AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0837
Study Code	D1250C00056
Edition Number	1
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A phase I, single-centre, open, randomized, two-way crossover study to evaluate the pharmacokinetics of the extended-release test formulation of AZD0837 compared to the extended-release AZD0837 reference formulation after repeated dosing in healthy volunteers

Study dates: First healthy volunteer enrolled: 1 April 2009
Last healthy volunteer completed: 27 May 2009

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

The study was conducted at Quintiles AB, Uppsala, Sweden. The first healthy volunteer entered the study on 1 April 2009 and the last healthy volunteer finished the study on 27 May 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective was to evaluate the pharmacokinetics (PK) of AZD0837 and the active metabolite AR-H067637XX for the extended-release (ER) test formulation of AZD0837 compared to the ER reference formulation after repeated oral dosing in fasting healthy volunteers.

The secondary objectives were:

- To evaluate the PK of the intermediate metabolite AR-H069927XX after repeated oral dosing of the ER test formulation and the ER reference formulation in fasting healthy volunteers
- To evaluate the PK of AZD0837, AR-H067637XX and AR-H069927XX for the ER test formulation of AZD0837 compared to the ER reference formulation after repeated oral dosing in fed healthy volunteers
- To evaluate the PK of AZD0837, AR-H067637XX and AR-H069927XX when administered with and without food for each of the formulations separately after repeated oral dosing in healthy volunteers
- To evaluate the safety and tolerability of AZD0837 in healthy volunteers, by assessment of electrocardiogram (ECG), pulse, blood pressure (BP), laboratory variables, physical examination and adverse events (AEs)

The tertiary objective was to investigate whether AZD0837 affects the level of CYP3A4 as indicated by measurement of plasma concentrations of 4β-hydroxycholesterol.

Study design

This was an open, randomized, two-way crossover, single-centre, phase I study. Each subject received 2 treatments in randomized order. AZD0837 was administered as the test and the reference formulations once daily for 6 days, in the fasted state on Days 1 to 5 and in the fed state on Day 6. The subjects were randomized to a high-calorie and high-fat breakfast or a light breakfast served on Day 6 in each study session. Each subject was served the same breakfast in both study sessions. The study sessions were not separated by a washout period.

Target healthy volunteer population and sample size

A total of 36 healthy volunteers were planned to be randomised in order to have at least 30 healthy volunteers completing the 2 study sessions. Thirty-six (36) healthy volunteers were randomised into the study and analysed.

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

Test formulation: 300 mg AZD0837 (2 ER tablets à 150 mg, batch no H1890-02-01-01) administered orally in the morning for 6 days (treatment I)

Reference formulation: 300 mg AZD0837 (2 ER tablets à 150 mg, batch no H1825-02-01-05) administered orally in the morning for 6 days (treatment II)

AZD0837 was administered in the fasted state on Days 1 to 5 and in the fed state on Day 6.

Duration of treatment

Each subject was administered the test formulation and the reference formulation in 2 study sessions, each consisting of 6 days. The study sessions were not separated by a washout period.

Criteria for evaluation - pharmacokinetics (main variables)

- Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) of AZD0837 and AR-H067637XX (primary variables)
- C_{max} and AUC_{τ} of AR-H069927XX
- Time to C_{max} (t_{max}) of AZD0837, AR-H067637XX and AR-H069927XX
- Plasma concentration of 4β-hydroxycholesterol

Criteria for evaluation - safety (main variables)

- AEs occurring during the study, safety laboratory variables, physical examination, BP, pulse and ECG

Statistical methods

The relative bioavailability was analysed with a mixed-effect analysis of variance model using the logarithm of AUC_{τ} and C_{max} for AZD0837, AR-H067637XX and AR-H069927XX after multiple dosing in fasting and fed subjects as the response variable and sequence, period and treatment as fixed factors and subject within sequence as random factor.

The PK variables were presented with descriptive statistics.

Safety variables were summarised by descriptive statistics per treatment group and time point.

The mean of the individual differences and the mean of the individual ratios of the plasma concentration of 4β-hydroxycholesterol between pre-dose and post-dose were estimated together with a confidence interval (CI) based on the t-distribution.

