Drug Substance	AZD1305	**SYNOPSIS**	(For national authority use only)
Study Code	D3190C00004		
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A Two-part, Single-centre, Open (part A) Single-blind (part B), Randomised, Placebo-controlled Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics after Single Doses with and without Food and Multiple Ascending Oral Doses of AZD1305 Extended-release Tablet in Healthy Young and Elderly Subjects

Study dates		**Phase of development**
First subject enrolled	12 April 2007	Clinical pharmacology (I)
Last subject completed	10 July 2008	

Objectives

The primary objectives of the study were:

- to (in part A of the study) evaluate the pharmacokinetics (PK) of AZD1305 for two extended-release (ER) tablets of AZD1305 after single oral dosing with and without food and relative to an oral solution of AZD1305
- to (in part B of the study) evaluate the safety and tolerability of AZD1305 when given as escalating single oral doses and as repeated escalating oral doses of an ER tablet of AZD1305

The secondary objectives of the study were:

- to (in part A of the study) evaluate the safety and tolerability of AZD1305 when given as a single oral dose of ER tablet and oral solution of AZD1305, with and without food

- to (in part B of the study) evaluate the PK of AZD1305 after repeated escalating oral doses of an AZD1305 ER tablet

- to evaluate the relationship between dose, plasma concentration of AZD1305 and electrocardiogram (ECG) variables

- to collect and store DNA samples for potential future research into genes which may influence drug response (disposition, safety and tolerability) of AZD1305

Study design

This was a randomised, two-part (A and B), phase I study conducted at one single centre in Sweden. Part A was open and part B was single-blind and placebo-controlled. Part A and B were separated, and an evaluation of data took place between the study parts. Part B was conducted after preliminary evaluation of Part A and one of the ER tablets from Part A was selected for Part B. Different subjects participated in part A and B.

Target subject population and sample size

70 young healthy male subjects and 24 elderly, healthy male and female, subjects were planned to be randomised, but up to maximally 92 young and 32 elderly could be randomised in case extra dose groups were needed or if drop-outs needed to be replaced.

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

In part A, two different ER tablets (ER10h and ER19h) were tested. Each subject received one of the ER tablets and was dosed at 2 occasions separated by a washout period of at least 7 days. The different regimens that was used in the cross-over design were:

- One AZD1305 ER tablet 125 mg (ER10h or ER19h), as a single oral dose + 20 mL of AZD1305-2H oral solution 125 mg, as a single oral dose without food.

- One AZD1305 ER tablet 125 mg (ER10h or ER19h), as a single oral dose + 20 mL of AZD1305-2H oral solution 125 mg, as a single oral dose with food.

After a preliminary evaluation of the PK results from Part A, the ER 19h tablet was selected and used in part B. Subjects in part B first received a single dose of AZD1305 ER tablet or placebo. This was after a 5-day washout period, followed by 10 days of repeated dosing with AZD1305 ER or placebo tablet(s) twice daily. This treatment was given in escalating dose levels (125, 250, and 375 mg). Subjects in part B in the extra group (randomisation group 8) only had one dosing period ie, 20 days with AZD1305 ER (250 mg) or placebo tablets repeated dosing twice a day (except day 20 when only the morning dose was given, see amended CSP). Each subject only participated at one dose level. 6 batches of

AZD1305/AZD1305 placebo were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of treatment

Part A: one single dose of AZD1305 at 2 separate occasions separated by a washout period of at least 7 days. Part B: one single dose of AZD1305 ER 19h tablet or placebo followed by a 5-day washout period, thereafter repeated twice daily dosing of AZD1305 ER 19h tablet or placebo during a 10 days, or as in the extra dose group (randomasation group 8), 20 days (according to amended CSP).

Variables

Pharmacokinetic

In both Part A and Part B: $AUC_{(0-t)}$, AUC, C_{max}, t_{max}, $t_{½}$ and CL/F.

Additionally in part A: relative bioavailability (test vs reference).

Additionally in Part B: AUC_{τ}, C_{min}, C_{ss}, A_e, CL_R, Rac and fluctuation index and evaluation of time-dependency.

Safety

Adverse events (AE), blood pressure (BP), pulse, physical examination, laboratory variables, ECG variables (RR, PQ [PR], QRS, QTtang (or estimation of repolarisation interval if QTtang is not appropriate), QTcF, QTcB, T-wave amplitude, body weight and body temperature.

