Clinical Study Report Synopsis

Drug Substance	AZD0837
Study Code	D1250C00032
Edition Number	1
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An open, single centre pharmacokinetic (phase I) study of the biliary excretion of AZD0837 and its metabolites following a single dose of 350 mg [^{3}H]AZD0837 given in the duodenum via a Loc-I-Gut catheter to young healthy male subjects

Study dates: First subject enrolled: 22 Jan 2009
Last subject last visit: 23 Feb 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 investigate the biliary excretion of AZD0837 and its metabolites following oral administration of [^{3}H]AZD0837 by determining the amount of total radioactivity and the metabolite pattern in bile, the amounts of AZD0837, AR-H069927XX, and AR-H067637XX in bile and to identify potential additional metabolites of AZD0837 in bile	Amount of total radioactivity excreted in bile Metabolite pattern of AZD0837 excreted in bile[a] Amounts of AZD0837, AR-H069927XX and AR-H067637XX in bile	Pharmaco kinetic
Secondary	**Secondary**	
To investigate 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 safety and tolerability of [^{3}H]AZD0837	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

[a] Will be reported in a separate report but summarised in the CSR

Study design

This was an open, single-centre phase I study. At the day of the study session the subjects arrived at the clinic at about 8 am and stayed 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. In order to have at least 5 subjects completing the study session, 8 healthy subjects could be included.

No formal sample size calculations were made for the primary variables since no statistical analyses were to be performed. The number of subjects was founded on feasibility.

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

350 mg [^{3}H]AZD0837 given as oral solution as a single dose, manufactured by AstraZeneca R&D, Sweden. The radioactive dose was 7.4 MBq (200 μCi). Batch number: 08-002921AZ.

Duration of treatment

Single dose.

Statistical methods

No formal analysis of the primary objective was planned. All results were summarized using descriptive statistics and subject listings.

Subject population

In total, 12 healthy male subjects were enrolled into the study. Of these, four subjects met the exclusion criteria and were excluded prior to receiving investigational product. Eight subjects received investigational product and all 8 completed the study.

Summary of efficacy results

Summary of pharmacokinetic results

All three compounds (AZD0837, AR-H069927XX and AR-H067637XX) were excreted into bile in various degrees in all eight subjects. The mean amount in bile of AR-H067637XX was 3.1% of dose compared to 1.0% of dose for AZD0837 and 0.26% of dose for AR-H069927XX.

The concentrations in bile were approximately 6, 7 and 300 times higher than in plasma for AZD0837, AR-H069927XX and AR-H067637XX, respectively, comparing the maximal mean concentration in bile and plasma respectively.

The mean biliary clearance ($CL_{biliary}$) of AR-H067637XX was 10.8 L/h and only 0.296 L/h and 0.341 L/h for AZD0837 and AR-H069927XX, respectively. The $CL_{biliary}$ for AZD0837, AR-H069927XX and AR-H067637XX varied substantially between individuals with a coefficient of variation of 154%, 89% and 132%, respectively.

The main metabolite found in bile was AR-H067637XX, the active direct thrombin inhibitor, and no additional metabolites of AZD0837 were found by radioactivity detection in bile.

AZD0837 and AR-H069927XX could be found at trace levels only by mass spectrometric detection.

Summary of safety results

There were no serious adverse events (SAEs) or discontinuation due to adverse events (DAEs) in the study. The only AE was a headache. There were no clinically relevant effects on laboratory variables, vital signs or ECG.