AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00015
Edition Number	1.0
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A Single-center, Single-blind, Randomized, Placebo-controlled, Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics After Single and Multiple Ascending Oral Doses of AZD1305 Extended-release Capsules in Healthy Male Japanese and Caucasian Subjects

Study dates:

First subject enrolled: 28 January 2009
Last subject last visit: 10 November 2009
Study terminated: 20 November 2009

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)

One (1) center with 18 Japanese healthy male volunteers. For center, see above.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary objective

- To evaluate the safety and tolerability of AZD1305 after single and repeated oral doses of AZD1305 extended-release (ER) capsules in healthy male Japanese and Caucasian subjects

Secondary objectives

- To evaluate the pharmacokinetics (PK) of AZD1305 after single and repeated oral doses of AZD1305 ER capsules in healthy male Japanese and Caucasian subjects
- To evaluate the relationship between dose / plasma concentration of AZD1305 and electrocardiogram (ECG) variables in healthy male Japanese and Caucasian subjects
- To collect and store DNA samples for potential future research into genes which may influence drug response (disposition, safety and tolerability) of AZD1305

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety and tolerability of AZD1305 after single and repeated oral doses of AZD1305 ER capsules in healthy male Japanese and Caucasian subjects	AEs Chemistry, hematology and urinalysis laboratory variables Vital signs: Blood pressure, Pulse, Body temperature dECG/ECG: resting 12-lead ECG, real time telemetry Physical examination

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Secondary	PK	To evaluate the PK of AZD1305 after single and repeated oral doses of AZD1305 ER capsules in healthy male Japanese and Caucasian subjects	Single dose parameters: AUC, $AUC_{(0-12)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, CL_R, A_e, and Total A_e after Day 1 morning dose and Day 3 evening dose Multiple dose parameters (Day 15): $AUC\tau_{\ Day\ 10}$, $C_{max\ Day\ 10}$, $t_{max\ Day\ 10}$, C_{min}, $C_{min\ Day\ 10}$, $C_{ss\ Day\ 10}$, $CL/F_{ss\ Day\ 10}$, $CL_{R\ Day\ 10}$, $A_{e\ Day\ 10}$, Fluctuation index after 10 days of multiple dose administration for both the morning dose and evening dose administered on Day 15 Comparative parameters: Rac, ratio for evaluation of the effect of time and ratio for evaluation of diurnal variation
	PK/PD	To evaluate the relationship between dose / plasma concentration of AZD1305 and ECG variables in healthy male Japanese and Caucasian subjects	Graphical methods for exploring PK and safety (dECG and laboratory) results.
Exploratory	PGX	To collect and store DNA samples for potential future research in to genes which may influence drug response (disposition, safety and tolerability) of AZD1305	Voluntary sample donation; no results to be presented in this report.

AEs = adverse events; dECG = digitial electrocardiogram; $AUC_{(0-12)}$ = area under the plasma concentration vs. time curve from time zero to 12 hours post-dose; $AUC_{(0-t)}$ = area under the plasma concentration vs. time curve from time zero to the last quantifiable concentration; t_{max} = time to C_{max}; $t_{1/2}$ = terminal half-life; CL/F = oral plasma clearance; CL_R = renal clearance of drug from plasma; A_e = amount of drug excreted unchanged in urine per collection interval; Total A_e = cumulative amount of drug excreted unchanged in the urine; $AUC_{\tau\ Day10}$ = area under the plasma concentration vs. time curve from time zero to the dose interval τ; $C_{max\ Day\ 10}$ = maximum plasma concentration on Day 15; $t_{max\ Day\ 10}$ = time to $C_{max\ Day10}$; $C_{min\ Day\ 10}$ = minimum plasma concentration on Day 15; C_{min} = trough concentration measured prior to each dose during multiple dosing; $C_{ss\ Day\ 10}$ = average plasma concentration at start of dosing interval Day 15; CL/F Day 10 = oral plasma clearance on Day 15; $CL_{R\ Day\ 10}$ = renal clearance of drug from plasma Day 15; $A_{e\ Day\ 10}$ = amount of drug excreted unchanged in urine Day 15; Rac = accumulation ratio; PGX = pharmacogenetic

Study design

In this single ascending dose (SAD) / multiple ascending dose (MAD) study, the starting dose of AZD1305 was 50 mg. Dose escalation was to continue until the maximum tolerated dose (MTD) and/or the predefined maximum exposure level was reached with respect to AZD1305 maximum plasma concentration (C_{max}) and/or area under the plasma concentration versus time curve from time zero to infinity (AUC).

