AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0837
Study Code	D1250C00029
Edition Number	1
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An open, randomised, cross-over, single centre pharmacokinetic (phase I) study of the biliary excretion following single doses of AZD0837 175 mg, given in the duodenum via a Loc-I-Gut catheter, alone or in combination with ketoconazole 400 mg (once daily for 4 days), to young healthy male subjects

Study dates: First subject enrolled: 07 Jan 2009
Last subject last visit: 26 March 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)

This study was conducted at one single centre in Sweden.

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 evaluate the effect of ketoconazole on the biliary excretion of AZD0837, AR-H069927XX, and AR-H067637XX. This was assessed by determination of the amount of these compounds in bile and biliary clearance ($CL_{biliary}$) of AZD0837, AR-H069927XX, and AR-H067637XX	Amounts of AZD0837, AR-H069927XX and AR-H067637XX excreted in bile Biliary clearance of AZD0837, AR-H069927XX and AR-H067637XX	Pharmaco kinetic
Secondary	**Secondary**	
To evaluate the effect of ketoconazole on the pharmacokinetics of AZD0837, AR-H069927XX, and AR-H067637XX by assessment of pharmacokinetic (PK) variables	AUC, $AUC_{(0-t)}$, $AUC_{(0-3)}$, C_{max}, t_{max}, and $t_{½}$ of AZD0837, AR-H069927XX and AR-H067637XX Plasma concentrations of AZD0837, AR-H069927XX and AR-H067637XX	Pharmaco kinetic
To evaluate the effect of the *ABCB1* 3435C>T polymorphism on biliary excretion of AZD0837, AR-H069927XX and AR-H067637XX and to collect DNA for archiving for potential future use to support evaluation of pharmacokinetics, safety, and tolerability of AZD0837	Genotype of the genetic variant 3435C>T of the *ABCB1* gene (coding for P glycoprotein)	Pharmaco genetic
To evaluate the safety and tolerability of AZD0837 in combination with ketoconazole	Adverse events (AEs) occurring during the study Physical examination Laboratory variables: Activated Partial Thrombin Time (APTT), clinical chemistry, haematology, urinalysis, faeces Vital signs: blood pressure (BP), pulse Electrocardiography (ECG): 12-led ECG after rest	Safety

Study design

This was an open, randomised, cross-over, single-centre phase I study with treatment with: I) single dose of AZD0837; and II) 4 days repeated dosing of ketoconazole together with a single dose of AZD0837 on day 4, on two different occasions separated by a wash-out period of 14±7 days. In both treatment I and II, on the day when AZD0837 was administered, the subjects arrived to the clinic at about 8 am and stayed for at least 24 hours at the investigational site for the study session. Administration of study drug and collection of bile were done using a catheter with multichannel tubing system (a Loc-I-Gut catheter) placed in the duodenum. Bile was collected continuously via the Loc-I-Gut catheter in 20-min intervals during 3 hours following administration of investigational product. Blood samples for determination of AZD0837, AR-H069927XX, and AR-H067637XX were taken for up to 24 hours after administration of investigational product.

Target subject population and sample size

Healthy male volunteers aged between 18 to 45 years and a body mass index (BMI) between 19 to 30 kg/m^2 could be included in this study. Up to 20 subjects could be randomised in order to obtain at least 10 evaluable subjects completing both study sessions.

No formal sample size calculations were made for the primary variables. The number of subjects was founded on feasibility.

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

Treatment I: 175 mg AZD0837 given as oral solution as a single dose, manufactured by AstraZeneca R&D, Sweden. Batch number: 08-002562AZ.

Treatment II: 4 days repeated dosing of ketoconazole 400mg (2x200mg tablets for 3 days followed by 400mg oral suspension on day 4), manufactured by Janssen-Cilag. Batch number: 08-002616AZ. On day 4, 175 mg AZD0837 oral solution was given as a single dose 15 minutes after the oral suspension of ketoconazole. AZD0837 was manufactured by AstraZeneca R&D, Sweden. Batch number: 08-002562AZ.

