AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7687
Study Code	D2710C00001
Edition Number	1
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A randomized, double-blind, placebo-controlled, single-centre phase I study in healthy volunteers to assess the safety, tolerability and pharmacokinetics of AZD7687 after single ascending oral doses

Study dates: First subject enrolled: 23 November 2009
Last subject last visit: 21 June 2010

Phase of development: Clinical pharmacology (I)

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 assess the safety and tolerability of AZD7687 following administration of single oral ascending doses	Adverse events, supine and standing blood pressure and pulse rate, respiratory rate, oral temperature, electrocardiogram variables, physical examination, clinical laboratory variables	Safety
Secondary	**Secondary**	
To evaluate the pharmacokinetics of AZD7687 and provisionally assess the dose proportionality of the pharmacokinetics following single oral ascending doses of AZD7687	AUC, $AUC_{(0\text{-}t)}$, C_{max}, t_{max}, λ_z, $t_{1/2\ \lambda z}$, and CL/F	Pharmacokinetic
To explore the effect of food on the pharmacokinetics of AZD7687	AUC, $AUC_{(0\text{-}t)}$, t_{max}, $t_{1/2\ \lambda z}$, and C_{max}	Pharmacokinetic
Exploratory	**Exploratory**	
To collect and store blood samples for potential future exploratory genetic research aimed at identifying/exploring genetic variations that may affect pharmacokinetics and pharmacodynamics, safety and tolerability related to AZD7687 treatment	Genetic analysis	Pharmacogenetic
To assess the effects of AZD7687 on postprandial plasma triacylglyceroles and possibly refined measurements of triacylglyceroles and diacylglyceroles	$AUC_{(0\text{-}8)}$, AUC_{rect}, $AUC_{incremental}$, change in $AUC_{incremental}$	Pharmacodynamic
To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism, metabolic diseases or the pharmacokinetics of AZD7687	Biomarker research	Pharmacogenetic

Results of genetic, refined measurements of triacylglyceroles and diacylglyceroles, and biomarker exploratory analyses are not reported in this clinical study report.

Study design

This was a single center, Phase I randomized double-blind placebo-controlled study to assess the safety, tolerability, and pharmacokinetics of AZD7687 following single ascending oral dose administration to healthy volunteers.

The study consisted of 2 parts, a dose escalation part and a food interaction part. The 2 parts were run in parallel.

The dose escalation part included safety, pharmacokinetic, and pharmacodynamic components. All doses of investigational product were administered after an overnight fast of at least 10 hours. AZD7687 or placebo was administered as a suspension of a total of 240 mL (including water). The on-study drug pharmacodynamic assessments (triacylglyceroles) followed a standardized mixed meal with a specified fat content given 4 hours after dosing. The same standardized mixed meal was also given on Day -1 and triacylglyceroles assessments were performed at times corresponding to Day 1. As dose escalation progressed, adjustments were made to the planned doses and fat content of the meal based on emerging safety and pharmacokinetic data.

The doses administered in this part of the study were 1, 5, 20, and 10 mg AZD7687 with the 60% fat meal for Cohorts A to D, respectively; 10, 20, and 60 mg AZD7687 with the 30% fat meal for Cohorts E to G, respectively; 5 and 20 mg AZD7687 with the 45% fat meal for Cohorts H and I, respectively; and 2.5 mg AZD7687 with the 60% fat meal for Cohort J. Eight volunteers participated in each cohort and received either AZD7687 or placebo, randomized 6:2. In the dose-escalation part of the study, each volunteer was only dosed once. Serial PK and safety assessments were performed for up to 48 hours postdose after which volunteers were discharged from the clinic. Volunteers were asked to return to the clinic on Day 4 (day after discharge) for a 72-hour PK sample collection and returned for a poststudy follow up of 7 to 14 days after dosing

