AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD9056
Study Code	D1520C00008
Edition Number	1
Date	27 April 2009

A Phase I, Single Centre, Open-Label Study to Assess the Pharmacokinetics of both AZD9056 (Steady State) and Simvastatin (Single Dose) when Co-Administered in Healthy Volunteers

Study dates: First healthy volunteer: 05 August 2008
Last healthy volunteer: 16 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

PAREXEL Clinical Pharmacology Research Unit, Northwick Park Hospital, Harrow, Middlesex, United Kingdom

Study period		**Phase of development**
First healthy volunteer enrolled	05 August 2008	I
Last healthy volunteer completed	16 September 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate whether simvastatin or simvastatin acid plasma concentration-time profiles and resulting pharmacokinetic parameters (single dose) were altered in the presence of steady state AZD9056 concentrations.

The secondary objectives of the study were:

1. to investigate whether AZD9056 plasma concentration-time profiles and resulting pharmacokinetic parameters (steady state) were altered when co-administered with simvastatin (single dose)

2. to investigate the safety and tolerability of AZD9056 when co-administered with simvastatin (single dose).

An exploratory objective of the study was:

1. to explore whether the variability in systemic AZD9056 exposures could be explained by genetic variation.

Study design

This study was designed as a 2-period, open-label, non-randomised, single-centre study to investigate the pharmacokinetics (PK) of a single oral dose of simvastatin (40 mg) in the presence of steady state AZD9056 concentrations (400 mg once a day) in healthy volunteers. Period I examined the PK of simvastatin alone, while Period II primarily examined the PK of simvastatin with AZD9056 at steady state.

Target healthy volunteer population and sample size

A total of 12 healthy female (of non-childbearing potential) and male subjects, aged 18 to 55 years (inclusive), with a Body Mass Index of 18 to 30 kg/m^2 (inclusive).

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

Drug: AZD9056
Formulation: Tablets for oral use
Strength: 200 mg
Daily dose: 400 mg once daily for 8 days
Batch number: 07-011250AZ

Drug: Simvastatin
Formulation: Tablet for oral use
Strength: 40 mg
Single dose: 40 mg
Batch number: Not applicable

On Day 7, simvastatin and AZD9056 were co-administered.

Duration of treatment

The study included 2 periods, which were separated by a wash-out period of at least 7 days (from the administration of the investigational product (IP) on Day 1 of the first period until IP administration on Day 1 of the second period). Study Period I took 4 days. Study Period II took 10 days. Considering a Screening Period of 21 days and Follow-up Visit between 4 to 7 days after final IP administration on Day 8 the total duration of this study for a subject was about 44 days.

Criteria for evaluation - pharmacokinetics (main variables)

Primary:

For simvastatin and simvastatin acid in plasma: C_{max} and AUC.

Secondary:

For simvastatin and simvastatin acid in plasma: t_{max}, $t_{1/2}$, CL/F, and V_z/F.

For AZD9056 in plasma: $AUC_{(0-24)}$, $AUC_{(0-t)}$, C_{max}, t_{max}, and CL_{ss}/F.

Criteria for evaluation - safety (main variables)

Vital signs, clinical chemistry, haematology, urinalysis, physical examination, standard 12-lead ECG and adverse events

Statistical methods

To address the primary objective, point estimates and 90% confidence intervals for the ratios of AUC and C_{max} of simvastatin and simvastatin acid (with AZD9056 / without AZD9056) were presented. This was obtained by an analysis of the log-transformed AUC and C_{max} using a paired t-test (comparing simvastatin + AZD9056 versus simvastatin alone). No clinically

significant drug-drug interaction was concluded if the 90% confidence interval fell within 0.7 and 1.43.

The influence of simvastatin on steady state PK of AZD9056 was evaluated in a similar fashion by analysis of the $AUC_{(0-24)}$ and C_{max} ratios of AZD9056 + simvastatin versus AZD9056 alone.

Time to peak concentration, t_{max} for simvastatin (simvastatin + AZD9056 versus simvastatin alone) and t_{max} for AZD9056 (AZD9056 + simvastatin versus AZD9056 alone) data were compared using non-parametric methods.

Subject population

Twelve healthy volunteers were planned and randomised; 12 subjects were included in the Safety analysis set and 11 subjects were included in the PK analysis set; one subject prematurely discontinued the study for an AE so that 11 subjects completed the study. Although the study was designed to include healthy male or female subjects, only men were included.

Summary of pharmacokinetic results

Simvastatin and simvastatin acid

The results of the statistical analysis of the primary endpoints of the study are summarised in Table S1.

