AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1305
Study Code	D3190C00014
Edition Number	1
Date	28 July 2009

A phase I, two-part, randomised, open, single-centre, crossover study to evaluate different extended-release formulations of AZD1305 when given as single oral doses to healthy male volunteers

Study dates: First healthy volunteer/patient enrolled: 21 February 2008
Last healthy volunteer/patient completed: 25 July 2008

Phase of development: Clinical pharmacology (I)

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

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Study centre(s)

PAREXEL Clinical Pharmacology Research Unit, Northwick Park Hospital, Harrow, Middlesex, UK

Study dates		**Phase of development**
First subject enrolled	21 February 2008	Clinical pharmacology (I)
Last subject completed	25 July 2008	

Publications

None at the time of writing this report

Objectives

The primary objective of the clinical study was:

To evaluate the pharmacokinetics of AZD1305 for six or seven extended release (ER) formulations of AZD1305 after single oral dosing relative to an AZD1305 reference (deuterium-labelled oral solution for Part A1, ER formulations for Parts A2 and B) during fasting and fed condition.

The secondary objectives of the study were:

1. To evaluate the safety and tolerability of AZD1305

2. To collect and store DNA (deoxyribonucleic acid) samples from all randomised subjects who gave additional informed consent for potential future exploratory research into genes which could influence human response to AZD1305 administration.

Study design

This was a phase-I, two-part (Parts A and B) randomised, open, single-centre, crossover study. Part A was subdivided according to the CSP into Part A1 and an optional Part A2. Part A1 was carried out before start of Part B and Part A2 was not conducted.

Part A1 consisted of four separate 2 x 2 crossover designs, with eight subjects in each. In each such design one ER test formulation (125 mg) was given orally together with an AZD1305 125 mg oral deuterium-labelled reference solution once under fasting and once under fed conditions.

Part B consisted of two separate 3 x 3 crossover designs, each with nine subjects, where the three treatment periods consisted of an ER test formulation co-administered with an immediate-release (IR) capsule under fasting and fed conditions, and an ER reference

formulation (250 mg) without food. In one of these designs 187.5 mg dose levels were used for test product, and in the other 250 mg dose levels.

Target healthy volunteer population and sample size

In total, 50 (Parts A1 and B) or 59 (Parts A1, A2 and B) healthy male subjects, aged 20 to 45 years inclusively, were planned to participate in this clinical study with Part A1 consisting of four separate 2 x 2 crossover designs with eight subjects each, and Part A2 and Part B consisting of two separate 3 x 3 crossover designs with nine subjects each.

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

Part A1: Single oral doses of 125 mg AZD1305 extended release capsules (ER-1, batch no. H1997-02-01-01; ER-2, batch no. H1997-03-01-01; ER-3, batch no. H1997-04-01-01; ER-4, batch no. H1997-05-01-01) each given in combination with 125 mg AZD1305-2H (batch no. H1896-01-01-02) as oral solution under fasting and under fed conditions.

Part B: single oral doses of 125 mg AZD1305 extended release capsules (ER-3) in combination with one (62.5 mg) and two (125 mg) immediate release capsules (batch no. H1996-01-01-01) given under fasting and fed conditions. The combinations were designated ER-6 and ER-7, respectively. Single oral doses of 2x 125 mg AZD1305 ER-3 in the fasted state were given as reference, ie designated ER-6R and ER-7R.

Duration of treatment

Part A1: Two single doses, separated by a wash-out period of seven to 21 days

Part B: Three single doses, each separated by a wash-out period of seven to 21 days

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

For AZD1305 and deuterium-labelled AZD1305:
AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, F_{rel}

Criteria for evaluation - safety (main variables)

Adverse Events, 12-lead ECG, safety laboratory, vital signs, physical examination

Pharmacogenetics

The purpose of the pharmacogenetic research was to generate data for use in future retrospective analyses. Future analyses may explore pharmacogenetic factors that may influence the pharmacokinetic profile, safety and tolerability of AZD1305 under investigation in this clinical study.

Statistical methods

The primary pharmacokinetic parameters AUC and C_{max} for AZD1305 were analysed by means of a mixed effect variance model to test for food effect (fed versus fasted) and effect of formulation (ER test formulation versus reference formulation (either deuterium-labelled oral solution or ER reference formulation) for each ER formulation separately.

For each test treatment (fed and fasted) symmetric 95%-confidence intervals for the mean treatment difference (test versus reference and fed versus fasted) for log(AUC) and log(C_{max}) were calculated. Each confidence interval (CI) was based on the t-distribution. The sum of squares of the residuals in the linear model was used to estimate the variance, which was assumed to be equal for both treatments. Applying the anti-logarithm transformation of the CIs thus obtained, CIs for the ratio of geometric means were provided.

Safety variables were analysed by descriptive methods only.

Subject population

The first healthy volunteer was enrolled on 21 February 2008 and the last healthy volunteer completed the study on 25 July 2008. In total, 52 healthy volunteers were randomised and 50 healthy volunteers received AZD1305. Two randomised healthy volunteers remained untreated and were withdrawn due to a delay in IMP administration after intake of food. All other randomised healthy volunteers received treatment as allocated except 1 healthy volunteer who was withdrawn due to an AE after dosing in the fasted state in Part A1 of the study. All 50 healthy volunteers who received treatment were included in the safety and PK analysis sets.

