AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD1305 |
| Study Code | D3190C00002 |
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# A single-centre, single-blind, randomised, placebo-controlled, single-dose phase I study to assess the safety, tolerability and pharmacokinetics after ascending intravenous doses of AZD1305 in healthy male volunteers

**Study dates:** First healthy volunteer enrolled: 15 January 2008
Last healthy volunteer completed: 7 May 2008

**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)

Quintiles AB, Phase I Services, Uppsala, Sweden

| Study dates | | Phase of development |
|---|---|---|
| First healthy volunteer enrolled: | 15 January 2008 | Clinical pharmacology (Phase I) |
| Last healthy volunteer completed: | 7 May 2008 | |

## Publications

None at the time of writing this report.

## Objectives

The primary objective of the study was to evaluate the safety and tolerability of AZD1305 after single ascending intravenous (iv) doses of AZD1305 by assessment of adverse events (AEs), electrocardiogram (ECG) variables, blood pressure (BP), pulse, physical examination, laboratory variables, body temperature and weight.

The secondary objectives of the study were:

1. To evaluate the pharmacokinetics (PK) of AZD1305 after single ascending iv doses of AZD1305 by assessment of PK variables of AZD1305

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

3. To collect and store DNA samples (from all randomised subjects who give additional informed consent) for potential future exploratory research into genes which may influence drug response of AZD1305

## Study design

This was a single-centre, single-blind, randomised (AZD1305:placebo; 2:1), placebo-controlled, single-dose phase I study where AZD1305 and placebo were administered as a 1-h continuous intravenous infusion in escalating doses to healthy male volunteers, aged 20 to 45 years.

## Target healthy volunteer population and sample size

A total of 36 healthy male volunteers (9 in each dose group) were randomised. Twenty-seven (27) healthy male volunteers were planned to be randomised with the possibility to additionally randomise 9 (ie, a total of 36) or 18 (ie, a total of 45) healthy male volunteers if needed.

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

AZD1305 (concentrate for solution for infusion 10 mg/mL, batch no H 1958-01-01-01) and placebo (NaCl 9 mg/mL solution for infusion, batch no H 0732-04-04-12) were given as a 1-h constant intravenous infusion. The final dose levels were 70 mg, 120 mg, 200 mg and 220 mg.

**Duration of treatment**

Single dose of AZD1305 or placebo

**Criteria for evaluation - pharmacokinetics (main variables)**

Secondary variables: 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 ($t_{½}$), total plasma clearance (CL), amount excreted unchanged in urine ($A_e$), renal clearance ($CL_R$), volume of distribution at steady state ($V_{ss}$) and fraction excreted unchanged in urine ($f_e$)

**Criteria for evaluation - safety (main variables)**

Primary variables: AEs, ECG variables (RR, PQ (PR), QRS, QT, QTcF, QTcB and T-wave amplitude), BP, pulse, physical examination, laboratory variables, body temperature and weight

**Statistical methods**

The data were summarized using descriptive statistics. Dose proportionality of AUC and $C_{max}$ was investigated using a power model. The relationship between plasma concentration of AZD1305 and ECG variables was evaluated using population PK/PD analysis.

**Subject population**

In total, 36 healthy male volunteers, 35 Caucasians and 1 of black origin, were randomised into the study at the study site, each healthy volunteer received 1 administration of study drug during the planned treatment visit. All healthy volunteers randomised to treatment completed the study. The infusion of AZD1305 was interrupted (due to technical problems) for 2 healthy volunteers. No PK variables were calculated for these healthy volunteers and they were not included in the statistical analysis, however, the plasma concentrations are presented and included in mean values. The safety analyses included all randomised healthy volunteers. Overall, the treatment groups were comparable with regards to demographic characteristics.

**Summary of pharmacokinetic results**

Peak plasma concentration of AZD1305 was reached at the end of infusion for almost all subjects. After the end of infusion, the plasma levels of AZ1305 declined multi-exponentially with a mean terminal half-life of 6.6 to 7.5 h.

Similar mean CL across all doses were seen in the study with a mean CL ranging from 34 to 39 L/h. There was a tendency of decreasing mean $V_{ss}$ with increasing dose, mean $V_{ss}$ was 212 L for 70 mg and 152 L for 220 mg. The mean $CL_R$ was 4.3 to 5.6 L/h, which means that $CL_R$ accounted only for a small part of the total CL of AZD1305. The mean fraction excreted unchanged in urine after iv infusion of AZD1305 was 13 to 16%.

There was a more than dose-proportional increase in $C_{max}$ of AZD1305 with increasing iv doses, whereas the increase in AUC with increasing doses was not statistically significant.

**Summary of pharmacokinetic/pharmacodynamic relationships**

The relationship between QTcF and plasma concentration of AZD1305 was described by an $E_{max}$ model with effect compartment, accounting for a delay between plasma concentration and change in QTcF. Thus, the maximum QTcF occurred shortly after $C_{max}$. The $E_{max}$, ie, the maximum change in QTcF that may be caused by the drug, was estimated to 140 ms (coefficient of variation (CV) 20%), corresponding to a 37% increase from the predicted baseline QTcF of 381 ms (CV 4%) in the typical healthy volunteer.

**Summary of safety results**

AZD1305 demonstrated an acceptable safety and tolerability profile when administered as single iv doses of 70 mg to 220 mg to healthy male volunteers. There were no deaths, other serious adverse events, discontinuations due to AEs or other significant AEs in the study.

A dose-dependent increase in mean QTcF was observed with AZD1305. A maximum mean QTcF of 492 ms was observed in the highest dose group (220 mg). This corresponded to a mean absolute change of 114 ms (mean relative change of 30%) from baseline, ie prolongation of QTcF. The mean maximum QTcF values were 453, 489, 498 and 504 ms after administration of 70, 120, 200 and 220 mg AZD1305, respectively and the mean maximum increases from baseline were 72, 108, 116 and 125 ms, respectively.

A prolongation of the PQ interval was observed after administration of AZD1305, a mean relative change from baseline of up to 14% was observed in the highest dose group (220 mg). Similarly, there was a prolongation of the QRS interval of up to 20% in mean relative change from baseline in the highest dose group (220 mg).