AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0837base
Study Code	D1250C00055
Edition Number	1
Date	28 September 2009

A single-blind, randomised, placebo-controlled, parallel-group, single centre phase I study to assess the safety, tolerability and pharmacokinetics of extended-release tablets AZD0837 after single and repeated oral administration to young healthy male Japanese subjects

Study dates: First subject enrolled: 14 May 2009
Last subject last visit: 17 June 2009

Phase of development: Clinical pharmacology (I)

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

AZD0837base as active substance code for clinical trial means that this investigational product is produced based on free base of AZD0837.

Study centre(s)

The study was conducted at one centre, Medical Corporation Kouryokai CPC Clinic in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of the study was to investigate the safety and tolerability of AZD0837 after single and repeated oral dosing of AZD0837 extended release (ER) tablet, in Japanese healthy subjects.

The secondary objective of the study was to investigate the pharmacokinetics (PK) of AZD0837, AR H069927XX and AR-H067637XX after single and repeated oral dosing of AZD0837 ER tablet, in Japanese healthy subjects.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary To investigate the safety and tolerability of AZD0837 after single and repeated oral dosing of AZD0837 extended release (ER) tablet, in Japanese healthy subjects.	Adverse events, laboratory variables, blood pressure, pulse, body temperature, and ECG	Safety
Secondary To investigate the pharmacokinetics (PK) of AZD0837, AR H069927XX and AR-H067637XX after single and repeated oral dosing of AZD0837 ER tablet, in Japanese healthy subjects.	$R_{ac,}$ AUC, $AUC_{\tau,}$ $AUC_{0\text{-}t}$, C_{max}, C_{min} and $C_{ss,}$ $t_{max,}$ $t_{½}$ of AZD0837, AR-H067637XX and AR-H069927XX, CL/F and V_z/F for AZD0837, CL/F_m and V_z/F_m for AR-H067637XX and AR-H069927XX.	Pharmacokinetics

Study design

This study was conducted as a single-blind, randomised, placebo-controlled, parallel group, single-centre phase I study in young healthy male Japanese subjects. Four treatment groups (150, 300, 450 mg and placebo) were studied.

For each active treatment group, 10 subjects were given single administration of AZD0837 and for placebo treatment group, 6 subjects were given single administration of AZD0837 placebo in the morning of Day 1 after overnight fasting. After a 48-hour washout period, once daily (for 5 additional days) repeated administration of AZD0837 or AZD0837 placebo was given in the morning after each overnight fasting.

Target subject population and sample size

A total of 36 Japanese healthy male subjects were to be randomised in this study.

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

Oral doses of 150, 300 and 450 mg or placebo were given once daily to fasting subjects in this study. The identity of the investigational product is specified below.

Investigational product	Dosage form and strength	Manufacturer	Formulation number
AZD0837 extended release tablet 150 mg, 1890-02 (free base)	Tablet, 150 mg	AstraZeneca	H1890-02-01
Placebo tablet	Tablet, N/A	AstraZeneca	H1428-05-01

Duration of treatment

The subjects were given a single administration of AZD0837, and then five-day once daily repeated administration of AZD0837 following a 48-hour washout period.

Statistical methods

Plasma concentrations of AZD0837, AR-H069927XX and AR-H067637XX at each timepoint were listed for each subject and summarised by dose using descriptive statistics.

Pharmacokinetics (PK) variables were listed for each individual subject and summarised by dose level except for placebo group. Log-transformed PK variables were analysed based on appropriate power models or ANOVA models.

All adverse events were listed for each subject and summarised by the body system and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary.

Haematology, coagulation, clinical chemistry, blood pressure, pulse rate, body temperature and ECG data at each time point and their changes from baseline were summarised. For urine analysis and faeces analysis, the number of subjects in each category of test results were summarised at each time point.

Subject population

- A total of 36 Japanese healthy subjects were randomised to treatment with AZD0837 ER tablet or placebo at one study centre.

- All the subjects completed the study and were included in the safety analysis set. A total of 30 subjects were included in the PK analysis set (10 each in the active treatment groups with AZD0837).

- The mean age ranged from 26 to 28 years, the mean weight raged from 58.3 to 72.3 kg, the mean BMI ranged from 20.5 to 23.6 kg/m^2.

- The demographic and baseline characteristics were well balanced among the treatment groups, and it is concluded that the study population allows for an evaluation of the study objectives.

Summary of pharmacokinetic results

- Following repeated administration of AZD0837 ER tablet, its active metabolite AR-H067637XX reached C_{max} ranging from 1.5 to 6.0 hours post dosing for each dose level. Also, AR-H067637XX were eliminated from the body with terminal half-lives of 9.53 to 10.9 hours.

- Mean trough concentration of AR-H067637XX in plasma reached steady-state within 5 days of repeated once daily oral administration of AZD0837. Also, trough concentration profiles of AZD0837 and AR-H069927XX were similar to AR-H067637XX.

- AUC_{τ} and C_{max} of AR-H067637XX at steady-state increased lower than dose-proportionality at dose range from 150 to 450 mg, whereas those of AZD0837 and AR-H069927XX increased following dose-proportional manner.

Summary of safety results

- No major safety or tolerability concerns were identified at doses of ≤450 mg after single and repeated administration of extended-release tablets (free base) in Japanese healthy subjects.

- There were no deaths, serious adverse events other than death, discontinuation of treatment with investigational product due to adverse event, or other significant adverse events in the study.

- The number of AEs was few in this study. All adverse events were transient and of mild intensity. One AE of ALT increased (up to 1.3 times ULN at the follow-up visit not accompanied by other LFT elevations and spontaneously resolved within 8 days) was reported.

- An increase in mean serum-creatinine of approximately 10% from baseline was observed in the study. The increase resolved during the follow-up period.

- There were no clinically important abnormalities in clinical laboratory, vital signs (pulse rate, systolic blood pressure/diastolic blood pressure, and body temperature), electrocardiogram observations, and physical examination in the study.