AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1981
Study Code	D9830C00016
Edition Number	1
Date	23 August 2011

A Phase I, Open Label, Randomised, Parallel Group Study of Repeated Oral Doses of AZD1981 (100 mg Twice Daily and 400 mg Twice Daily via Tablet) for Eight days and Single Doses of Pravastatin (Pravachol® Tablet 40 mg) to Evaluate the Pharmacokinetic Interaction of AZD1981 and Pravastatin in Healthy Male Volunteers

Study dates: First subject enrolled: 4 February 2011
Last subject last visit: 21 April 2011

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 in

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate whether pravastatin plasma concentration-time profiles and resulting pharmacokinetic parameters (single dose) are altered in the presence of steady-state AZD1981 concentrations in healthy subjects	Pharmacokinetic variables for pravastatin on Day 1 (before AZD1981) and Day 8 (after 8 days of 100 or 400 mg AZD1981 twice daily): Primary variables: C_{max}, AUC Secondary variables: $AUC_{(0-t)}$, t_{max}, CL/F, $t_{1/2\lambda z}$, V_z/F, MRT	Pharmaco-kinetic
Secondary	**Secondary**	
To investigate whether AZD1981 plasma concentration-time profiles and resulting pharmacokinetic parameters (steady-state) are altered when co-administered with pravastatin (single dose) in healthy subjects	Pharmacokinetic variables[c] for AZD1981 on Day 7 (alone) and Day 8 (concomitantly with a single dose of pravastatin): AUC_τ, $C_{ss,max}$, $t_{max,ss}$, CL_{ss}/F	Pharmaco-kinetic
Safety	**Safety**	
To investigate the safety and tolerability of AZD1981 when co-administered with pravastatin (single dose) in healthy subjects	Adverse events, blood pressure, pulse, laboratory variables, electrocardiogram, physical examination	Safety
Exploratory[a]	**Exploratory**	
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, and tolerability) to AZD1981 or pravastatin	Not applicable	Pharmaco-genetic

a Exploratory analysis, if conducted, will be reported separately from this clinical study report.
AUC area under the plasma concentration-time curve from time zero to infinity; $AUC_{(0-t)}$ area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; AUC_τ area under the plasma concentration-time curve during a dosing interval; CL/F apparent plasma clearance after a single dose; CL_{ss}/F apparent plasma clearance at steady-state; C_{max} maximum plasma concentration; $C_{ss,max}$ maximum plasma concentration at repeat dosing; MRT apparent mean residence time for pravastatin; t_{max} time to reach C_{max}; $t_{max,ss}$ time to reach $C_{ss,max}$; $t_{1/2\lambda z}$ terminal half-life; V_z/F volume of distribution during terminal phase

Study design

This was a Phase I study with an open-label, randomised and parallel group design to access the pharmacokinetic interaction of AZD1981 and pravastatin.

Single oral doses of pravastatin were administered alone (Visit 2, Period A) and in combination with AZD1981 at steady-state (Visit 4, Period B). The subjects were randomised to 1 of 2 doses of AZD1981 twice daily for 8 days during Period B to ensure that steady-state conditions had been reached. The two treatment periods (A and B) were separated by a washout period of at least 4 days.

Target subject population and sample size

The target population was healthy male subjects, aged 18 to 55 years, with a body mass index between 19 and 30 kg/m^2, and a weight of at least 50 kg and no more than 100 kg.

Thirty (30) subjects were to be randomised to ensure evaluable data from at least 12 subjects in each dose group.

Investigational products: dosage, mode of administration and batch numbers

Pravastatin (Pravachol®), oral tablet 40 mg (Bristol-Meyer Squibb, batch no 11-000069AZ), was administered as a single dose (1 x 40 mg).

AZD1981, oral tablet 100 mg (AstraZeneca, batch no 10-003598AZ), was administered twice daily (bid) as a dose of 100 mg (1 x 100 mg) or 400 mg (4 x 100 mg).

Duration of treatment

Pravastatin (Pravachol®) was given as a single dose on 2 occasions: on Day 1 (Visit 2) in Period A and on Day 8 (Visit 4) in Period B.

AZD1981 was administered twice daily for 8 days during Period B.

Statistical methods

AUC and C_{max} of pravastatin were analysed using a linear mixed effects model. The model included time (pre AZD1981 or post AZD1981 dose), group (100 or 400 mg AZD1981) and time*group as fixed factors and subject as a random factor. The analyses were based on log e-transposed variables and the results were exponentially back-transformed in order to provide estimates of the true ratios post-dose/pre-dose. Least-squares means point estimates and corresponding 95% confidence intervals were presented by dose and time. Estimates and 95% confidence intervals of the ratio post AZD1981 dose/pre AZD1981 dose for each dose were presented.

A similar model was used for the analyses of AZD1981 with the exception that pre-dose/post-dose was for pravastatin.

Safety was evaluated by descriptive statistics.

Subject population

Thirty (30) healthy subjects, all white male subjects aged 18 to 54 years, were randomised and completed the study. Their mean (±standard deviation) weight and body mass index were

79.6 (±10.3) kg and 24.53 (±2.83) kg/m^2, respectively. The 2 treatment groups, 100 mg and 400 mg AZD1981, were comparable with regard to demographic and baseline characteristics.

Summary of pharmacokinetic results

Oral administration of AZD1981 tablets 100 and 400 mg twice daily dose-dependently interacted with the single-dose pharmacokinetics of orally administered pravastatin 40 mg.

The 95% CIs of the AUC ratios in the 100 mg AZD1981 treatment group did not include 1 and the estimate indicated an increase of 27% when pravastatin was given in the presence of AZD1981 100 mg steady-state concentrations. The 95% CIs for C_{max} in the 100 mg AZD1981 treatment group included 1, however the wide CI interval indicated C_{max} also to be increased (29%) in the presence of AZD1981 100 mg steady-state concentrations compared to after pravastatin alone.

The 95% CIs of the AUC and C_{max} ratios in the 400 mg AZD1981 treatment group did not include 1. The statistical analysis indicated that the pravastatin AUC and C_{max} were increased by approximately 57% and 35%, respectively, when pravastatin was given in the presence of AZD1981 400 mg steady-state concentrations compared to pravastatin alone.

Pre-treatment with AZD1981 resulted in lower CL/F, smaller V_z/F, but unchanged t_{max} and $t_{1/2\lambda z}$ of pravastatin.

The pharmacokinetics of AZD1981 100 or 400 mg twice daily at steady-state were not changed by co-administration of pravastatin 40 mg.

Summary of safety results

There were no serious adverse events, no other significant adverse events and no discontinuations due to an adverse event in the study. There were no adverse events of severe intensity and the majority were mild in intensity. The most common adverse events were nasopharyngitis, headache and dry mouth.

There were no clinically relevant findings in safety laboratory variables, electrocardiogram, vital signs, physical examination or weight during the study.