Genetics

AstraZeneca intend to apply pharmacogenetics to the AZD1305 clinical trial program in order to have the possibility to, in the future, explore how genetic variations may affect clinical parameters associated with AZD1305.

Statistical methods

All data are descriptively presented. Geometric means of PK variables and geometric means of ratios are presented with 95% confidence intervals. The relationship between dose and/or plasma concentration of AZD1305 and ECG variables were exploratory evaluated. Time-dependency, dose-dependency, and food-interaction in elderly vs young subjects with regard to PK were evaluated.

Subject population

The first subject was enrolled on 12 April 2007 and the last subject completed the study on 10 July 2008. A total of 180 healthy, subjects were enrolled at a single centre, of whom 94 were randomised. All subjects completed the study.

All 94 randomised subjects receiving IP were included in the safety analysis set and all subjects receiving active drug (n=64) were included in the pharmacokinetic analysis sets. The PK analysis set was used for the primary analysis in part A and the safety analysis set was used for the primary analysis in part B.

Seven subjects discontinued the treatment prematurely during part B of wich 4 subjects discontinued the treatment due to AE

A summary of the demographic and baseline characteristics and subject disposition is shown in Table S 1.

Table S 1 Subject population demographic and disposition (all randomised subjects)

Demographic characteristic		Subject/Treatment group			
		Young subjects AZD1305 (n=52)	Elderly subjects AZD1305 (n=12)	Young subjects Placebo (n=18)	Elderly Subjects Placebo (n=12)
Sex (n and % of subject)	Male	52(100%)	5(42%)	18(100%)	7(58%)
	Female	0	7(58%)	0	5(42%)
Age(Years)	Mean(SD)	25(5)	60(6)	25(4)	61(6)
	Range	20 to 41	52 to 69	20 to 38	51 to 68
Baseline characteristic					
Weight(kg)	Mean(SD)	77(8)	76(11)	76(9)	78(13)
BMI(kg/m2)	Mean(SD)	23(2)	26(2)	23(2)	26(3)
SBP(mmHg)	Mean(SD)	123(11)	134(16)	127(16)	134(15)
DBP(mmHg)	Mean(SD)	68(6)	79(9)	70(8)	75(8)
Pulse(bpm)	Mean(SD)	57(8)	62(9)	60(9)	64(12)
QTcF interval(ms)	Mean(SD)	389(15)	409(16)	391(18)	403(19)
Disposition					
N(%) of subject who	Completed study	52(100%)	12(100%)	18(100%)	12(100%)
	Discontinued treatment	4(16%)	2(17%)	0	1(8%)
N analysed for pharmacokinetics		52	12	0	0
N analysed for safty		52	12	18	12

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Summary of pharmacokinetic results

Part A

The deuterium labeled oral solution, AZD1305-2H, was used as a reference in part A and will be referred to as oral solution in following sections.

The bioavailability was significantly higher when AZD1305 was given as ER tablets compared to oral solution, during fasting condition as shown with estimated geometric means

for $AUC_{test}/AUC_{reference}$ of AZD1305 of 1.22 for ER10h and 1.23 for ER19h and $C_{max,\ test}/C_{max,\ reference}$ of 0.59 for ER10h and 0.39 for ER19h. For both ER tablets, C_{max} of AZD1305 was lower and t_{max} occurred later compared to when given as an oral solution.

ER10h was not affected by food whereas ER19h had a statistically significant increase of C_{max} when given with food (high-fat and high-calorie breakfast). The estimated geometric means for $AUC_{with\ food}/AUC_{without\ food}$ of AZD1305 were 0.98 for ER10h and 1.02 for ER19h and $C_{max,\ with\ food}/C_{max,\ without\ food}$ were 0.98 for ER10h and 1.39 for ER19h.

The AUC was significantly increased when oral solution was given with food compared to without with estimated geometric means of $AUC_{with\ food}/AUC_{without\ food}$ of 1.26 and 1.24. Whereas C_{max} was similar when oral solution was given with or without food.

Based on the pharmacokinetic data (primarily as the ER19h table gave somewhat lower exposure) in part A, the ER19h tablet was selected for part B where different doses were given as single and repeated dosing for 10 or 20 days.

Part B

Pharmacokinetic steady state was reached within two to five days for almost all subjects on 125 and 250 mg twice daily repeated dosing of AZD1305 ER19h tablets.

