AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3480
Study Code	D3690C00016
Edition Number	1
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A Phase I, Double-blind, Randomized, Two-Way Cross Over, Single-Centre Study in Healthy CYP2D6 Extensive Metabolisers (EMs, ≥ 1.5 functional CYP2D6 alleles) and Poor Metabolisers (PMs, no functional CYP2D6 allele) to Investigate the Potential of AZD3480 to Inhibit Cytochrome P450 1A2, 2C19, 3A4, 2C8, 2B6 and UGT1A1 Activity

Study dates: First healthy volunteer enrolled: 14 November 2007
Last healthy volunteer completed: 19 September 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

This was a single centre study conducted at ICON Development Solutions Manchester, Skelton House, Manchester Science Park, Lloyd Street North, Manchester, M15 6SH, UK.

Study dates		**Phase of development**
First subject enrolled	14 November 2007	Clinical pharmacology (I)
Last subject completed	19 September 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to assess the effect of AZD3480 on Cytochrome P450 1A2, 2C19, 3A4, 2C8, 2B6 and UGT1A1 activity using single oral doses of caffeine (100 mg), omeprazole (20 mg), midazolam (7.5 mg), rosiglitazone (4 mg), bupropion (150 mg) and endogenous bilirubin as probes and assessing the pharmacokinetic (PK) variables of the probes in plasma or urine following multiple oral doses of AZD3480.

The secondary objectives of this study were:

1. To assess the effect of single oral doses of the probes on AZD3480 steady-state PK.

2. To evaluate the safety and tolerability of AZD3480 by assessment of adverse events (AEs), physical examination, laboratory variables and vital signs when co-administered with single oral doses of caffeine, bupropion, rosiglitazone, omeprazole and midazolam and endogenous bilirubin.

Study design

This was a Phase I, single-centre, double-blind (with respect to AZD3480), randomised, 2-way crossover study in healthy subjects who were extensive metabolisers (EMs) (≥1.5 functional alleles of CYP2D6) or poor metabolisers (PMs) (no functional allele of CYP2D6) with respect to CYP2D6 genotype.

Target healthy volunteer population and sample size

Healthy male subjects were to be enrolled to ensure 18 evaluable subjects. Twelve were to be EMs (ie, ≥1.5 functional alleles of CYP2D6) and 6 were to be PMs (ie, no functional allele of CYP2D6).

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

AZD3480 25 mg (batch number: 05069) and 50 mg capsules (batch number: 05073A) and placebo capsules (batch number: 05071A) were administered orally at doses of 50 mg (PMs) and 125 mg (EMs) once daily for 9 days. AZD3480 was administered as capsules of the 4-hydroxybensoate salt, for which 1 mg corresponded to 0.629 mg free base. The doses of 50 mg (PMs) and 125 mg (EMs) corresponded to 31.5 mg and 78.7 mg of free base, respectively.

Caffeine 100 mg tablets were administered as a single oral dose of 100 mg on Day 5 in both periods. Omeprazole 20 mg entero capsules were administered as a single oral dose of 20 mg on Day 5 in both periods. Midazolam 7.5 mg tablets were administered as a single oral dose of 7.5 mg on Day 5 in both periods. Rosiglitazone 4 mg tablets were administered as a single oral dose of 4 mg on Day 6 in both periods. Bupropion 150 mg tablets were administered as a single oral dose of 150 mg on Day 7 in both periods.

Duration of treatment

There were 2 treatment periods of 9 days each in the study, separated by a 10-day wash-out period. Subjects received multiple oral doses of AZD3480 in one treatment period and multiple oral doses of placebo (with respect to AZD3480) in the other treatment period. AZD3480/placebo were administered once daily in the morning for 9 days during each treatment period. Caffeine, omeprazole, midazolam, rosiglitazone and bupropion were administered as a single dose in both treatment periods.

Criteria for evaluation - pharmacokinetics (main variables)

The following PK parameters were determined for AZD3480 on Days 4, 5, 6 and 7:

- Area under the plasma concentration time curve during a dosing interval (AUC_{τ})
- Maximum plasma concentration at steady-state ($C_{ss,max}$)
- Time to maximum plasma concentration at steady-state ($t_{ss,max}$)
- Minimum plasma concentration at steady-state ($C_{ss,min}$)
- Apparent total body clearance from plasma after oral dosing at steady-state (CL_{ss}/F)

The following PK parameters were determined for midazolam and 1'-hydroxymidazolam on Day 5, for rosiglitazone on Day 6 and for bupropion and hydroxybupropion on Day 7:

- Area under the plasma concentration time curve (AUC)
- Area under the plasma concentration time curve from time zero to the last quantifiable concentration ($AUC_{(0-t)}$)

- Maximum plasma concentration (C_{max})
- Time to maximum plasma concentration (t_{max})
- Terminal half-life ($t_{½}$)
- Apparent total body clearance from plasma after oral dosing (CL/F) (midazolam ad bupropion only)

The paraxanthine/caffeine metabolic ratio was calculated as the ratio of the plasma concentrations at 4 hours post-dose on Day 5.