Summary of pharmacokinetic results

In contrast to when AZD1305 is given as oral solution all four ER formulations (ER-1 to ER-4) tested in Part A1 had an initial lag-phase of minimal absorption of AZD1305 both in fed and fasting conditions. The t_{max} occurred later (median t_{max} ranging from 5 to 12 hours during both fed and fasting conditions) for all four ER-formulations (ER-1 to ER-4) compared to oral solution (reference) with a median t_{max} of 1 hour.

Under fasting conditions, AUC of AZD1305 was higher for all 4 tested formulations in Part A1 compared to the oral solution (reference) with estimated geometric mean ratios (95% CI) for AZD1305 of of 1.61 (1.42; 1.83) for ER-1, 1.27 (1.13; 1.43) for ER-2, 1.21 (1.005; 1.45) for ER-3 and 1.42 (1.32; 1.53) for ER-4. Whereas the AUC for all four tested ER formulations in Part A1 was similar compared to oral solution (reference), C_{max} of AZD1305 was lower for all four formulations in Part A1 compared to the oral solution (reference) in fasting condition with estimated geometric mean ratios (95% CI) for AZD1305 C_{max} of 0.56 (0.43; 0.74) for ER-1, 0.395 (0.31; 0.51) for ER-2, 0.24 (0.18; 0.32) for ER-3 and 0.48 (0.38; 0.62) for ER-4. C_{max} of AZD1305 was also lower compared to oral solution (reference) in fed state for all ER formulations tested in Part A1 except for ER-2 where C_{max} was similar to the oral solution. The estimated geometric mean ratios (95% CI) were 0.45 (0.36; 0.57) for ER-1,

0.68 (0.45; 1.05) for ER-2, 0.33 (0.29; 0.39) for ER-3 and 0.499 (0.39; 0.64) for ER-4. No difference of C_{max} to reference was determined for ER-2 under fed conditions.

Intake of a high-fat, high calorie breakfast had no effect on AUC and C_{max} of AZD1305 in comparison to fasting conditions for ER-1, ER-2, ER-3 and ER-4, except for AZD1305 C_{max} of ER-2 and ER-3 that were increased. The estimated geometric mean AUC ratios (95% CI) were 0.96 (0.83; 1.12) for ER-1, 1.14 (1.00; 1.29) for ER-2, 1.12 (0.94; 1.33) for ER-3 and 1.00 (0.82; 1.20) for ER-4 and the corresponding Cmax ratios (95% CI) were 0.84 (0.64-1.12) for ER-1, 2.04 (1.41; 2.94) for ER-2, 1.38 (1.08; 1.78) for ER-3, and 1.14 (0.89; 1.46) for ER-4.

The intake of food increased AUC of AZD1305-2H between 29.6 and 55.4% whereas C_{max} was similar when AZD1305-3H was given as oral solution with or without food.

T_{max}, both in fasting and fed condition occurred within hours after dosing for ER-6 (1.0 h; 8.0 h) and ER-7 (2.0 h; 2.5 h), although with a somewhat variable t_{max} for ER-6 in fed state.

The AUC and C_{max} for ER-6 (dose-adjusted) and ER-7 were similar to the reference formulations which consisted of ER-3 pellets.

Administration of a high-fat, high-calorie breakfast had no effect on AUC or C_{max} of AZD1305 when administered as the ER-6 and ER-7 formulations.

Summary of safety results

Overall, 60 AEs were reported by 38 subjects, 45 AEs by 23 subjects in Part A1 and 14 AEs by 14 subjects in Part B. Clear differences in the type and frequency of AEs by fasted and fed conditions across all treatments of Part A1 and of Part B, respectively, were not evident. The vast majority of AEs were of mild intensity, 5 moderate AEs were reported and no AE of severe intensity was observed. The most frequent AEs were ECG abnormalities (QT prolongations), headache, palpitations and diarrhoea.

One subject experienced 4 beats of a non-sustained monomorphic tachyarrhythmia while the observed QTcF levels were normal, ie below levels usually associated with proarrythmia. This AE led to discontinuation of the subjects from study participation and was judged by the Investigator as not being related to treatment.

Reversible QT prolongations were observed after all treatments either in the fed or fasted state. In Part A1, maximum change of mean QTcF from baseline in fasted state was 31 (±16.5) ms at 1 hour post-dose and in fed state 29 (±14.5) ms at 4 hours post-dose; in Part B, the maximum increase of mean QTcF was 22 (17.5) ms at 2 hours post-dose in the fasted state, 17 (±12.9) ms at 4 hours post-dose in the fed state, and approximately 23 ms from 12 to 24 hours post-dose for the reference treatment. The maximum individual QT_{cF} interval in this study was 544 ms.

There were no clinically relevant and treatment-related changes over time evident for safety laboratory variables, vital signs, physical examination and body temperature.