Responsible staff at the investigational site dispensed and labelled the IPs, which were delivered by the pharmacy. Ketoconazole tablets, used for suspension, were suspended in purified water (50 mL) before administration.

Duration of treatment

For this crossover study, treatment period I was one single dose of AZD0837 solution. Treatment II started with administration of ketoconazole tablets in the mornings of Day 1-3 and ketoconazole suspension was administered at Day 4 before administration of AZD0837 solution. The study sessions were separated by a 7 to 21 days wash-out period.

Statistical methods

Log-transformation of the variables biliary clearance ($CL_{biliary}$) and total amount excreted in bile (A_e) of AZD0837, AR-H069927XX, and AR-H067637XX were each analysed in a mixed linear model with treatment, sequence and period as fixed effects and subject within sequence as a random effect. True within-treatment geometric means and between-treatment ratios of true geometric means, together with corresponding 95% were estimated from the model.

Subject population

In total, 20 healthy male subjects were enrolled into the study. Of these, one subject was never randomised and two were randomised but discontinued prior to intake of investigational products. Seventeen subjects received IP and all 17 completed the study.

Summary of efficacy results

Summary of pharmacokinetic results

The plasma exposure of AZD0837 was increased by 87% for AUC and 38% for maximum plasma concentration (C_{max}) when AZD0837 was given with ketoconazole (strong CYP3A4 inhibitor and modulator of P-gp). This was followed by a decrease in plasma exposure of AR-H069927XX by 39% for C_{max}. The plasma exposure of AR-H067637XX was increased by 116% for AUC and 64% for C_{max}.

AR-H067637XX had higher $CL_{biliary}$ than both AZD0837 and AR-H069927XX, 0.77 L/h compared to 0.10 L/h and 0.13 L/h, respectively.

Concomitant treatment with ketoconazole appeared to decrease the biliary excretion of AR-H067637XX. Treatment ratios for $CL_{biliary}$ and the total amount excreted in bile during the 3-hour collection period were numerically below 1 and indicated decreases of approximately a factor of 2. However, the confidence intervals were wide because of the variability and the decreases were not statistically significant. Although the biliary excretion of AZD0837 and AR-H069927XX were low compared with that for AR-H067637XX, treatment ratios of $CL_{biliary}$ for AZD0837 and AR-H069927XX were also below 1. The confidence intervals of these treatment ratios were wide and the numerical decreases were not statistically significant. The treatment ratio for total A_e of AR-H069927XX was statistically significant below 1. However, the total amount of AR-H069927XX excreted in bile was <0.2% both when AZD0837 was given alone and when combined with ketoconazole.

After both treatments, the concentrations in bile of AZD0837, AR-H069927XX and AR-H067637XX were substantially higher compared to in plasma.

Summary of pharmacogenetic results

The allele frequency of 3435T allele was found as 56% and 44% for the 3435C allele.

In the present study, no impact of the 3435C/T polymorphism in P-glycoprotein coding gene (*ABCB1*) was observed on AUC, $CL_{biliary}$ or A_e of the active metabolite AR-H06737XX while AUC tended to be lower for AZD0837 and higher for AR-H069927XX in 3435T allele

carriers. However, the number of subjects was too few to assess the impact of this polymorphism on the evaluated pharmacokinetic parameters.

Summary of safety results

There were no serious adverse events (SAEs) or discontinuation due to adverse event (DAEs) in the study. AEs were few and of mild or moderate intensity and of common nature in a phase I study. The most common AE during treatment was headache. APTT increased more when AZD0837 was co-administered with ketoconazole and most subjects had to stay longer than the minimum 24 hours post dose before leaving study site to reach the safety limit of APTT within baseline +10 s. There were no clinically relevant effects on other laboratory variables, vital signs or ECG.