In the food interaction arm, AZD7687 or placebo were given to the same volunteers from Cohorts D and H of the dose escalation arm of the study. Data from these volunteers in a fasting condition were used as comparison in this arm of the study, making it possible to study the impact of food intake. The volunteers in the food interaction cohorts received 2 AZD7687 doses in a non-randomized, crossover design separated by a washout period of at least 14 days. Volunteers received AZD7687 or placebo under fasted conditions in Period 1 as part of the dose-escalation design followed by dose administration under fed conditions in Period 2. The volunteers received the same treatment on both dosing occasions (AZD7687 or placebo). For Period 2, volunteers received a Food and Drug Administration recommended high-fat standard breakfast 30 minutes prior to the scheduled dose administration. The breakfast was to be eaten within 30 minutes. The high-fat and high-calorie breakfast included the following: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces (approximately 113 g) of hash brown potatoes, and 8 ounces (approximately 240 mL) of whole milk. This meal derived approximately 150, 250, and 500 to 600 calories (kcal) from protein, carbohydrate, and fat, respectively.

Volunteers remained in the clinic until discharge on Day 3 and returned to the clinic on Day 4 (day after discharge) for the 72-hour PK sample followed by a poststudy follow up 7 to 14 days after dosing. Safety and PK assessments followed those of Period 1 with the exception of select exploratory assessments.

Target subject population and sample size

Eighty healthy male volunteers between the ages of 20 to 45 years, having a body mass index between 19 and 30 kg/m^2 were enrolled.

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

AZD7687 2 mg/mL, administered as an oral suspension, Batch number 09-006968AZ

AZD7687 40 mg/mL, administered as an oral suspension, Batch number 09-006958AZ

Placebo to match AZD7687, administered as an oral suspension, Batch number 09-001039AZ

Duration of treatment

The duration of each volunteer's participation in the dose escalation arm of the study was approximately 45 days, including a screening period of up to 30 days, 1 inpatient treatment period consisting of 4 days and 3 nights, and a follow-up visit 7 to 14 days postdosing from the treatment period. Each volunteer received a single dose of AZD7687 or placebo except for the volunteers included in the dose steps repeated for food interaction.

For volunteers in the food interaction arm, volunteer's participation included an additional inpatient treatment period of 4 days and 3 nights, and the 2 treatment periods were separated by a washout period of at least 14 days.

Statistical methods

Safety data were summarized using descriptive statistics.

The pharmacokinetic concentrations and parameters for AZD7687 were summarized using descriptive statistics and plotted as appropriate.

For dose escalation and dose proportionality assessment, pharmacokinetic parameters were estimated by noncompartmental methods using actual elapsed time from dosing. Dose proportionality of AZD7687 was assessed based on whether 90% confidence intervals constructed for the estimate of slope fell within the interval (0.95, 1.05). The power model parameters were estimated using least-squares regression. Dose proportionality analysis was not performed for the secondary pharmacokinetic parameters.

For food effect assessment, an exploratory analysis of the effect of food on AZD7687 was carried out by fitting an analysis of variance model to the log-transformed values of the primary pharmacokinetic parameters (AUC, $AUC_{(0-t)}$, and C_{max}) of AZD7687. The values of the pharmacokinetic parameters were dose normalized for this analysis. The term for

treatment period (fed or fasted) was included as a fixed effect in the model. From these analyses, least-squares means, least-squares treatment differences, and 90% confidence interval for the treatment differences on log-scale were obtained.

Subject population

The first volunteer was enrolled on 23 November 2009 and the last volunteer completed the study on 21 June 2010. A total of 80 male volunteers were enrolled in the dose escalation part of the study; 8 volunteers (6 active and 2 placebo) in each of the 10 treatment groups. Overall, 79 volunteers completed the study per protocol. One volunteer (E0001108) was lost to follow-up after completing Period 1 of the food interaction arm. All 80 volunteers received at least 1 dose of investigational product during the planned treatment visit and were included in the safety analyses.

Sixteen of the 80 male volunteers from the dose escalation part of the study were also studied in the food interaction arm. Fifteen volunteers completed the food interaction arm per protocol. Volunteer E0001108 was lost to follow-up after completing Period 1.

There were no important protocol deviations during study conduct, and there were no protocol deviations that led to exclusion of data from the safety analyses.