In total, 18 healthy male Japanese subjects from 20 to 45 years of age (inclusive) were randomized into the study. Two dose levels were enrolled. In each group 6 subjects received an oral AZD1305 ER capsule(s), and 3 subjects received placebo capsules. The study was not ended after the first two dose levels due to any of the above mentioned reasons. The clinical development programmes for AZD1305 were stopped, which included this study.

After each dose panel, an SRC evaluated the safety, tolerability and the PK of AZD1305 and decided on the dose for the next group; the evaluation resulted in continued dose escalation, the succeeding dose level could have been lowered or repeated, or the study could have been stopped.

Target subject population and sample size

Healthy male Japanese and Caucasian subjects between the ages of 20 and 45 years (inclusive)

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

Table S2 Details of IP and other study treatments

Investigational product	Dosage form and strength	Appearance	Manufacturer	Formulation number
AZD1305	ER capsules 50 mg	Swedish orange capsule (size 3)	AstraZeneca PAR&D, Sweden	H2076-01-01-01
AZD1305	ER capsules 125 mg	Swedish orange capsule (size 1)	AstraZeneca PAR&D, Sweden	H1997-02-01-02
Placebo	capsules	Swedish orange capsule (size DBA)	Fisher Clinical Services GmbH, Schweiz	H1604-01-01-17

Duration of treatment

Each subject was to receive a single dose of AZD1305 or placebo on Days 1 and 3 and twice a day from Day 6 through Day 15. The duration of each subject's participation was to be approximately 50 days including: 21 day screening period, 18 days/17 nights in the clinical pharmacology unit (CPU), and a follow-up visit 10 to 14 days post-dose.

Statistical methods

All analyses were performed under the direction of the Biostatistics Group, AstraZeneca. All calculations were performed with the Statistical Analysis System (SAS® version 9.1) software, unless otherwise stated.

The PK analysis of the plasma and urine concentration data for AZD1305 was performed using the WinNonlin Version 5.1 or later (Pharsight Corporation, Mountain View, California, USA).

The safety analysis set included all subjects who received at least 1 dose of AZD1305 or placebo and for whom post-dose data were available.

To achieve the primary objective, AZD1305 safety and tolerability were evaluated in terms of AEs, vital signs, physical examinations, ECG, and clinical laboratory assessments. Continuous variables were summarized using descriptive statistics (number [n], mean, standard deviation [SD], minimum [min], median, maximum [max]) by treatment group. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment group. Graphical presentations, including line graphs showing individual or mean development over time and shift plots showing pre-treatment values on horizontal axis and post-treatment values on vertical axis, were used as appropriate.

The PK analysis population included all subjects who satisfied all the following: (1) received at least 1 dose of study compound measured for PK analyses; (2) completed the study without any major protocol deviation that interfered with the absorption, distribution, metabolism, or excretion of the compound to be measured; and (3) provided evaluable data in support of the PK analyses.

To achieve the secondary objectives, the PK of AZD1305 was evaluated by assessment of drug concentrations in plasma and urine. If available, plasma concentration and PK parameters (as detailed in Section 12.2 of the CSP) were listed for the subjects. All PK parameters were summarized for the PK analysis population, by dose. All parameters were summarized by n, arithmetic mean, SD, geometric mean (gmean), coefficient of variation (CV), geometric coefficient of variation (GCV), median, min, and max.

Dose proportionality was analyzed separately for single dose and after repeated dosing. A linear mixed effect analysis model using the logarithm of the PK variable (AUC and C_{max} for single dose and AUCτ and C_{max} for repeated dosing) as dependent variable and the logarithm of dose as independent variable (covariate) was performed.

Subject population

Eighteen healthy Japanese male subjects were enrolled and randomized to active treatment or placebo in a ratio of 2:1. Demography and baseline characteristics were similar across the two active treatments, as were active treatments compared to placebo.

Safety data were available for all 18 randomized subjects.

PK data were available for all 12 subjects on active treatment following single dose and for 10 subjects on active treatment following multiple dose. Two subjects administered AZD1305 50 mg (subjects 107 and 108) discontinued from the study due to personal reasons.

