AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00010
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A Phase I, Single-center, Randomised, Double-blind, Placebo-controlled Single Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of AZD7325 in Healthy Male Japanese Subjects

Study dates: First healthy volunteer/patient enrolled: 15 October 2008
Last healthy volunteer/patient completed: 09 March 2009

Phase of development: Clinical Pharmacology (1)

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

Study centre(s)

This study was conducted at a single center in the United States of America. The first healthy volunteer was enrolled on 15 October 2008. The last volunteer completed the study on 09 March 2009.

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 the study was to investigate safety and tolerability of AZD7325 in healthy male Japanese subjects by assessment of adverse events (AEs), vital signs, physical examinations, electrocardiograms (ECGs) and clinical laboratory assessments	Adverse events Clinical laboratory variables Vital signs: Blood pressure, heart rate; Body temperature, weight and height ECG: resting 12-lead ECG, real time telemetry Physical examination	Safety
Secondary	**Secondary**	
The secondary objective of this study was to characterize the PK profile of AZD7325 in healthy male Japanese subjects when given orally in ascending single doses by assessment of drug concentrations in plasma and urine.	Area under total plasma concentration-time curve from zero to infinity (AUC), Area under the total plasma concentration-time curve from zero to last quantifiable concentration ($AUC_{(0-t)}$), Maximum plasma concentration (C_{max}), Time to reach C_{max} following oral administration (t_{max}), Apparent terminal elimination half-life ($t_{1/2}$), Cumulative amount of unchanged drug excreted into urine (A_e), Fraction of systemically available drug excreted into urine (f_e; parent compound only), Renal clearance of drug from plasma (CL_R)	Pharmacokinetic
An exploratory objective was to collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence response (ie distribution, safety, tolerability and efficacy of AZD7325 treatment).	Voluntary sample donation; no results to be presented in this report.	Pharmacogenetic

Study design

This was a Phase I, randomised, double-blind, placebo-controlled, SAD study in healthy Japanese male volunteers conducted at a single centre. The study design allowed a gradual escalation of dose with intensive safety monitoring by a Safety Review Committee (SRC) to

ensure the safety of the subjects. Up to 48 healthy subjects aged 20 to 50 years participated in a maximum of 6 cohorts. Eight subjects participated in each cohort and received either AZD7325 or placebo, randomised 6:2. In each cohort, subjects were dosed sequentially in order of random number.

Target subject population and sample size

Healthy Japanese male volunteers from 20 to 50 years of age were selected for this study.

Forty-eight, male subjects were enrolled; 6 subjects received AZD7325 at each dose level and 2 subject received placebo. All 48 subjects completed the study and were evaluated for safety and PK data.

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

Single oral doses of 2, 5, 15, 30, 50 and 75 mg AZD7325 or placebo were administered.

Table S2 Details of investigational product

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD7325	1 mg capsule	AstraZeneca	F13581	Lot #: 08-001689AZ
AZD7325	5 mg capsule	AstraZeneca	F13582	Lot #: 08-001718AZ
AZD7325	10 mg capsule	AstraZeneca	F13583	Lot #: 08-001719AZ
Placebo to match AZD7325 capsules	0 mg to match 1, 5, and 10 mg capsules	AstraZeneca	F13586	Lot #: 08-001709AZ

Duration of treatment

Single dose

Statistical methods

All analyses were performed under the direction of the Biostatistics Group, AstraZeneca. All calculations were performed with the SAS® software, unless otherwise stated. Given the exploratory nature, no formal statistical hypothesis testing was performed in this study.

All subjects who received at least one dose of randomised investigational product, AZD7325 or placebo, and for whom post-dose data were available were included in the safety population. See CSP Section 13.1.3 for details of PK analysis population.

Data for all enrolled subjects are presented in the data listings. For those listings or data summaries where baseline and change from baseline measurements were presented, unless

stated otherwise, the last observed measurement prior to the first dose of treatment medication was considered the baseline measurement.

To achieve the primary objective, safety and tolerability were evaluated in terms of AEs, vital signs, physical examinations, ECG, and clinical laboratory assessments. Adverse events were and summarized by system organ class, and dose. Vital signs (including orthostatic vitals), clinical laboratory measures and digital ECG (dECG) were summarized using descriptive statistics by protocol time and dose. Data were presented by actual dose (not by the cohort), and subjects receiving placebo were pooled across cohorts for the purposes of summarization of safety results.

