnia and night sweats. Some volunteers reported multiple adverse events. In the 10 mg AZD5213 group, 2 volunteers experienced insomnia, feeling hot and night sweat, and one volunteer experienced feeling hot and insomnia. In the 6 mg AZD5213 group, one volunteer experienced feeling hot and night sweats. All the events were of mild intensity with the exception of 1 moderate event of insomnia that was observed in 1 volunteer (E0001085) who received 10 mg of AZD5213. This event was considered related to AZD5213 by the investigator.

No clinically relevant treatment-related changes or trends were noted in clinical laboratory variables and no AEs were reported for abnormal laboratory findings. No clinically relevant treatment-related changes or trends were noted in mean or median vital sign findings in any position (supine, 2 minute standing, and 5-minute standing) and no clinically relevant orthostatic changes were noted in mean or median blood pressure or pulse following dosing. No clinically relevant treatment-related changes or trends were noted in mean or median digital ECG intervals.

There were no clinically significant changes in physical examination including neurological examination. The results of C-SSRS assessments indicated there were no volunteers with suicidal ideation or behaviour during the study. No volunteers who had abnormal finding in ophthalmological examination at the screening and the follow-up.

Self-reported quality of sleep assessments were similar across dose groups in young volunteers up to 6 mg AZD5213. In the 10 mg AZD5213 group, 4 (66.7%) of young volunteers reported a difficult or very poor night as the single worst sleep event. Elderly volunteers in all dose groups, including the placebo, tended to have worse quality of sleep than young volunteers. However, there were no obvious difference across dose groups.

No obvious change in sleep duration (self-reported or derived from sleep log) in young volunteers up to 6 mg AZD5213 was noted. However self-reported sleep duration decreased during the 10 mg AZD5213 treatment. There was no obvious change in self-reported sleep duration in elderly volunteers at 10 mg AZD5213 and placebo, however self-reported sleep duration decreased during the 6 mg AZD5213 treatment.

There was no obvious relationship between AZD5213 doses up to 10 mg in young volunteers and up to 10 mg in elderly volunteers and the number of volunteers with night-time awakenings/day-time sleep period.