AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00016
Edition Number	1
Date	4 December 2008

An open, randomised, three period crossover, single centre, phase I pharmacokinetic interaction study of the reflux inhibitor AZD3355 150 mg bid and esomeprazole 40 mg od after 7 days of treatment in healthy volunteers

Study dates: First healthy volunteer enrolled: 27 March 2008
Last healthy volunteer completed: 3 July 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

The study was conducted at a single centre: Quintiles AB, Phase I Unit, Strandbodgatan 1, SE-753 23 Uppsala, Sweden. The principal investigator was Jan Vouis, MD.

The first healthy volunteer was enrolled on 27 March 2008 and the last healthy volunteer completed the study on 3 July 2008.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to evaluate the effect of esomeprazole on the pharmacokinetics (PK) of AZD3355 and the effect of AZD3355 on the PK of esomeprazole by assessment of AUC_{τ} and $C_{ss,max}$.

The secondary objectives of the study were:

1. To evaluate the PK of AZD3355 and esomeprazole by assessment of AUC_t, t_{max}, $t_{1/2}$ and CL_{ss}/F after repeated dosing of both substances
2. To study the safety and tolerability of AZD3355 both alone and in combination with esomeprazole by assessment of adverse events (AEs), blood pressure (BP), pulse and laboratory variables
3. To study possible cytochrome P450 (CYP) 3A induction by AZD3355 by measurement of 4-beta-hydroxy (4-β-OH) cholesterol in plasma

Study design

This was an open label, randomised study with three crossover periods. All healthy volunteers were to receive the three treatment regimens (AZD3355, AZD3355 plus esomeprazole, and esomeprazole) in random order. The treatment periods were separated by washout periods of 13 to 18 days. During each treatment period, PK sampling for determination of AZD3355 and esomeprazole in plasma was carried out on Day 7.

Target healthy volunteer population and sample size

Healthy male or female volunteers (hereafter referred to as subjects), aged 18 to 45 years.

The study was planned to randomise 30 subjects in order to have at least 24 evaluable subjects.

Investigational product: dosage, mode of administration and batch numbers

Investigational product	Dosage form and strength	Mode of administration	Batch number
AZD3355	Modified release, hard capsules, 150 mg	Oral administration	H 2015-01-01-01
Esomeprazole	Clinical trial capsules 40 mg (as esomeprazole magnesium trihydrate 44.5 mg)	Oral administration	H 1222-04-01-16

Duration of treatment

Each subject was to receive three 7-day treatment regimens (A, B and C) in random order. The details of the three treatment regimens are given below. Treatment periods were separated by washout periods of 13 to 18 days. All doses were administered at the clinic.

Treatment regimens:

A: AZD3355 150 mg bid (morning and evening, 12 h dosing interval) on Days 1 to 6, and once on Day 7 (in the morning).

B: Esomeprazole Magnesium capsules 40 mg od (in the morning) for seven days.

C: AZD3355 150 mg bid on Days 1 to 6, and once on Day 7 and esomeprazole Magnesium 40 mg od for seven days.

Criteria for evaluation - pharmacokinetics (main variables)

Primary variables: AUC_{τ} and $C_{ss,max}$ for AZD3355 and esomeprazole after seven days of repeated dosing with both substances alone and in combination

Secondary variables: AUC_t, t_{max}, $t_{1/2}$ and CL_{ss}/F for AZD3355 and esomeprazole

Criteria for evaluation - safety (main variables)

AEs, BP, pulse and laboratory variables

Statistical methods

The log-transformed variables AUC_{τ} and $C_{ss,max}$ were analysed using a mixed model ANOVA with fixed effects for sequence, period and treatment and a random effect for subject within sequence.

In order to evaluate the effect of esomeprazole on the PK of AZD3355, 90 and 95% confidence intervals for the ratio of geometric means for AUC_{τ} and $C_{ss,max}$ were calculated. Corresponding confidence intervals were calculated for esomeprazole in order to evaluate the effect of AZD3355 on esomeprazole.

For the analysis of 4-β-OH-cholesterol, log-transformed results from the two assessments (before first dose and before last dose of AZD3355 alone) were used to calculate the difference within each subject. The mean of the differences was estimated and a 95% CI based

on the t-distribution was calculated. The mean and the confidence limits were transformed back to the original scale by antilogarithm transformation in order to give an estimate of the ratio of geometric means and corresponding 95% CI.

Subject population

Thirty male subjects aged 18 to 35 years were randomised and 28 completed the study. This was in accordance with the CSP. All 30 randomised subjects were included in the PK analysis set and the safety analysis set. Subject E0001018 who discontinued the study due to an AE (fever) before completion of period 1 did not have available data for all analyses; therefore data from all 30 subjects were used for the descriptive statistics of plasma concentrations and data from 29 subjects were used for the descriptive statistics of PK parameters, descriptive statistics of 4-β-OH cholesterol and comparative statistical analysis of PK parameters. Due to missing data at baseline for one subject (E0001012), 28 subjects were included in the comparative statistical analysis of 4-β-OH cholesterol.

