AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3690C00017
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An Open, Two Period, Single Dose, Phase I Study of the Excretion of Radioactivity, Metabolic Profiles and Pharmacokinetics Following Oral Administration of [^{14}C]-AZD3480 and the Pharmacokinetics of AZD3480 Following Intravenous Administration to Healthy Male Volunteers with Different CYP2D6 Genotypes

Study dates:	First healthy volunteer enrolled: 13 October 2008 Last healthy volunteer completed: 29 October 2009
Phase of development:	Clinical Pharmacology (Phase 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 England at the Clinical Pharmacology Unit (CPU), AstraZeneca R&D Alderley Park. The unit was closed in December 2009 and the study was expected to continue and restart at Quintiles Drug Research Unit at Guy's Hospital, London, that was added as a study centre in Amendment Number 4 to the Clinical Study Protocol (CSP). Before the study was initiated at the new site, it became apparent that recruitment of this limited study population (healthy male volunteers with different cytochrome P450 [CYP] 2D6 genotypes) would be increasingly difficult and the study was prematurely terminated before any enrolment of healthy volunteers at this centre.

First healthy volunteer enrolled: 13 October 2008

Last healthy volunteer completed: 29 October 2009

Publications

None at the time of writing this report.

Objectives

Primary objectives

The primary objectives of this study in healthy volunteers with different CYP2D6 genotypes were:

1. to investigate the extent of excretion of radioactivity in urine and faeces following oral administration of [^{14}C]-AZD3480

2. to study the metabolic profiles [^{14}C], ie, estimation of the relative abundance of major metabolites, in plasma and excreta following oral administration of [^{14}C]-AZD3480

3. to study the pharmacokinetics of AZD3480 in plasma and urine following intravenous (iv) administration

Secondary objectives

The secondary objectives of this study in healthy volunteers with different CYP2D6 genotypes were:

1. to identify major metabolites of AZD3480 in plasma and excreta following oral administration

2. to assess the safety and tolerability following single oral and iv administration of AZD3480 to healthy male volunteers by assessment of adverse events (AEs), vital signs (supine blood pressure [BP] and pulse rate), electrocardiogram (ECG), and laboratory variables

Study design

This was an open-label, single-centre[1], two period, single dose study to evaluate the excretion of radioactivity, metabolic profiles and pharmacokinetics following iv administration of AZD3480 and oral administration of [^{14}C]-AZD3480 in healthy male volunteers.

Target healthy volunteer population and sample size

Healthy volunteers participating in the study were males aged 40 to 65 years, with 0, 1 or 2 functional CYP2D6 alleles and a body mass index (BMI) ranging from 22.4 to 28.4 kg/m^2. Due to involvement of the polymorphic CYP2D6 enzyme no formal sample-size calculation was made with respect to recovery (% of dose) of radioactivity retrieved in urine and faeces, metabolic profiles, or pharmacokinetics of total radioactivity and unchanged AZD3480. Normally, a mass balance study is performed in about 6 to 8 healthy volunteers but it was judged appropriate to expand the study to 12 healthy volunteers in order to obtain adequate amount of data from different CYP2D6 genotypes. A total of 9 healthy male volunteers were randomised and completed the study.

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

The following single doses of AZD3480 were administered:

- 25 mg of non-labelled AZD3480 as a single 4 hours constant rate iv infusion of 500 ml AZD3480 infusion solution 0.05 mg/mL (concentration diluted with sodium chloride 9 mg/mL)
- 50 mg of [^{14}C]-labelled (containing 3.7 MBq/100 µCi) AZD3480 as an oral solution (10 mL containing 5 mg/mL+10 µCi/mL (0.37 MBq/mL).

The following batches were used in the study:

- TC-1734-226 (AZD3480), Concentrate for Solution for infusion 5 mg/mL, Batch number H 2010-01-01-01
- [^{14}C]-labelled TC-1734-226 (AZD3480), Oral solution 5 mg/mL+10 µCi/mL (0.37 MBq/mL), Batches number H 2031-01-01-01 and H 2031-01-01-02

Duration of treatment

The study consisted of 2 treatment periods, separated by a washout period of at least 8 days. Each healthy volunteer received a single iv 25 mg dose of AZD3480, followed by a single oral 50 mg dose of [^{14}C]-AZD3480.

[1] Another study centre was planned to be added in Amendment No. 4 to the CSP but it never enrolled any healthy volunteers.

Criteria for evaluation - pharmacokinetics (main variables)

- **Total radioactivity:** Amount of radioactivity (% of dose) in urine and faeces within each collection interval and cumulative for the total collection period.

- **Pharmacokinetics:** pharmacokinetic parameters of AZD3480 and its metabolite TC-1784 were, as appropriate, estimated in plasma and urine (iv and/or oral dosing):
  AUC, AUC_t, C_{max}, t_{max}, CL/F, $t_{1/2}$, V_{ss}, CL, CL_R, A_e, f_e, fe_{po} and F

  Total radioactivity was estimated, as appropriate, in blood and plasma (oral dosing):
  AUC, AUC_t, AUC_{0-12}, C_{max}, t_{max}, $t_{½}$ and the blood to plasma ratio
  The metabolic patterns of AZD3480 and potential identification of metabolites in plasma, urine and faeces

Criteria for evaluation - safety (main variables)

- AEs, clinical laboratory evaluation (haematology, clinical chemistry and urinalysis) vital signs (supine systolic and diastolic BP and pulse rate), ECG, and physical examination

Statistical methods

All analyses were carried out on evaluable healthy volunteers. The primary and secondary objectives were mainly analysed by means of descriptive statistics (mean, median, standard deviations etc), summary tables and graphs, as appropriate. When relevant, the data were presented grouped by number of functional CYP2D6 alleles, ie, 0, 1, and 2 functional CYP2D6 alleles.

