AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00025
Edition Number	1
Date	7 April 2009

A Phase I, Single Centre, Open-label Study to Assess the Pharmacokinetics of Both AZD5672 (Steady-state) and Atorvastatin (Single dose) when Co-administered in Healthy Volunteers

Study dates: First healthy volunteer enrolled: 14 July 2008
Last healthy volunteer completed: 03 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	14 July 2008	Clinical pharmacology (I)
Last healthy volunteer completed	03 September 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate whether atorvastatin plasma concentration-time profiles and resulting pharmacokinetic parameters (single dose) were altered in the presence of steady-state AZD5672 concentrations in healthy volunteers.

The secondary objectives of the study were:

1. to investigate whether AZD5672 plasma concentration-time profiles and resulting pharmacokinetic parameters (steady-state) were altered when co-administered with atorvastatin (single dose) in healthy volunteers
2. to investigate the safety and tolerability of AZD5672 when co-administered with atorvastatin (single dose) in healthy volunteers
3. to investigate whether the plasma concentration-time profiles and resulting pharmacokinetic parameters (single dose) of atorvastatin metabolites (atorvastatin lactone, o-hydroxy atorvastatin acid and p-hydroxy atorvastatin acid) were altered in the presence of steady-state AZD5672 concentrations in healthy volunteers.

An exploratory objective of the study was:

1. to explore whether the variability in systemic AZD5672 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 atorvastatin (40 mg) in the presence of steady-state AZD5672 concentrations (100 mg once a day) in healthy volunteers. Period I examined the PK of atorvastatin alone, while Period II primarily examined the PK of atorvastatin with AZD5672 at steady-state.

Target healthy volunteer population and sample size

A total of 12 healthy female (of non-childbearing potential) and male volunteers, aged 18 to 55 years (inclusive).

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

Drug: AZD5672
Formulation: tablets for oral use
Strength: 50 mg
Daily dose: 100 mg once daily
Batch number: 08-013001AZ

Drug: atorvastatin
Formulation: tablet for oral use
Strength: 40 mg
Single dose: 40 mg
Batch number: 0454048 U

On Day 10, atorvastatin and AZD5672 were co-administered.

Duration of treatment

The study comprised 2 periods which were separated by a wash-out period of at least 7 days. Study Period I comprised a single dose administration with subsequent assessments across 3 days. Study Period II comprised 10 days under active treatment. Considering the Screening period (21 days) and the Follow-up visit (4 to 7 days post final administration of the investigational product AZD5672 on Day 10) the total duration of this study for a healthy volunteer was about 43 days at maximum.

Criteria for evaluation - pharmacokinetics (main variables)

Primary:

For atorvastatin in plasma: C_{max}, AUC, $AUC_{(0-t)}$, $AUC_{(0-24)}$ and t_{max}

Secondary:

For atorvastatin in plasma: $t_{1/2}$, CL/F, V_z/F

For AZD5672 in plasma: $C_{ss,max}$, AUC_{ss}, $t_{max,ss}$

For o-hydroxy atorvastatin acid in plasma: C_{max}, $AUC_{(0-t)}$, $AUC_{(0-24)}$, t_{max}, $t_{1/2}$

Criteria for evaluation - safety (main variables)

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

Criteria for evaluation - pharmacogenetics (main variables)

The purpose of the pharmacogenetic research was to generate data for use in future retrospective analyses in relation to AZD5672. Future analyses could explore pharmacogenetic factors which could help to explain some of the variability associated with pharmacokinetic parameters and/or observed safety profiles.

Statistical methods

To address the primary objective, a point estimate and 90% confidence intervals for the ratio of AUC and C_{max} of atorvastatin (with AZD5672 : without AZD5672) was presented. This was obtained by an analysis of the log-transformed AUC and C_{max} using a paired t-test (comparing atorvastatin + AZD5672 versus atorvastatin alone). No clinically significant drug-drug interaction was to be concluded if the 90% confidence interval fell within 0.74 and 1.43. The AUC and C_{max} of o-hydroxy atorvastatin acid were analysed in a similar fashion.

The influence of atorvastatin on steady-state PK of AZD5672 was evaluated in a similar fashion by analysis of the AUC_{ss} and $C_{ss,max}$ ratios of AZD5672 + atorvastatin versus AZD5672 alone.

Time to peak concentration, t_{max} for atorvastatin (atorvastatin + AZD5672 versus atorvastatin alone) and $t_{max,ss}$ for AZD5672 (AZD5672 + atorvastatin versus AZD5672 alone) data were compared using non-parametric methods.