Table S3 Details of IP and other study treatments

	Treatment Group		
	Japanese 50 mg N = 6	**Japanese 125 mg N = 6**	**Placebo N = 6**
Enrolled	6 (100.0%)	6 (100.0%)	6 (100.0%)
Randomised	6 (100.0%)	6 (100.0%)	6 (100.0%)
Received IP	6 (100.0%)	6 (100.0%)	6 (100.0%)
Completed the study	4 (66.7%)	6 (100.0%)	5 (83.3%)
Discontinued from the study	2 (33.3%)	0	1 (16.7%)
Reason for discontinuation			
Subject Decision	2 (33.3%)	0	1 (16.7%)

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Single dose data

The predefined maximum exposure limits for AUC (41 µmol * h/L) and C_{max} (5.5 µmol/L) were not reached. The maximum C_{max} was 0.275 µmol/L following a single morning dose and the maximum AUC was 4.45 µmol*h/L after a single evening dose.

Morning Dose (Day 1)

Geometric mean C_{max} after a single morning dose of AZD1305 was 0.08 µmol/L and 0.14 µmol/L and was attained at a median t_{max} of 8.5 hours and 8 hours, respectively, for the 50 and 125 mg doses. Geometric mean AUC was 0.99 h*µmol/L and 1.92 h*µmol/L, respectively, for the 50 and 125 mg doses.

Geometric mean $t_{½}$ was approximately 8 hours at both dose levels. Geometric mean CL/F was 117 L/h and 150 L/h, respectively, at the 50 and 125 mg doses.

Evening Dose (Day 3)

Geometric mean C_{max} after a single evening dose of AZD1305 was 0.08 µmol/L and 0.18 µmol/L and was attained at a median t_{max} of 14 hours and 11.5 hours, respectively, for the 50 and 125 mg doses. Geometric mean AUC was 1.16 h*µmol/L and 2.70 h*µmol/L, respectively, for the 50 and 125 mg doses.

Geometric mean $t_{1/2}$ was 10 and 8 hours, respectively, for the 50 and 125 mg doses. Geometric mean CL/F was 99 L/h and 107 L/h, respectively, at the 50 and 125 mg doses.

The single dose data suggest that AZD1305 exposure increased with dose with moderate variability between dose levels (based on GCV%). Higher total exposure (AUC) was observed after the evening dose especially in the 125 mg dose, while peak exposure (C_{max}) was similar after morning and evening single doses.

Multiple dose data

The predefined maximum exposure limits for AUC (41 h*nmol/L) and C_{max} (5.5 nmol/L) were not reached after multiple doses of 50 mg and 125 mg AZD1305. The maximum C_{max} was 0.626 µmol/L following multiple morning doses and the maximum AUC was 5.25µmol/L after multiple morning doses.

Morning Dose

Geometric mean C_{max} was 0.21 µmol/L and 0.35 µmol/L, respectively, for the 50 and 125 mg doses and was attained at median t_{max} of 5.5 hours for both dose levels. Geometric mean AUC_{tau} was 1.86 h*µmol/L and 3.27 h*µmol/L, respectively, for the 50 and 125 mg doses.

Geometric mean fluctuation index was 0.31 and 0.46, respectively for the 50 and 125 mg doses.

Evening Dose

Geometric mean C_{max} of 0.13 µmol/L and 0.21 µmol/L was attained at a median t_{max} of 12 hours and 9.5 hours, respectively, for the 50 and 125 mg dose. Geometric mean AUC_{tau} was 0.91 h*µmol/L and 1.83 h*µmol/L, respectively, for the 50 and 125 mg doses.

Geometric mean fluctuation index was 0.37 and 0.18, respectively, for the 50 and 125 mg doses.

Multiple dose data suggest that AZD1305 exposure increased with dose. Variability between dose levels was low to moderate (based on GCV%). AZD1305 exposure was higher and absorption was faster in the morning compared to the evening.

To adjust for possible carryover effects of the morning dose, geometric mean CL/F_{ss} was calculated for the morning and evening doses combined and was 83 L/h and 112 L/h, respectively, at the 50 and 125 mg doses.

Influence of time (MAD)

Median $t_{½}$ ranged from 8 to 10 hours after single dose administration suggesting that steady state should be attained after 2 days of twice daily dosing which was observed when looking at the median trough plasma concentrations.

The accumulation ratio (Rac) was 3.22 for the 50 mg dose level and 2.60 for the 125 mg dose level; suggesting AZD1305 accumulates with multiple twice daily administration.

AUC ratios for evaluation of the effect of time and corresponding 95% confidence intervals (CIs) were 1.16 [0.61, 1.80] and 1.10 [0.90, 1.33], respectively, for 50 and 125 mg doses, suggesting time independence in total exposure.

C_{max} ratios for evaluation of the effect of time and corresponding 95% CIs were 1.91 [0.86, 3.16] and 1.67 [1.26, 2.18], respectively, for 50 and 125 mg doses, suggesting higher peak exposures after 10 days of twice daily dosing compared to Day 1.