Subject population

A total of 36 healthy volunteers were planned to be randomised in order to have at least 30 healthy volunteers completing the 2 study sessions. Thirty-six (36) healthy volunteers were randomised into the study and all completed the study.

All 36 randomized healthy volunteers were included in the safety analysis set. The following numbers of healthy volunteers were included in the PK analyses: 36 healthy volunteers for test vs reference, fasting; 36 healthy volunteers for test vs reference, fed (18 for fed light, 18 for fed heavy); 36 healthy volunteers for fed vs fasting (18 for fed light vs fasting, 18 for fed heavy vs fasting).

Summary of pharmacokinetic results

In the fasting state, the AUC_{τ} of AZD0837 and AR-H067637XX for the ER test formulation was slightly smaller, while C_{max} was similar, compared to respective values of the ER reference formulation. The estimated geometric mean ratios (95% CI) of AUC_{τ} and C_{max}, test vs reference, for AZD0837 and AR-H067637XX are shown in Table S1 and Table S2, respectively.

The same statement as above was also valid for AR-H069927XX with estimated geometric mean ratios (95% CI) of AUC_{τ} and C_{max}, test vs reference, of 0.93 (0.88 to 0.99) and 0.91 (0.79 to 1.04), respectively. Median t_{max} of AZD0837 and its metabolites was comparable between formulations.

In the fed light state, the ER test formulation plasma exposure for AZD0837 and its metabolites was similar compared to that of the ER reference formulation. The estimated geometric mean ratios (95% CI) of AUC_{τ} and C_{max}, test vs reference, for AZD0837 and AR-H067637XX are shown in Table S1 and Table S2, respectively. The corresponding ratios for AR-H069927XX were 1.04 (0.94 to 1.16) and 1.04 (0.89 to 1.21), respectively. Median t_{max} of AZD0837 and its metabolites was comparable between formulations.

In the fed heavy state, the ER test formulation plasma exposure for AZD0837 and its metabolites was similar compared to that of the ER reference formulation. The estimated geometric mean ratios (95% CI) of AUC_{τ} and C_{max}, test vs reference, for AZD0837 and AR-H067637XX are shown in Table S1 and Table S2, respectively. The corresponding ratios for AR-H069927XX were 0.99 (0.93 to 1.05) and 0.94 (0.81 to 1.08), respectively. Median t_{max} of AZD0837 and its metabolites was generally comparable between formulations.

Table S1 **Least squares means estimate and 95% CI of the ratio between treatment with test and reference formulation for AUC_τ and C_{max} of AZD0837 (PK analysis set)**

					95% confidence interval	
Variable	**Fed/Fasting**	**Comparison**	**n**	**Estimate**	**Lower**	**Upper**
AUC_τ	Fasting	300 mg ER test/reference tablet	36	0.911	0.856	0.971
	Fed heavy	300 mg ER test/reference tablet	18	1.00	0.928	1.08
	Fed light	300 mg ER test/reference tablet	18	1.01	0.898	1.14
C_{max}	Fasting	300 mg ER test/reference tablet	36	0.906	0.793	1.03
	Fed heavy	300 mg ER test/reference tablet	18	0.976	0.836	1.14
	Fed light	300 mg ER test/reference tablet	18	1.01	0.841	1.21

Table S2 **Least squares means estimate and 95% CI of the ratio between treatment with test and reference formulation for AUC_τ and C_{max} of AR-H067637XX (PK analysis set)**

					95% confidence interval	
Variable	**Fed/Fasting**	**Comparison**	**n**	**Estimate**	**Lower**	**Upper**
AUC_τ	Fasting	300 mg ER test/reference tablet	36	0.924	0.884	0.965
	Fed heavy	300 mg ER test/reference tablet	18	1.01	0.959	1.07
	Fed light	300 mg ER test/reference tablet	18	0.994	0.924	1.07
C_{max}	Fasting	300 mg ER test/reference tablet	36	0.984	0.916	1.06
	Fed heavy	300 mg ER test/reference tablet	18	0.992	0.919	1.07
	Fed light	300 mg ER test/reference tablet	18	0.958	0.875	1.05