Subject population

In total, 1 female and 11 male healthy volunteers between the age of 20 and 51 were enrolled into the study and randomised; all of them received treatment and completed the study as per protocol. All volunteers were healthy based on the screening examination, complied with the inclusion criteria and none met any exclusion criteria. The 12 subjects were all included in the safety and in the PK analysis set. No major protocol deviations were recorded.

Summary of pharmacokinetic results

Atorvastatin and o-hydroxy metabolites

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 atorvastatin and o-hydroxy atorvastatin acid alone (Period I) or at steady-state AZD5672 100 mg (Period II), (PK analysis set)

Pharmacokinetic parameter	Atorvastatin		Atorvastatin + AZD5672		Point estimate of geomean ratio of atorvastatin + AZD5672 to atorvastatin	90%CI of geomean ratio of atorvastatin + AZD5672 to atorvastatin
	N	GeoMean	N	GeoMean		
Atorvastatin						
C_{max} (ng/mL)	12	12.51	12	13.79	1.10	0.84, 1.46
AUC (ng.h/mL)	11	63.13	12	86.82	1.44	1.33, 1.55
$AUC_{(0-t)}$ (ng.h/mL)	12	55.27	12	81.09	1.47	1.35, 1.60
$AUC_{(0-24)}$ (ng.h/mL)	12	57.56	12	76.84	1.33	1.24, 1.44
o-hydroxy atorvastatin acid						
C_{max} (ng/mL)	12	8.63	12	3.62	0.42	0.34, 0.52
$AUC_{(0-t)}$ (ng.h/mL)	12	71.99	12	48.49	0.67	0.60, 0.76
$AUC_{(0-24)}$ (ng.h/mL)	12	69.53	12	45.04	0.65	0.57, 0.73

AUC= area under the plasma concentration-time curve from 0 to infinity; $AUC_{(0-t)}$= 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 atorvastatin was notably affected by steady-state AZD5672; overall exposure (AUC) to atorvastatin increased by about 1.4-fold (90% CI: 1.33, 1.55). Geometric mean C_{max} was less affected by AZD5672 at steady-state, the estimate of the geometric mean ratio was 1.10 and the corresponding 90%CI (0.84, 1.46) was almost completely included in the pre-defined interval of [0.74, 1.43].

A significant difference between t_{max} after administration of atorvastatin alone and in combination with AZD5672 was not revealed.

In contrast to the parent, geometric mean $AUC_{(0-t)}$, $AUC_{(0-24)}$ and C_{max} of the metabolite o-hydroxy atorvastatin acid were significantly decreased by AZD5672 at steady-state. The corresponding 90% CIs were clearly below unity indicating an interaction with AZD5672.

AZD5672

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 AZD5672 100 mg alone (Day 8) or with atorvastatin 40 mg (Day 10), (PK analysis set)

Pharmacokinetic parameter	AZD5672		AZD5672 + Atorvastatin		Point estimate of geomean ratio of AZD5672 + atorvastatin to AZD5672	90%CI of geomean ratio of AZD5672 + atorvastatin to AZD5672
	N	Geomean	N	Geomean		
$C_{ss,max}$ (ng/mL)	12	191.01	12	192.99	1.01	0.84, 1.21
AUC_{ss} (ng.h/mL)	12	1060.83	12	1148.00	1.08	1.01, 1.16

AUC_{ss} area under the plasma concentration-time curve from 0 to infinity at steady-state
CI confidence interval
$C_{max,ss}$ maximum plasma concentration at steady-state
geomean geometric mean
LSMean least square mean
N number of subjects.

A single 40 mg atorvastatin dose did not change the PK of AZD5672 at steady-state. The geometric mean plasma concentration-time profiles of AZD5672 were similar after administration of AZD5672 with and without atorvastatin.

The analysis of the estimates and the 90% CIs of the geometric mean ratios of $C_{max,ss}$ and AUC_{ss} excluded an effect of atorvastatin on the PK of AZD5672; 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

A total of 12 AEs were reported by 7 (58%) subjects on AZD5672, alone and in combination with atorvastatin, while under atorvastatin alone 4 AEs were reported by 3 (25%) subjects. Adverse events considered by the Investigator to be causally related to treatment comprised diarrhoea, dizziness, feeling hot, and headache. All AEs were of mild to moderate intensity and no AE of severe intensity, SAE, discontinuation due to AE, or other significant AEs were observed.

There were no clinically relevant changes in safety laboratory variables, vital signs, ECG, and physical examination.