Subject population

In total, 9 healthy male volunteers were enrolled and randomised in the study and all 9 healthy volunteers completed the study. The disposition of functional CYP2D6 alleles in the randomised healthy volunteers was: 1 healthy volunteer had 0 functional CYP2D6 alleles, 2 healthy volunteers had 1 functional CYP2D6 allele and 6 healthy volunteers had 2 functional CYP2D6 alleles.

Summary of pharmacokinetic results

- Following an oral administration of [^{14}C]-AZD3480, the majority of the radioactivity was excreted in the urine, 95%, 101% and 99±3% of the administered dose for healthy volunteers with 0, 1 and 2 functional CYP2D6 alleles, respectively. Faecal recoveries were 3%, 2% and 2±1% of the dose for the these three groups, respectively.

- In pooled plasma from healthy volunteers with 2 and 1 functional CYP2D6 alleles three metabolites (M1, M2 and M5) were the major circulating metabolites, and they accounted each for between 11 to 48% of the total peak area in the radiochromatograms. Only a minor amount of the parent compound was observed.

In the plasma from the healthy volunteer with 0 functional CYP2D6 alleles, AZD3480 and one metabolite (M12) were detected and accounted for up to 82 and 24% of the total peak area in the radiochromatograms, respectively.

- In urine from from healthy volunteers with 2 and 1 functional CYP2D6 alleles two major metabolites, M2 and M5 accounted for ca 45 and ca 25% of the dose, respectively. Only minor amount of AZD3480 was detected in urine. In the healthy volunteer with 0 functional CYP2D6 alleles, AZD3480 accounted for 28% of the fraction of dose excreted within 72 h in urine. Seventeen metabolites were detected which all represented less than 8% of the dose each.

- Following oral administration of [^{14}C]-AZD3480 the major metabolic pathways in healthy volunteers with 2 and 1 functional CYP2D6 alleles were *O*-dealkylation followed by subsequent glucuronidation and sulphation. In the healthy volunteer with 0 functional 2D6 alleles, the turn over was low and unchanged AZD3480 the major metabolites excreted in urine together with metabolites formed by glucuronidation and/or *N*-dealkylation and oxidation.

- Following oral administration of [^{14}C]AZD3480, the ratio between AUC for AZD3480 and AUC for total radioactivity was in the range 0.3% to 1.0% in 6 healthy volunteers with 2 CYP2D6 alleles, which was lower than those observed in 2 healthy volunteers with 1 CYP2D6 allele (2.0%) and in 1 healthy volunteer with 0 CYP2D6 alleles (46.3%). AZD3480 and TC-1784 (M9) together accounted for 0.36% to 1.3% of radioactivity in the healthy volunteers with 2 CYP2D6 alleles, 2.3% and 2.4% in the healthy volunteers with 1 CYP2D6 allele and 53.7% (AZD3480 accounted for 46.3%) in the healthy volunteer with 0 CYP2D6 alleles.

- The clearance of AZD3480 was in the range 73 to 113 L/h in the healthy volunteers with 1 or 2 CYP2D6 alleles and 7.5 L/h in the healthy volunteer with 0 CYP2D6 alleles.

- The healthy volunteers with 1 or 2 CYP2D6 alleles had 4 to 8% of the iv dose excreted as unchanged AZD3480, whereas the renal excretion was the main route for elimination of AZD3480 in one healthy volunteer with 0 CYP2D6 alleles (86% of the iv dose excreted as unchanged AZD3480).

- The volume of distribution of AZD3480 at steady state was in the range 278-542 L in the 6 healthy volunteers with 2 CYP2D6 alleles, 431 and 447 L in the 2 healthy volunteers with 1 CYP2D6 allele, and 150 L in the healthy volunteer with 0 CYP2D6 alleles.

- The absolute bioavailability of AZD3480 following oral administration was in the range 5 to 18% in the 6 healthy volunteers with 2 CYP2D6 alleles, which was much lower than those observed in the 2 healthy volunteers with 1 CYP2D6 allele (42% and 48%) and in 1 healthy volunteer with 0 CYP2D6 alleles (43%).

- The decline of total radioactivity in plasma and in blood was similar and the blood to plasma ratio of total radioactivity was in the range 0.28 to 1.1 in 6 healthy volunteers with 2 CYP2D6 alleles, 0.7 and 0.76 in 2 healthy volunteers with 1 CYP2D6 allele and 0.87 in 1 healthy volunteer with 0 CYP2D6 alleles.

Summary of safety results

- AZD3480 demonstrated an acceptable safety and tolerability profile after iv administration of 25 mg AZD3480 or oral administration of 50 mg [^{14}C]-AZD3480 in healthy male volunteers.

- In total, 17 AEs were reported in the study, whereof 6 following iv administration of 25 mg AZD3480 and 11 following oral administration of 50 mg AZD3480. The number of healthy volunteers who reported at least 1 AE was 5 following iv administration of 25 mg AZD3480 and 6 following oral administration of 50 mg AZD3480. The preferred terms most commonly affected by AEs included Dizziness, Headache, Libido decreased and Vessel puncture site haematoma. Three AEs (Dizziness, Bradycardia and Hypotension), reported following oral administration of 50 mg AZD3480, were considered to be severe in intensity. All other AEs reported in the study were considered to be mild in intensity. There were no serious adverse events (SAEs), AEs leading to discontinuation of treatment or other significant adverse events (OAEs) reported in the study.

- Following oral and iv administration of AZD3480 there were no apparent clinically relevant treatment related changes or trends in any laboratory parameters, vital signs or ECG.