AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | AZD1305 |
| Study Code | D3190C00008 |
| Edition Number | 1 |
| Date | 17 June 2009 |

# A Phase I, Open, Randomised, Single-Centre, Crossover Study to Assess the Absorption, Distribution, Metabolism and Excretion (ADME) after Oral and Intravenous Administration of $^{14}$C-labelled and Non-labelled AZD1305 to Healthy Male Volunteers

**Study dates:** First healthy volunteer enrolled: 1 April 2008
Last healthy volunteer completed: 13 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)

The study was conducted in the UK at the Alderley Park Clinical Pharmacology Unit, AstraZeneca R&D Alderley Park, Macclesfield, Cheshire. The first healthy volunteer was enrolled 1 April 2008.

## Publications

None at the time of writing this report.

## Objectives

The primary objective of the study was to evaluate the absorption, distribution, metabolism and excretion of AZD1305, in healthy male subjects after oral and iv administration of single doses of $^{14}$C-labelled AZD1305 and non-labelled AZD1305 by assessment of pharmacokinetic variables of AZD1305 and total radioactivity.

The secondary objectives of the study were:

- to evaluate safety and tolerability after oral and iv administration of single doses of $^{14}$C-labelled AZD1305 and non-labelled AZD1305 by assessment of adverse events (AEs), blood pressure (BP), pulse, laboratory variables, electrocardiogram (ECG) and physical examination.

- to collect and store DNA samples for potential future research into genes, which may influence drug response of AZD1305 (Not reported in the Clinical Study Report).

## Study design

AZD1305 is a novel rhythm control agent being developed for treatment of atrial fibrillation. AZD1305 was tested in a phase I study of open, single-centre, randomised, and 2-way crossover design. Non-labelled AZD1305 was given to all subjects on the first dosing occasion, 5 subjects receiving one oral dose each and 5 subjects receiving one iv dose each. On the second dosing occasion, $^{14}$C-labelled AZD1305 was planned to be given to all subjects, 5 subjects receiving one oral dose each and 5 subjects receiving one iv dose each. At this occasion, the subjects crossed-over from oral to iv administration and *vice versa*.

## Target healthy volunteer population and sample size

Ten (10) healthy male subjects aged 35-55 years of age.

## Investigational product dosage, mode of administration and batch numbers´

180 mg non-labelled AZD1305 oral solution (9 mg/mL), batch H 2017-01-01-01
180 mg $^{14}$C-labelled AZD1305 oral solution (9 mg/mL), containing 5.0 MBq in a concentration of 250 kBq/mL, batch H 2018-01-01-01

70 mg non-labelled AZD1305 solution for infusion (1.4 mg/mL), batch H 1958-01-01-03
70 mg $^{14}$C-labelled AZD1305 solution for infusion (1.4 mg/mL), containing 2.5 MBq in a concentration of 50 kBq/mL, batch H 2019-01-01-01.

### Duration of treatment

Single dose

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

Total recovery of radioactive dose, total radioactivity in urine and faeces, metabolite profile, and PK variables of AZD1305 ($AUC_{0-t}$, AUC, $C_{max}$, $t_{max}$, $t_{1/2}$, F, CL, CL/F, $CL_R$, $A_e$, total $A_e$, $f_e$ and $V_{ss}$ ) and of total radioactivity (AUC, $C_{max}$, $t_{max}$ and $t_{1/2}$).

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

Adverse events (AEs), blood pressure (BP), pulse, laboratory variables, electrocardiogram (ECG) variables and physical examination.

### Statistical methods

Descriptive statistics including confidence intervals were calculated for all pharmacokinetic variables. Safety variables were presented with descriptive statistics.

### Subject population

In the study, 10 healthy male volunteers were randomised, 9 volunteers were white and 1 had an ethnic origin reported as “other”. One volunteer could not attend visit 3 due to personal circumstances. He did not receive $^{14}$C-labelled AZD1305 oral solution.

**Table S 1 Summary of baseline characteristics of healthy male volunteers included in the safety analysis set (n=10)**

| Statistics | Age (years) | Height (cm) | Weight (kg) | BMI (kg/m2) |
|---|---|---|---|---|
| Mean | 42.9 | 174.6 | 79.7 | 26.1 |
| SD | 5.5 | 5.1 | 9.2 | 2.4 |
| Min | 38 | 163 | 66 | 21.8 |
| Median | 40 | 176 | 78.5 | 26.2 |
| Max | 53 | 180 | 93 | 29.7 |

### Summary of pharmacokinetic results (see Conclusions)

See Conclusion Section.

## Summary of safety results

In the study population of healthy male subjects, AZD1305 was generally safe and well tolerated after a single oral 180 mg dose and a single iv 70 mg dose given by 1 h infusion.

No significant changes in PR(PQ) or QRS intervals were observed.

After oral administration of 180 mg AZD1305, mean QTcF increased over time up to a maximum increase of 49 ms from baseline. Similarly, after intravenous administration of 70 mg AZD1305, mean QTcF increased over time up to a maximum increase of 63 ms from baseline. The QTcF changes were reversible and had returned to baseline within 24 h.

No subject had a QTcF interval > 500 ms and no proarrhythmias were observed.