To achieve the secondary objectives, PK of AZD7325 was evaluated by assessment of drug and metabolite concentrations in plasma and urine. If possible, individual PK parameters were calculated and tabulated along with descriptive statistics for each dosing group. Dose linearity was explored through graphical presentation. Pharmacokinetic analyses were performed using WinNonlin, Version 5.1 (Pharsight Corporation, Mountain View, California, USA).

Subject population

The first healthy volunteer entered the study on 15 October 2008, and the last healthy volunteer finished the study on 09 March 2009. In total, 48 Japanese male healthy volunteers were randomised into the study at a single study site. Each received 1 administration of study drug during the planned treatment visit. All healthy volunteers randomised to treatment completed the study.

A few protocol deviations were reported in the study; most involved the timing of study procedures. There were no protocol deviations that led to exclusion of data from the PK or safety analyses. The safety analysis included all randomised healthy volunteers. The PK population included all subjects randomized to AZD7325.

Overall, the treatment groups were comparable with regards to demographic and baseline characteristics. All of the subjects enrolled were male of Asian race and Japanese ethnicity

The study progressed through the dose escalation with none of the subjects fulfilling any of the stopping criteria.

Summary of pharmacokinetic results

C_{max} and AUC after all oral doses of AZD7325 were below the pre-set human maximum plasma exposure safety levels (C_{max} = 1240 ng/mL and AUC = 8399 hr*ng/mL).

The plasma PK profile of AZD7325 was assessed from predose to 48 hours post-dose. Most subjects had quantifiable plasma concentrations through 36 to 48 hours post-dose.

AZD7325 was absorbed quickly following oral administration of all dose levels. Median t_{max} was 0.51 h for the 5 mg dose level, 0.75 h for the 2 and 30 mg dose levels, 1.00 h for the 15 mg dose level, and 1.25 h for the 50 and 75 mg dose levels.

The geometric mean C_{max}, $AUC_{(0-t)}$ and AUC steadily increased with each increasing dose level. Geometric mean C_{max} increased from 10.7 ng/mL (2 mg) to 427 ng/mL (75 mg), across the dose levels. $AUC_{(0-t)}$ and AUC parameter values were very similar for each dose level. Geometric mean AUC ranged from 43.8 ng*h/mL to 2239 ng*h/mL for the 2 mg to 75 mg dose range. For AZD7325, the increases in AUC and C_{max} over a dose range of 2 to 75 mg appear dose-proportional.

AZD7325 PK data exhibit low to moderate variability: C_{max} %CV ranged from 25 to 47% depending on the dose. AUC %CV ranged from 15 to 45%, with exception of the 2 mg dose level, which had a high %CV at 79%.

Geometric mean $t_{½}$ and CL/F were consistent across dose levels; range 8.9 (2 mg) to 15.6 h (30 mg) for t½ and range 33.1 L/h (50 mg) to 45.7 L/h (2 mg) for CL/F.

Visual inspections of the plots for systemic exposure (C_{max} and AUC) show the increases in C_{max} and AUC to be dose proportional when plotted on a linear scale and a logarithmic scale.

The AZD7325 urine PK profile was assessed from 0-72 hours post-dose. Urine concentrations for the 2 mg and 5 mg dose levels were below the limit of quantification. Quantifiable AZD7325 urine concentrations were available only for the 15, 30, 50 and 75 mg doses.

The renal elimination of AZD7325 was insignificant. The amount of unchanged drug excreted in urine (A_e) was minimal but increased with each dose level; geometric mean range 1044 ng (15 mg dose) to 4067 ng (75 mg dose). The fraction of drug excreted into urine (f_e) was minimal but remained consistent across the mid to higher dose levels; geometric mean range 0.006 to 0.007%.

Renal clearance from plasma (CL_R) was also low and remained consistent; geometric mean CL_R was 0.0026, 0.0025, 0.0019 and 0.0018 L/h for the 15, 30, 50 and 75 mg dose levels.

Summary of safety results

There were no deaths, serious adverse events (SAEs), or other significant AEs in the study.

During this study, a total of 33 AEs were reported by 24 subjects (20 [56%] subjects on active and 4 [33%] subjects on placebo). All AEs were of mild intensity and resolved by the completion of the study without medical intervention. Of the 33 AEs reported, 88% (29 events) had at least a possible causality to the study treatment.

