AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7687
Study Code	D2710C00004
Edition Number	1
Date	19 December 2011

A Phase I, Single Centre, Single-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability and Pharmacokinetics of oral AZD7687 after Administration of Single and Multiple Ascending Doses in healthy male Japanese Subjects

Study dates: First subject enrolled: 23 November 2010
Last subject last visit: 07 July 2011

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator:

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Sponsor's Responsible Medical Officer:

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

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 safety and tolerability of AZD7687 following administration of single and multiple doses.	Adverse events, Laboratory variables, Vital signs: Blood pressure, Pulse, Body temperature ECG: 12-lead paper, 12-lead digital, telemetry.	
Secondary	**Secondary**	
To evaluate the pharmacokinetics (PK) (plasma and urine) of AZD7687 and its glucuronic acid metabolite (AZ13128940) after single and multiple doses.	AUC, C_{max}, t_{max}, $t_{½}$, CL/F, Ae, CL_R, fe	
Exploratory	**Exploratory**	
To investigate if there is tendency to body weight reduction during treatment with AZD7687.	Body weight reduction	
To investigate if treatment with AZD7687 will decrease waist circumference.	Waist circumference	
To collect and store samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and endocrine function.	Exploring biomarkers involved in nutrient metabolism and endocrine function	
To collect and store blood samples for potential future exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and PD, safety and tolerability related to AZD7687.	Identifying/exploring genetic variations that may affect PK, PD and safety related to AZD7687	

Study design

This was a Phase I, randomised, single-blind, parallel group, placebo-controlled, single and multiple ascending dose study in healthy male Japanese subjects conducted at a single centre. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects. Thirty-six (36) healthy male Japanese subjects aged ≥20 to ≤45 years were to participate in four cohorts.

Nine subjects participated in each cohort and received either AZD7687 or placebo, randomised as 6:3. Each subject was dosed in one cohort only. Subjects started with an initial single dose that was followed by a wash-out period of 48 hours to adequately define the single-dose PK. Thereafter the subjects were dosed for 7 days (8 days of dosing, including first single dose given). Each subject was only dosed in one cohort.

Target subject population and sample size

Twenty seven healthy subjects aged 20 to 34 years participated in 3 cohorts. Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar Phase I studies with other compounds.

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

The investigational product was supplied by AstraZeneca as study specific labelled bulk containers for each treatment. AZD7687 and matched placebo oral suspensions were white to off-white suspensions filled into bottles. The suspensions were stored in a freezer according to the labels and Handling Instructions. The IP was dispensed by the Pharmacy staff at RPL according to the randomisation scheme and separate instructions, provided by AstraZeneca.

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number	Expiry date
AZD7687	5 mg/mL, oral suspension	AstraZeneca	10-000495AZ	Feb 2012
AZD7687	0.1 mg/mL, oral suspension	AstraZeneca	10-000491AZ	Feb 2012
Placebo	Oral suspension	AstraZeneca	09-007026AZ	Oct 2013

Duration of treatment

Single oral dose on Day 1 of AZD7687 (1 mg, 2.5 mg and 5 mg). From Day 3 subjects received multiple oral doses of AZD7687.

Statistical methods

The safety, tolerability, pharmacokinetic and pharmacodynamic data were summarised descriptively including tables, listings and graphs, as appropriate. Placebo subjects from different dose levels were pooled for the comparisons.

Subject population

Eighteen (18) healthy male subjects received AZD7687 at doses ranging from 1 to 5 mg and 9 subjects received placebo. The safety and PD analysis sets included all 27 randomised

subjects, the PK analysis set included all subjects who received active study drug (18 subjects).

Summary of safety results

Due to poor gastrointestinal tolerability it was decided that dose escalation above the 5 mg dose level would not be beneficial. Multiple doses of AZD7687 up to 5 mg over 7 days given to Japanese healthy male subjects did not show any clinically significant findings in terms of laboratory variables, vital signs and ECG assessments. The most common AE reported was nausea followed by abdominal pain, constipation, diarrhoea and vomiting. The systemic exposure (AUC and C_{max}) of escalating single doses and repeated doses of 1-5 mg was well within the predefined exposure limits.

Summary of pharmacokinetic results

AZD7687 was rapidly absorbed and C_{max} was generally reached within 1 hour after both single and repeated dosing. The estimated geometric mean CL/F was low ranging between 1.18-1.58 L/h including both Day 1 and 9 data. The exposure (AUC and C_{max}) increased approximately proportionally with dose. Plasma concentrations declined with a geometric mean terminal half-life ranging between 11.4-15.5 hours. The degree of accumulation after 7 days repeated dosing was low and no major time-dependency in the PK of AZD7687 was detected. The fraction of AZD7687 excreted unchanged in urine was low, <0.5% and the contribution of the renal clearance to the total CL/F was minimal. The plasma exposure of the acylglucuronide metabolite AZ13128940 was low in comparison to that of AZD7687, less than 3%.

Summary of pharmacodynamic results

During the study, there was no significant trend observed in the reduction of weight and waist circumference.