Table S1 **Geometric mean, geometric mean ratio and 90% CIs for ratio of simvastatin and simvastatin acid alone (Period I) or at steady state AZD9056 400 mg (Period II), (PK analysis set)**

Pharmacokinetic parameter	Simvastatin		Simvastatin + AZD9056		Point estimate of geomean ratio of simvastatin + AZD9056 to simvastatin	90%CI of geomean ratio of simvastatin + AZD9056 to simvastatin
	n	Geomean	N	Geomean		
Simvastatin						
C_{max} (ng/mL)	11	8.99	11	23.29	2.59	1.93; 3.47
AUC (ng.h/mL)	9	37.02	9	129.58	3.50	2.64; 4.64
$AUC_{(0-t)}$ (ng.h/mL)	11	36.15	11	126.23	3.49	2.71; 4.49
$AUC_{(0-12)}$ (ng.h/mL)	11	31.00	11	109.20	3.52	2.81; 4.42
Simvastatin acid						
C_{max} (ng/mL)	11	1,69	11	6.37	3.77	3.04; 4.67
AUC (ng.h/mL)	5	30,87	5	86.27	2.79	2.07; 3.77
$AUC_{(0-t)}$ (ng.h/mL)	11	15,25	11	56.17	3.68	2.86; 4.74
$AUC_{(0-12)}$ (ng.h/mL)	10	14,04	10	46.67	3.32	2.71; 4.08

AUC= area under the plasma concentration-time curve; $AUC_{(0-t)}$= area under the plasma concentration-time curve from time point 0 to the time of the last quantifiable concentration; CI= confidence interval; C_{max}= maximum plasma concentration; geomean= geometric mean; n= number of observations.

The PK of simvastatin was notably affected by steady state AZD9056; overall exposure (AUC) to simvastatin increased by 3.5-fold (90% CI: 2.64, 4.64) and peak exposure (C_{max}) increased by 2.6-fold (90% CI: 1.93, 3.47).

There was significant difference between in simvastatin t_{max} after administration of simvastatin alone and in combination with AZD9056 (90% CI: 0.235; 3.485).

Like the parent, geometric mean AUC parameters and C_{max} of the metabolite simvastatin acid were significantly increased by AZD9056 at steady state. The corresponding 90% CIs were all clearly above the pre-defined range [0.7; 1.43] indicating the effect of AZD9056.

AZD9056

The results of the statistical analysis of the primary endpoints of the study are summarised in Table S2.

Table S2 **Geometric mean, geometric mean ratio and 90% CIs for ratio of AZD9056 100 mg alone (Day 5) or with simvastatin 40 mg (Day 7), (PK analysis set)**

Pharmacokinetic parameter	AZD9056		AZD9056 + simvastatin		Point estimate of geomean ratio of AZD9056 + simvastatin to AZD9056	90%CI of geomean ratio of AZD9056 + simvastatin to AZD9056
	N	Geomean	N	Geomean		
$C_{ss,max}$ (nM)	11	1937.56	11	2065.27	1.07	0.99; 1.14
$AUC_{(0-24,)ss}$ (nM.h)	11	26689.27	11	26426.67	0.99	0.92; 1.06

AUC_{ss}= area under the plasma concentration-time curve at steady state; CI= confidence interval;
$C_{ss,max}$= maximum plasma concentration at steady state; geomean= geometric mean; n= number of observations.

A single 40 mg simvastatin dose did not change the PK of AZD9056 at steady state. The geometric mean plasma concentration-time profiles of AZD9056 were similar after administration of AZD9056 with and without simvastatin.

The analysis of the estimates and the 90% CIs of the geometric mean ratios of $C_{ss,max}$ and $AUC_{(0-24),ss}$ excluded an effect of simvastatin on the PK of AZD9056; point estimates of the ratios were close to unity and the corresponding 90%CIs were both well contained in the pre-defined interval of 0.74 and 1.43.

Summary of safety results

Co-administration of AZD9056 at steady state (400 mg once daily over 7 days) with a single 40 mg dose of simvastatin was generally well-tolerated. The AEs were mostly of mild intensity and no AE of severe intensity was reported. Leading AEs were diarrhoea, abdominal pain and flatulence, which were reported upon AZD9065 treatment, alone or in combination with simvastatin. The gastrointestinal events observed in this study reflect the type of AEs commonly seen in other studies conducted with AZD9056. There were no clinically relevant changes in safety laboratory variables, vital signs, ECG and physical examination.