The highest incidence of AE reporting (6 of 6 subjects, 100%) occurred at the 30 mg and 75 mg dose levels. The lowest incidence of AE reporting (0%) occurred at the 2 mg dose, followed by the 50 mg dose (2 of 6 subjects, 33%) and the 5 and 15 mg doses (3 of 6 subjects,

50% each) per reporter. Four of 12 subjects (33%) of the subjects administered placebo reported an AE.

The most frequently (> 20% of subjects per dose) reported AEs in any system organ class at any dose level were: psychiatric disorders (euphoric mood [an exaggerated feeling of well being]); gastrointestinal disorders (dry mouth), and nervous system disorders (dizziness, dysaesthesia [tactile impairment], and somnolence).

Euphoric mood was the most common AE, reported by 6 active subjects. The next most common AE was somnolence, reported by 5 active subjects.

There were no clinically significant chemistry, haematology or urinalysis laboratory values measured in healthy volunteers exposed to AZD7325 during the study, and no AEs were related to abnormal laboratory values.

There were no clinically relevant (treatment related) changes or trends in blood pressure or heart rate during the study in healthy volunteers exposed to AZD7325. Variations in mean supine and orthostatic vital signs were similar between the AZD7325 treatment groups and placebo.

None of the abnormalities exhibited on resting ECG were assessed as clinically significant, at any time point for any subject. There were no AEs related to ECG measurements.

There were no resting QTcF > 500 msec. There was no change from baseline > 30 msec in resting QTcF measured at follow-up.

For continuous ECG monitoring, a categorical summary of maximum prolongation from baseline for QT interval parameters showed a few instances of increases from baseline > 30 and < 60 msec for QTcB, QTcF and QTcX intervals. There were no increases from baseline > 60 msec. The QTc increases were observed at 4 h (75 mg), 8 h (2 mg) and 24 h (75 mg) post dose for QTcX, 6 h (2 mg) and 8 h (2 mg) post dose for QTcF and at 1 h (15 mg), 6 h (2, 15 and 30 mg) and 8 h (2 and 30 mg) post dose for QTcB. Only the single QTcB increase at the 1 h post dose for the 15 mg dose occurred at t_{max} (median 1.0 h).

Isolated increases in QTc intervals were not accompanied by signs/symptoms, and no AEs were reported at these times, with exception of Subject 303 (15 mg AZD7325) who experienced mild dizziness, somnolence and hypoaethesia (onset 30 minutes post dose) and a 35.5 msec increase from baseline in QTcB at 1 h post dose. These events occurred close to the time of peak AZD7325 plasma concentration for this subject, which was 1.5 h post dose.

None of the subjects exhibited an absolute prolongation of QTcF > 500 msec. None of the subjects exhibited a QTcF, QTcB or QTcX prolongation from baseline > 60 msec and none of the subjects had QTc intervals > 480 msec.

QTcB and QTcF did not exhibit any significant changes following AZD7325 administration compared to placebo. None of the changes in QTcB, QTcF and QTcX were dose dependent.

For the time points measured when peak plasma AZD7325 concentrations were observed (median t_{max} 0.51 to 1.25 h), mean QTcB did not increase over baseline at 0.5 h post dose; increased over baseline at 1 h post dose for the 2 mg (0.50 msec), 15 mg (5.77 msec) and 75 mg (1.57 msec) dose levels, and increased at 1.5 h post dose for 2 mg (4.15 msec), 15 mg (4.72 msec), 50 mg (0.47 msec) and 75 mg (5.03 msec). The increase for placebo at 1 h post dose was 0.47 msec and no increase was seen 0.5 and 1.5 h post dose.

Mean QTcF did not increase over baseline at 0.5 h post dose; increased over baseline at 1 h post dose for the 5 mg (2.97 msec), 15 mg (3.00 msec) and 75 mg (2.65 msec) dose levels, and increased at 1.5 h post dose for 2 mg (1.45 msec), 5 mg (2.38 msec), 15 mg (3.40 msec), 50 mg (1.23 msec) and 75 mg (6.83 msec). The placebo group did not have mean QTcF increases at 0.5, 1.0 or 1.5 h post dose.

Mean QTcX increased over baseline at 0.5 h post dose for the 5 mg (1.52) dose level; increased at 1 h post dose for the 5 mg (8.43 msec), 50 mg (0.43 msec) and 75 mg (4.52 msec) dose levels, and increased at 1.5 h post dose for 5 mg (8.23 msec), 15 mg (1.42 msec), 30 mg (2.80 msec), 50 mg (2.62 msec) and 75 mg (9.77 msec). The placebo group did not have mean QTcX increases at 0.5, 1.0 or 1.5 h post dose.