The omeprazole/5-hydroxyomeprazole metabolic ratio was calculated as the ratio of the plasma concentrations at 3 hours post-dose on Day 5.

Serum total and direct (or conjugated) bilirubin was measured pre-dose and at 2 and 4 hours post-dosing with AZD3480 on Days 2 and 4. Indirect (or un-conjugated) bilirubin was calculated by subtracting direct (or conjugated) bilirubin from total bilirubin.

Criteria for evaluation - safety (main variables)

The safety variables were AEs, pulse, supine blood pressure, electrocardiograms (ECGs) and clinical laboratory variables (clinical chemistry, haematology and urinalysis).

Statistical methods

Following $\log_e$ transformation, total and un-conjugated bilirubin in the presence of AZD3480 (test treatment) and following placebo administration (reference treatment) were compared statistically using analysis of covariance (ANCOVA). Differences in least squares means (LSmeans) between substrate concentration in the presence of AZD3480 compared with placebo at each time-point and associated 90% confidence interval (CI) were determined for each CYP2D6 genotype.

Following $\log_e$ transformation, the paraxanthine/caffeine ratio at 4 hours on Day 5 and the omeprazole/5-hydroxyomeprazole ratio at 3 hours on Day 5 in the presence of AZD3480 (test treatment) and following placebo administration (reference treatment) were compared statistically using ANOVA. Differences in LSmeans between substrate concentration in the presence of AZD3480 compared with placebo and associated 90% CI were determined for each CYP2D6 genotype.

Following $\log_e$ transformation, the PK parameters AUC, $AUC_{(0-t)}$ and C_{max} of midazolam and 1'-hydroxymidazolam on Day 5 in the presence of AZD3480 (test treatment) and following placebo administration (reference treatment) were compared statistically using ANOVA. Differences in LSmeans between PK parameter estimates of midazolam and 1'-hydroxymidazolam in the presence of AZD3480 compared with midazolam and 1'-hydroxymidazolam given alone (placebo) and associated 90% CI were determined for each CYP2D6 genotype. Similarly, the PK parameters AUC, $AUC_{(0-t)}$ and C_{max} of rosiglitazone on

Day 6 and the PK parameters AUC, $AUC_{(0-t)}$ and C_{max} of bupropion on Da7, in the presence of AZD3480 (test treatment) and following placebo administration (reference treatment), were compared statistically using ANOVA.

The log_e transformed pharmacokinetic parameters AUC_τ and $C_{ss,max}$ of AZD3480 at steady-state were compared between days using ANOVA to assess the effect of the cocktail on the PK of AZD3480. Differences in LS means between PK parameter estimates compared between days and associated 90% CIs will be determined for each CYP2D6 genotype.

Subject population

Twenty subjects were randomised onto the study. Three subjects were withdrawn from the study and 17 subjects completed the study as per the protocol. All 20 subjects enrolled and randomised onto the study had at least one dose of study medication and were included in the safety population. One subject was excluded from the PK population as he was incorrectly enrolled in the study and any data for this subject was subsequently excluded from the PK analysis.

Summary of pharmacokinetic results

- AZD3480 was shown to be a weak inhibitor of CYP1A2 to a similar degree in PMs and EMs by approximately 35%.
- Overall, AZD3480 was shown to be a strong inhibitor of CYP2C19 causing >7-fold increase in the omeprazole/5-hydroxyomeprazole concentration ratio. The inhibition was more pronounced in PMs compared to EMs (approximately 10-fold vs 5-fold increase).
- AZD3480 did not demonstrate clinically significant inhibition of CYP3A4, CYP2C8, CYP2B6 or UGT1A1 in either PMs or EMs.
- Bupropion (a weak to moderate CYP2D6 inhibitor) caused a 54% increase in AZD3480 AUC in EMs, but not in PMs. Otherwise, AZD3480 PK was essentially unaffected by any of the cocktail probe drugs.

Summary of safety results

Study medication was generally well tolerated following administration of AZD3480, placebo and the cocktail probes. There were no deaths or SAEs reported during the study. During the active treatment periods, the most commonly reported TEAEs were dizziness and headache with the majority of cases being mild in intensity. One subject (Subject 0030) was withdrawn from the study after 2 days of dosing with placebo in Period 1 due to catheter site erythema and rash and dermatitis allergic (all mild). There were no significant safety issues with regards to vital signs, ECGs or safety laboratory tests.