Overall, the volunteer population consisted of 80 healthy males with a mean age of 29 years and a mean body mass index of 25.5 kg/m^2.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Dose escalation

Following single dose oral administration in the 1 mg to 60 mg dose range, the geometric mean AZD7687 plasma concentrations were above limits of quantitation for 32 hours (1 mg dose), 48 hours (2.5 mg dose), or 72 hours (5 to 60 mg doses).

AZD7687 was rapidly absorbed following single oral dose administration with median t_{max} being 0.34 to 0.84 hours across the 1 mg to 60 mg doses. Following t_{max}, the AZD7687 plasma concentrations declined in a mostly biphasic manner with mean terminal half-life ($t_{1/2, \lambda z}$) of approximately 9 to 14 hours across the 1 mg to 60 mg doses.

The key pharmacokinetic parameters for AZD7687 are presented in Table S2.

Table S2 Geometric mean (GCV%) of key AZD7687 plasma pharmacokinetic parameters (dose escalation)

	AZD7687 Pharmacokinetic parameter (unit)					
Cohort/ AZD7687 dose	**C_{max} (µmol/L) N= 6**	**t_{max}[a] (h) N= 6**	**AUC (µmol*h/L) N= 6**	**$AUC_{(0-t)}$ (µmol*h/L) N= 6**	**$t_{½\lambda z}$ (h) N= 6**	**CL/F (L/h) N= 6**
A/1 mg (60% fat meal)	0.170 (16.7)	0.67 (0.33-0.68)	1.69 (20.5)	1.49 (21.1)	8.98 (13.7)	1.61 (20.6)
B/5 mg (60% fat meal)	0.918 (18.9)	0.67 (0.33-1.00)	10.8 (24.4)	10.4 (24.0)	11.6 (13.9)	1.26 (24.3)
C/20 mg (60% fat meal)	3.46 (21.3)	0.68 (0.33-1.00)	43.1 (32.9)	42.2 (31.9)	13.7 (16.6)	1.26 (32.9)
D/10 mg (60% fat meal)	1.85 (12.5)	0.67 (0.67-0.67)	18.9 (19.6)	18.6 (20.0)	12.5 (25.4)	1.44 (19.6)
E/10 mg (30% fat meal)	1.6 (17.3)	0.53 (0.33-0.67)	18.1 (7.9)	17.5 (7.9)	13.2 (16.9)	1.51 (7.9)
F/20 mg (30% fat meal)	2.93 (21.3)	0.67 (0.33-1.00)	32.6 (24.8)	31.6 (24.3)	13.8 (30.4)	1.67 (25.0)
G/60 mg (30% fat meal)	12.4 (16.4)	0.67 (0.67-0.67)	110 (23.1)	108 (22.3)	12.1 (19.7)	1.49 (23.1)
H/5 mg (45% fat meal)	0.964 (20.4)	0.34 (0.33-0.67)	10.8 (29.9)	10.4 (28.6)	13.6 (26.0)	1.26 (29.8)
I/20 mg (45% fat meal)	3.34 (11.1)	0.84 (0.33-2.00)	41.7 (13.9)	40.6 (12.9)	11.9 (13.4)	1.30 (14.0)
J/2.5 mg (60% fat meal)	0.367 (15.9)	0.68 (0.67-1.35)	5.19 (23.6)	4.9(23.9)	12.2 (12.9)	1.31 (23.6)

[a] Presented as median (range)

The geometric mean maximum (C_{max}) as well total (AUC) exposure of AZD7687 in plasma increased approximately proportionally to dose in the 1-60mg dose range.

The fat content of meal administered 4 hours after dosing did not have any clinically relevant effect on the pharmacokinetics of AZD7687.

Food Interaction

Following administration of 5 mg or 10 mg AZD7687 with a standardized high-fat breakfast, the mean AZD7687 plasma concentrations were quantifiable for 72 hours (last time point observed) postdosing.

AZD7687 t_{max} was delayed by several hours when given with food (median t_{max}: 5 to 6.5 hours following 5 mg and 10 mg AZD7687 dosing) as compared to the fasting state (median t_{max}: 0.34 to 0.67 hours following 5 mg and 10 mg AZD7687 dosing).

The mean terminal half-life of AZD7687 was similar in both the fasted and fed states.

The statistical analysis of effect of food on key AZD7687 plasma pharmacokinetic parameters is presented in Table S3.