For the ER test formulation, the plasma exposure of AZD0837, AR-H067637XX and AR-H069927XX was higher in both fed light and fed heavy state compared to in fasting state. The estimated geometric mean ratios (95% CI) of AUC_τ and C_{max}, fed light vs fasting and fed heavy vs fasting, for AZD0837 and AR-H067637XX are shown in Table S3 and Table S4, respectively. The corresponding ratios for AR-H069927XX were 1.17 (1.04 to 1.31) and 1.22 (1.05 to 1.41), respectively (fed light vs fasting) and 1.33 (1.21 to 1.47) and 1.58 (1.33 to 1.88), respectively (fed heavy vs fasting). Median t_{max} of AZD0837 and its metabolites was comparable in fed light but longer in fed heavy state compared to fasting state.

For the ER reference formulation, the plasma exposure of AZD0837, AR-H067637XX and AR-H069927XX was comparable in fed light, and higher in fed heavy state, compared to fasting state. The estimated geometric mean ratios (95% CI) of AUC_τ and C_{max}, fed light vs fasting and fed heavy vs fasting, for AZD0837 and AR-H067637XX are shown in Table S3 and Table S4, respectively. The corresponding ratios for AR-H069927XX were 1.01 (0.92 to 1.10) and 1.09 (0.88 to 1.36), respectively (fed light vs fasting) and 1.30 (1.23 to 1.38) and 1.49 (1.25 to 1.79), respectively (fed heavy vs fasting). Median t_{max} of AZD0837 and its metabolites was generally longer in both fed light and fed heavy state compared to fasting state.

There was no indication of any clinically significant effect of repeated oral dosing of AZD0837 on the levels of 4β-hydroxycholesterol, a biomarker for CYP3A4 activity, thereby indicating lack of effect on CYP3A4.

Table S3 Least squares means estimates and 95% CI of the ratio between fed and fasting condition for AUC_τ and C_{max} of AZD0837 (PK analysis set)

					95% confidence interval	
Variable	**Treatment**	**Comparison**	**n**	**Estimate**	**Lower**	**Upper**
AUC_τ	300 mg ref tablet	Fed heavy / fasting	18	1.31	1.23	1.39
		Fed light / fasting	18	0.983	0.902	1.07
	300 mg test tablet	Fed heavy / fasting	18	1.37	1.25	1.49
		Fed light / fasting	18	1.15	1.02	1.28
C_{max}	300 mg ref tablet	Fed heavy / fasting	18	1.56	1.28	1.89
		Fed light / fasting	18	1.13	0.895	1.43
	300 mg test tablet	Fed heavy / fasting	18	1.72	1.48	2.01
		Fed light / fasting	18	1.23	1.04	1.45

Table S4 Least squares means estimates and 95% CI of the ratio between fed and fasting condition for AUC_τ and C_{max} of AR-H067637XX (PK analysis set)

					95% confidence interval	
Variable	**Treatment**	**Comparison**	**n**	**Estimate**	**Lower**	**Upper**
AUC_τ	300 mg ref tablet	Fed heavy / fasting	18	1.15	1.10	1.20
		Fed light / fasting	18	0.996	0.952	1.04
	300 mg test tablet	Fed heavy / fasting	18	1.22	1.13	1.31
		Fed light / fasting	18	1.11	1.04	1.18

Table S4 **Least squares means estimates and 95% CI of the ratio between fed and fasting condition for AUC_{τ} and C_{max} of AR-H067637XX (PK analysis set)**

					95% confidence interval	
Variable	**Treatment**	**Comparison**	**n**	**Estimate**	**Lower**	**Upper**
C_{max}	300 mg ref tablet	Fed heavy / fasting	18	1.39	1.31	1.47
		Fed light / fasting	18	1.09	1.01	1.19
	300 mg test tablet	Fed heavy / fasting	18	1.41	1.29	1.54
		Fed light / fasting	18	1.06	0.964	1.16

Summary of safety results

There were no serious adverse events or discontinuations due to adverse events in the study. The majority of AEs were of mild or moderate intensity. The most common AEs during treatment were headache, dizziness, nausea, flatulence and abdominal pain.

Activated partial thrombin time increased as expected and there was a discrete (<10%) reversible mean creatinine increase. There were no other effects on laboratory safety variables, including liver function tests. There were no clinically relevant effects on vital signs or ECG.