The treatment sequences were well-balanced with regard to demographic and baseline characteristics.

Summary of pharmacokinetic results

Both the 90 and 95% CIs of the geometric mean ratios comparing AUC_{τ} and $C_{ss,max}$ of AZD3355 after repeated administration of AZD3355 with esomeprazole vs AZD3355 alone were contained within the interval 0.8 to 1.25 (see Table S 1).

Corresponding CIs for AUC_{τ} and $C_{ss,max}$ of esomeprazole after repeated administration of esomeprazole alone and in combination with AZD3355 were also contained within the interval 0.8 to 1.25 (see Table S 2).

Similar results as for AUC_{τ} and $C_{ss,max}$ were obtained when using AUC_t for both comparisons (see Table S 1 and Table S 2).

Plots of individual C_{trough} values on Day 4 to Day 7 indicated that steady state for plasma concentrations of AZD3355 was reached on Day 4 for most subjects both after administration of AZD3355 alone and AZD3355 in combination with esomeprazole.

Table S 1 Geometric mean ratio and confidence intervals for AUC_τ, $C_{ss,max}$ and AUC_t of AZD3355 from ANOVA model (PK analysis set)

Pharmacokinetic variable	Comparison	n	Point estimate	90% confidence interval		95% confidence interval	
				Lower	Upper	Lower	Upper
AUC_τ	AZD3355 + esomeprazole vs AZD3355	29	0.92	0.85	1.00	0.84	1.02
$C_{ss,max}$	AZD3355 + esomeprazole vs AZD3355	29	0.90	0.82	1.00	0.80	1.03
AUC_t	AZD3355 + esomeprazole vs AZD3355	29	0.92	0.85	1.00	0.84	1.02

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Table S 2 Geometric mean ratio and confidence intervals for AUC_τ, $C_{ss,max}$ and AUC_t of esomeprazole from ANOVA model (PK analysis set)

Pharmacokinetic variable	Comparison	n	Point estimate	90% confidence interval		95% confidence interval	
				Lower	Upper	Lower	Upper
AUC_τ	AZD3355 + esomeprazole vs Esomeprazole	29	0.97	0.90	1.05	0.89	1.07
$C_{ss,max}$	AZD3355 + esomeprazole vs Esomeprazole	29	1.04	0.95	1.15	0.93	1.17
AUC_t	AZD3355 + esomeprazole vs Esomeprazole	29	0.97	0.90	1.05	0.89	1.07

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Median t_{max}, geometric mean $t_{½}$ and geometric mean CL_{ss}/F of AZD3355 were comparable after repeated administration of AZD3355 alone (3.0 h, 6.2 h and 30.4 L/h, respectively) and in combination with esomeprazole (3.0 h, 6.6 h and 32.9 L/h, respectively).

Geometric mean $t_{½}$ and geometric mean CL_{ss}/F of esomeprazole were comparable after repeated administration of esomeprazole alone (1.4 h and 10.2 L/h, respectively) and in combination with AZD3355 (1.4 h and 10.3 L/h, respectively). Median t_{max} differed slightly after esomeprazole alone (2.5 h) and esomeprazole in combination with AZD3355 (1.5 h), but the means and ranges of t_{max} were comparable.

According to exploratory measurements, there was no increase in 4-β-OH-cholesterol concentrations in plasma during treatment with AZD3355 alone. The geometric mean ratio (95% CI) for pre-dose Day 7 vs pre-dose Day 1 was 0.91 (0.88 to 0.94).

At the time of writing the CSR the bioanalytical method for 4-β-OH cholesterol measurement had not been validated for long term stability of the samples. Therefore the 4-β-OH cholesterol results presented in the CSR are considered to be exploratory until such a validation has been completed.

Summary of safety results

In this open-label treatment study, there were no serious adverse events and most AEs were of mild or moderate intensity. One AE (fever) led to discontinuation but this was not considered related to the investigational product. The most common AEs during active treatment were paraesthesiae, flatulence, pharyngitis, rhinitis, dizziness, diarrhoea and headache. There was no apparent difference in the number or types of AEs after administration of AZD3355 alone and in combination with esomeprazole.

At orthostatic tests, the mean reflectory pulse increase from supine to standing (measured after 1 and 3 minutes of standing) was higher at 1 h post dose on Day 1 compared to pre-dose during treatment with AZD3355 and AZD3355 plus esomeprazole. This effect was not seen during administration of esomeprazole alone.

There were no clinically relevant safety findings based on laboratory safety variables, ECG or physical examinations.