Drug Substance	AZD1305	**SYNOPSIS**	(For national authority use only)
Study Code	D3190C00001		
Edition Number	1		
Date	29 November 2007		

A single-centre, single-blind, randomised, placebo-controlled, single-dose phase I study to assess the safety, tolerability and pharmacokinetics after single ascending oral and intravenous doses of AZD1305 in healthy male subjects

Study dates		**Phase of development**
First subject enrolled	15 January 2007	Clinical pharmacology (I)
Last subject completed	12 June 2007	

Objectives

The primary objective of the study was to evaluate the safety and tolerability of AZD1305 after single ascending oral and intravenous (iv) doses.

The secondary objectives of the study were:

1. To evaluate the pharmacokinetics (PK) of AZD1305 after single ascending oral and iv doses.

2. To evaluate the relationship between dose, plasma concentration of AZD1305 and electrocardiogram (ECG) variables.

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

Study design

Single-centre, single-blind, randomised (AZD1305:placebo; 2:1), placebo-controlled, single-ascending-dose study.

Target subject population and sample size

Thirty (30) healthy, male subjects were planned to be randomised, but up to maximally 42 healthy male subjects could be randomised if needed.

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

Oral solution of AZD1305 (Batch no. H 1873-01-01-01 and H 1874-01-01-01) was given as single ascending doses; 10 mg, 30 mg, 90 mg, 180 mg, 360 mg, 430 mg and 500 mg. The highest dose level was determined by either safety limits or when 2 or more subjects exceeded a maximum exposure of AUC 41 µmol*h/L and/or C_{max} 5.5 µmol/L.

Two single iv doses (10 mg and 70 mg) of AZD1305 (Batch no. H 1875-01-01-01) given at a constant infusion rate during 30 min were also administered. The iv doses were set to be lower than the maximum tolerated dose achieved in the oral part of the study and pre-defined exposure levels of AUC and/or C_{max}.

Placebo doses were given in parallel with active drug at all dose levels.

Duration of treatment

Each subject received, at maximum, 2 single doses of AZD1305 or placebo at 2 separate occasions with a wash-out period of at least 14 days.

Variables

- **Pharmacokinetic**

  Area under the plasma concentration versus time curve from time zero to the last quantifiable plasma concentration ($AUC_{(0-t)}$), area under the plasma concentration versus time curve (AUC), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{½}$), oral plasma clearance (CL/F), total plasma clearance (CL), amount excreted unchanged in urine (Ae), renal clearance (CL_R), absolute systemic bioavailability (F), volume of distribution at steady state (V_{ss}) and fraction excreted unchanged in urine (fe).

- **Pharmacogenetics**

  To obtain DNA samples for possible future exploratory research into genes, which may influence the clinical parameters associated with AZD1305.

- **Safety**

  Adverse events (AEs), ECG variables (RR, PQ (PR), QRS, QT, QT_{cF}, QT_{cB} and T-wave amplitude), blood pressure (BP), pulse, physical examination, laboratory variables, body temperature and body weight.

Statistical methods

All data were descriptively presented. Dose proportionality was investigated by regression. The relationship between dose and/or plasma concentration of AZD1305 and ECG variables were exploratory evaluated.

Subject population

The first subject was enrolled on 15 January 2007 and the last subject completed the study on 12 June 2007. A total of 55 healthy, male subjects were enrolled at a single centre, of whom 29 were randomised and 23 completed the study. All 29 randomised subjects were included in the safety analysis set. Nineteen (19) subjects received AZD1305 and were included in the pharmacokinetic analysis set. The safety analysis set was used for the primary analysis.

Three subjects discontinued the study due to fulfilling a discontinuation criterion (QT_{cF} interval >500 ms) and 3 subjects discontinued due to administrative reasons.

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

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

Demographic or baseline characteristic		AZD1305	Placebo
Age(Years)	Mean(SD)	25(4)	26(5)
	Range	20 to 37	21 to 36
Baseline characteristics			
Weight(kg)	Mean(SD)	80(8)	76(7)
BMI(kg/m2)	Mean(SD)	24(2)	24(2)
Disposition			
N(%) of subject who	Completed	15(79%)	8(80%)
	Fulfilled discontinuation criteria	3(16%)	0(0%)
	Discontinued due to administrative reason	1(5%)	2(20%)
N analysed for pharmacokinetics		19	0
N analysed for safety		19	10

Summary of pharmacokinetic results

At all dose levels (except the lowest; 10 mg), the plasma concentration of AZD1305 increased rapidly and the maximum plasma concentration of AZD1305 was reached at about 0.5-2 h after intake of oral solution during fasting conditions. The plasma levels of AZ1305 declined multi-exponentially with a mean terminal half-life of 5-9 h after oral administration.

The mean oral bioavailability was 38% and 53% in oral doses of 360 mg and 430 mg, respectively. The mean CL was 45-57 L/h and the mean V_{ss} was 260-344 L. The mean CL_R was 4.0-5.4 L/h, which means that CL_R only accounts for a small part of the total CL of AZD1305. The mean fraction excreted unchanged in urine after iv infusion of AZD1305 was only 9%.

There was a more than dose-proportional increase in exposure (AUC and C_{max}) of AZD1305 with increasing oral doses.

Summary of pharmacokinetic/pharmacodynamic correlations

The relationship between QT_{cF} and plasma concentration was described by an E_{max} model with effect compartment, accounting for a small delay between plasma concentration and change in QT_{cF}. Thus, the maximum QT_{cF} occurs very shortly after C_{max}. The E_{max} ie, the maximum change in QT_{cF} that may be caused by the drug, was estimated to 152 ms (CV 22%), corresponding to a 40% increase from the predicted baseline QT_{cF} of 378 ms (CV 4%) in the typical subject.

Summary of safety results

Overall, AZD1305 was safe and well tolerated at single oral doses of up to 430 mg. Single iv infusions of 10 mg and 70 mg were also safe and well tolerated. After single oral doses of 500 mg, two subjects had QT_{cF} intervals >500 ms. Thus, the pre-defined stopping criteria for dose escalation were met, and dosing was not escalated further.

AZD1305 dose-dependently increased the QT_{cF} interval, with a maximal mean change from baseline of 158 ms (corresponding to 40% mean relative change) in the highest dose group (500 mg) and 103 ms (mean relative change 27%) in the 430 mg dose group. An increase in the PQ interval was observed after oral administration of AZD1305, of up to 10% in mean relative change from baseline (mean absolute change 14 ms) in the highest dose group. Similarly, there was an increase in the QRS interval of up to 11% in mean relative change from baseline (mean absolute change of 12 ms) in the highest dose group.

No SAEs or discontinuations due to AE were reported. The overall frequency of AEs was similar in the AZD1305 and placebo groups. However, gastrointestinal disorders were somewhat more frequent in the higher oral dose groups, compared to placebo. Most AEs were of mild intensity and of a kind commonly observed in clinical studies in healthy volunteers.

There were no signs of negative haemodynamic effects with AZD1305, nor clinically relevant changes in laboratory variables or body temperature.