Table S3 Comparison of key AZD7687 pharmacokinetic parameters with and without food

Parameter	AZD7687 treatment	n	Geometric LS mean	Fed/Fasted ratio (%)	90% confidence interval for the ratio
AUC (µmol*h/L)	Fasted	12	2.019	92.32	(84.34, 100.94)
	Fed	11	1.864		
$AUC_{(0-t)}$ (µmol*h/L)	Fasted	12	1.965	90.91	(83.24, 99.3)
	Fed	11	1.786		
C_{max} (µmol/L)	Fasted	12	0.1887	36.86	(33.43, 40.63)
	Fed	11	0.06954		

LS least squares

Food had no or a minor effect on total AUC of AZD7687, whereas the geometric mean maximum plasma AZD7687 exposure was 63% lower with food as compared to the fasted state.

Summary of pharmacodynamic results

The pharmacodynamic markers were measured only in the dose escalation part of the study.

With the high-fat meal (60% of energy from fat), there was an increase in the serum triacylglycerole concentrations following dosing in the untreated condition (Day -1). A similar but lower in magnitude increase in serum postprandial triacylglycerole concentration following the meal was observed with the intermediate-fat meal (45% of energy from fat) while there was a barely perceptible increase in the postprandial serum triacylglycerole with the 30% fat meal.

The increase in postprandial serum triacylglycerole concentrations was supressed by AZD7687 in a dose-dependent manner for both the 60% and 45% fat meal groups.

Summary of pharmacokinetic/pharmacodynamic relationships

With the 60% fat meal, there was a negative trend between the change in incremental TAG AUC and pre-meal AZD7687 concentration (the change in incremental TAG AUC was more negative with increasing AZD7687 pre-meal concentration). A similar, although shallower, negative trend was observed with the 45% fat meal, whereas no trend was observed with the 30% fat meal.

Summary of pharmacogenetic results

A summary of pharmacogenetic results will be provided in a separate report.

Summary of safety results

In the dose escalation arm, the numbers of volunteers who experienced adverse events overall and adverse events assessed by the Investigator as causally related to investigational product were greater in Cohort C (20 mg AZD7687 with 60% fat meal) and Cohort D (10 mg AZD7687 with 60% fat meal) and the highest AZD7687 dose group (Cohort G [60 mg AZD7687 with 30% fat meal]) compared to other AZD7687 cohorts and placebo. The most common adverse events in AZD7687-treated volunteers were gastrointestinal in nature (including nausea [21/60; 35.0%]; diarrhea [15/60; 25.0%]; and vomiting [13/60; 21.7%]).

In the food interaction arm, the most common adverse events reported in AZD7687-treated volunteers were similar to those reported in AZD7687-treated volunteers during the dose escalation arm. Most adverse events were gastrointestinal in nature (including nausea [7/12; 58.3%]; diarrhea [5/12; 41.7%]; vomiting [3/12; 25.0%]; and dyspepsia [3/12; 25.0%]).

There were no deaths, other serious adverse events, or discontinuations of investigational product due to adverse events in the study. No other significant adverse events were identified for this study.

There were no adverse events of severe intensity during study conduct. There were 11 adverse events of moderate intensity in AZD7687-treated volunteers, including moderate nausea in 7 volunteers, and moderate diarrhea, vomiting, flatulence, and abdominal distension all in 1 volunteer each. All other adverse events reported in AZD7687-treated and placebo volunteers were considered mild in intensity. It was noted that if volunteers had both nausea and emesis, the nausea resolved sooner and did not gradually increase in intensity once the volunteer vomited. Three of the moderate nausea adverse events were in volunteers who did not experience emesis with the nausea.

In general, changes in laboratory safety values, vital signs, electrocardiogram findings, and physical examination findings were unremarkable and any changes of note were not considered significant enough to discontinue volunteers from the study due to the results.

There were 3 volunteers overall with adverse events related to electrocardiogram findings, including 2 volunteers with nonsustained asymptomatic ventricular tachycardia and 1 volunteer with second degree atrioventricular block. All 3 events were assessed by the Investigator as mild in intensity and not related to study drug.