The ratio for evaluation of diurnal variation suggests no diurnal variation after single dosing:

- Single dose AUC: 0.85 and 0.71 for 50 and 125 mg dose levels
- Single dose C_{max}: 1.13 and 0.79 for 50 and 125 mg dose levels

The ratio for evaluation of diurnal variation shows higher AZD1305 exposure after multiple morning dosing than after multiple evening dosing.

- Multiple dose AUC: 2.04 and 1.79 for 50 and 125 mg dose levels
- Multiple dose C_{max}: 1.53 and 1.69 for 50 and 125 mg dose levels

Dose proportionality

Single dose

The systemic exposure (AUC and C_{max}) increase in a manner slightly less than dose proportional after administration of a single morning dose. The relationships were well described by a power model, predicting a 1.50 to 1.65–fold increase in exposure with a 2-fold increase in dose (Table 9).

Following a single evening dose, AUC and C_{max} increased in a dose proportional manner. The relationships were well described by a power model, predicting a 1.97 to 1.90–fold increase in exposure with a 2-fold increase in dose (Table 9).

Multiple dose

The systemic exposure (AUC and C_{max}) increased in a manner slightly less than dose proportional after multiple bid dosing. The relationships were well described by a power model, predicting a 1.39 to 1.69–fold increase in exposure with a 2-fold increase in dose.

Urine parameters

Single dose

Morning Dose (Day 1)

Total A_e (geometric mean) was 5.9 μmol and 13.0 μmol, respectively, for the 50 and 125 mg doses. CL_R (geometric mean) was 5.99 L/h and 6.79 L/h, respectively, for the 50 and 125 mg doses.

Evening Dose (Day 3)

Total A_e (geometric mean) was 5.2 µmol and 14.0 µmol, respectively, for the 50 and 125 mg doses. CL_R (geometric mean) was 4.51 L/h and 5.17 L/h, respectively, for the 50 and 125 mg doses.

A_e increased with dose. CL_R was similar for the 50 mg dose group, morning compared to evening; the confidence interval corresponding to the ratio contained 1.00 [0.486, 1.164]. However; the CL_R for the 125 mg dose group was higher after the morning dose compared with the evening dose and the confidence interval fell below 1.00 [0.660, 0.879].

Multiple dose

Morning Dose (Day 15)

Total A_e (geometric mean) was 7.75 µmol and 18.35 µmol, respectively, for the 50 and 125 mg doses. CL_R (geometric mean) was 4.2 L/hr and 5.2 L/hr, respectively, for the 50 and 125 mg doses.

Evening Dose (Day 15)

Total A_e (geometric mean) was 4.44 µmol and 12.17 µmol, respectively, for the 50 and 125 mg doses. CL_R (geometric mean) was 4.9 L/hr and 6.7 L/hr, respectively, for the 50 and 125 mg doses.

A_e increased with dose. CL_R varied little across the dose groups.

A_e was lower in the evening compared to the morning. CL_R varied little in the morning and evening.

Summary of pharmacokinetic/pharmacodynamic relationships

Scatter plots show that QTcF change from baseline increases with increases in AZD1305 concentration for single morning and evening dose and following 10 days of multiple dosing.

Scatter plots did not show that QRS duration change from baseline increases in AZD1305 concentration for single morning and evening doses or after 10 days of multiple dosing.

A concentration effect relationship was seen with increasing AZD1305 plasma concentrations and QTcF increase from baseline. Although there was moderate prolongation of QTcF, none of the QTcF increases from baseline were considered a safety concern by the investigator.

Although data are sparse with quite a lot of variability, a scatter plot shows that maximum QTcF increases with maximum AZD1305 concentration.

Summary of safety results

AZD1305 was well tolerated at the 50 and 125 mg dose levels and no safety concerns were identified. All AEs were of mild intensity and resolved by the completion of the study.

The most commonly reported AE was contact dermatitis secondary to ECG lead placement. Only one AE (palpitations) experienced by a placebo subject was considered related to treatment.

There were no clinically significant clinical laboratory parameters, vital signs measurements or physical examination findings following any dose of AZD1305 or placebo. There were no safety ECG measurements that were clinically significant and deemed a safety concern.

AZD1305 did not cause inflammatory reactions based on the CRP and body temperature data. AZD1305 did not cause negative hemodynamic effects based on the blood pressure and pulse data.

A concentration effect relationship was seen with increasing AZD1305 plasma concentrations and QTcF increase from baseline. Although there was moderate prolongation of QTcF, none of the QTcF increases from baseline were considered a safety concern by the investigator.