The mean accumulation ratio ($AUC_{\tau,\ day\ 10,\ morning}/AUC_{\tau,\ single\ dose}$) was 2.67 for 125 mg, 2.75 for 250 mg and 1.58 for 375 mg given twice daily as AZD1305 ER19h tablets. The ratios after evening dosing were similar.

The pharmacokinetics of AZD1305 was independent of time for 125 mg given twice daily as ER19h tablets for 10 days. For the 250 mg dose level, AUC_{τ} after morning dose was increased by 33% (95% CI 1% to 74%) and unchanged after evening dose (95% CI –6% to 62%) on day 10 compared to AUC after a single dose. However, the exposure (measured as AUC_{τ}-ratio on day 20 vs 10 or 5) was not changed over time when 250 mg AZD1305 was given twice daily for 20 days. After the highest dose 375 mg, the pharmacokinetics of AZD1305 seems to be altered with time as the AUC_{τ} was 17% to 23% lower (95% CI –28% to –4% after morning, and –34% to –11% after evening dose, respectively) compared to a single dose. For a few subjects receiving 375 mg, there was a decrease in the plasma concentrations over time resulting in similar mean exposure on day 10 as for 250 mg. Diurnal variations with significantly higher C_{min} values (31% higher with 95% CI of 26% to 135% for 250 mg) in the morning after 250 and 375 mg twice daily have confounded the calculated AUC_{τ}.

The average plasma concentration of AZD1305 during a dosing interval (C_{ss}) after a morning dose on day 10 was 0.303 µmol/L after 125 mg, 0.464 µmol/L after 250 mg and 0.462 µmol/L after 375 mg twice daily dosing. There was no indication of CYP3A4 induction as measured by change in plasma concentration of 4β-hydroxycholesterol. The mean fluctuation index of AZD1305 ranged from 0.403 to 0.865 across the doses.

AUC or AUC_τ and C_{max} after single and 10 days of treatment were statistically signficantly non-dose-proportional (except for C_{max} after single dosing) with the largest deviation from dose-proportionality after repeated administration. A two-fold increase in dose was estimated to result in a 27% higher AUC_τ (95% CI –7.5% to 74%) and 39% higher C_{max} (95% CI 2.4% to 88%) after a morning dose on day 10. For an evening dose, a two-fold increase in dose was estimated to result in a 15% higher AUC_τ (95% CI –13% to 52%) and 11% higher C_{max} (95% CI 16% to 44%).

The analysis of dose-proportionality and time-dependency after repeated dosing should be interpreted with care as steady state had not been reached in the highest dose group and the co-founding contribution of diurnal variation on the PK parameters.

The pharmacokinetics of AZD1305 seem to be similar in young and elderly healthy subjects receiving 250 mg AZD1305 as ER19h tablets twice daily for 10 days.

Summary of pharmacokinetic/pharmacodynamic correlations

An increase in plasma concentrations of AZD1305 resulted in prolongation of the QTcF intervals.

Summary of safety results

Overall, AZD1305 was generally safe and well tolerated after single and repeated doses of up to 250 mg administered as ER tablets. Two subjects in the 375 mg group discontinued the treatment due to QTcF>550 ms, which was a predefined study specific discontinuation criterion. Thus, dose escalation was stopped.

The occurrence of AEs was similar in the AZD1305 and placebo groups and of a kind commonly reported in clinical studies with healthy subjects. The most commonly reported AEs were dizziness, headache, and common cold (nasopharyngitis).There were no serious adverse events (SAEs) but 4 discontinuations of treatment due to AEs (DAEs) in part B. Ten (10) cases of fever and elevated CRP underwent adjudication and there were no indications of flu-like inflammatory reactions that were judged to be related to AZD1305.

In general, there were no trends of laboratory abnormality among the subjects receiving AZD1305 compared to placebo. There were no clinically relevant changes in vital signs or body temperature and no signs of negative haemodynamic effects.

The ECG findings did not raise any safety concerns, the QTcF prolongation was an expected finding due to the mechanism of action of AZD1305. The mean values of change in QTcF on day 10, 6 h after the morning dose were: 39,7 ms (125 mg), 66,2 ms (250 mg), 43.0 ms (250 mg elderly), 46.9 ms (375 mg), -8,9 ms (placebo), and -15,1 ms (placebo elderly). In parallel to the QTcF prolongation, changes in T-wave morphology were observed with AZD1305, reflected as T-wave flattening and notching.