AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD7687
Study Code	D2710C00002
Edition Number	1
Date	14 February 2012

A Phase I, Single Centre, Single-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral AZD7687 after Administration of Multiple Ascending Doses in Overweight to Obese but Otherwise Healthy Male Subjects

Study dates: First subject enrolled: 23 April 2010
Last subject last visit: 8 March 2011

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

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 multiple ascending doses	Adverse events, laboratory variables, vital signs (blood pressure, pulse rate, body temperature), fat content in faeces, ECG (12-lead ECG, dECG, and telemetry), and physical examination	Safety
Secondary	**Secondary**	
To evaluate the PK (plasma and urine) of AZD7687 and its glucuronic acid metabolite (AZ13128940) after single and multiple doses	Single dose: C_{max}, t_{max}, $AUC_{(0-\tau)}$, $AUC_{(0-48)}$, $AUC_{(0-t)}$, AUC, λ_z, $t_{1/2}$, CL/F, Ae, fe(%), CL_r, MR C_{max}, MR AUC. Multiple doses: $C_{max,ss}$, $C_{min,ss}$, $C_{avg,ss}$, $t_{max,ss}$, $AUC_{(0-\tau),ss}$, $\lambda_{z,ss}$, $t_{1/2}$, CL_{ss}/F, $Ae_{,ss}$, $fe_{,ss}$(%), $CL_{r,ss}$, R C_{max}, R $AUC_{(0-\tau)}$, %Fluct, MR $C_{max,ss}$, MR $AUC_{(0-\tau),ss}$	PK
To investigate if AZD7687 inhibits DGAT1 activity in subcutaneous adipose tissue	TAG, DAG, TAG/DAG	PD
To investigate if AZD7687 inhibits DGAT1 activity in the gut	Serum TAG_{total}, (serum TAG_{total} $AUC_{incremental}$ and change in $AUC_{incremental}$)	PD
Exploratory	**Exploratory**	
To investigate the effect of AZD7687 on gastrointestinal peptides	Total GLP-1, GIP, PYY	Exploratory
To investigate if treatment with AZD7687 will decrease body weight	Weight	Exploratory
To investigate if treatment with AZD7687 will decrease waist circumference	Waist circumference	Exploratory
To investigate if treatment with AZD7687 will affect production of chylomicrons	Not applicable[a]	Exploratory
To investigate if treatment with AZD7687 has an effect on energy balance	Not applicable[a]	Exploratory
To investigate if treatment with AZD7687 has an effect on insulin sensitivity	Insulin, free fatty acids	Exploratory
To investigate if treatment with AZD7687 results in a delayed gastric emptying	Paracetamol: C_{max}, t_{max}, $AUC_{(0-t)}$	Exploratory

Objectives	Outcome variables	Type
To collect and store adipose tissue samples for potential future exploratory analysis of AZD7687 concentration in adipose tissue if no effect on TAG/DAG is seen, and for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and endocrine function	Not applicable[a]	Exploratory
To collect and store blood samples for potential future exploratory research aimed at exploring factors involved in DGAT1 effects	Not applicable[a]	Exploratory
To investigate the presence and/or identity of drug metabolites of AZD7687 after multiple doses of AZD7687 and, if appropriate, characterise their PK	Not applicable[a]	Exploratory
To collect and store faecal samples for potential future exploratory research aimed at exploring factors involved in DGAT1 effects	Not applicable[a]	Exploratory
To collect and store 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	Not applicable[a]	Exploratory

λ_z: terminal elimination rate constant; %Fluct: percent fluctuation; Ae: amount of analyte excreted in the urine; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-\tau)}$: area under the plasma concentration-time curve during a dosing interval (τ); $AUC_{(0-48)}$: area under the plasma concentration-time curve from zero to 48 hours; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to time t; $AUC_{incremental}$: difference in area under the TAG concentration-time curve and area of rectangle with height = pre-meal TAG value and width = 8 hours; $C_{avg,ss}$: average plasma concentration at steady state; CL/F: oral clearance of drug from plasma; CL_r: renal clearance; C_{max}: maximum plasma (peak) drug concentration; $C_{min,ss}$: minimum (trough) drug concentration in plasma during the dosing interval at steady state; CSP: clinical study protocol; DAG: diacylglycerol; dECG: digital ECG; DGAT1: diacylglycerol acyltransferase-1; ECG: electrocardiogram; fe(%): fraction of analyte excreted in the urine; GIP: gastric inhibitory polypeptide; GLP-1: glucagon-like peptide-1; MR: metabolite to parent ratio; PD: pharmacodynamics; PK: pharmacokinetics; PYY: peptide YY; R: accumulation ratio; ss: steady state; $t_{1/2}$: half-life; TAG: triacylglycerol; TAG_{total}; total TAG; t_{max}; time to reach maximum concentration

a These results are not reported in the clinical study report.

Study design

This was a phase I, randomised, single-blind, placebo-controlled multiple ascending dose (MAD) study in overweight to obese but otherwise healthy male subjects conducted at a single study centre.

Target subject population and sample size

It was planned to enrol up to 90 overweight to obese but otherwise healthy male subjects aged ≥20 to ≤45 years in up to 10 cohorts. Nine subjects participated in each cohort and received either AZD7687 or placebo, randomised in a 6:3 ratio. Each subject was allocated to only 1 cohort.

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

Batch numbers: 10-001603AZ (0.1 mg/mL AZD7687), 10-001605AZ (5 mg/mL AZD7687), 10-001606AZ (placebo).

Each subject received a single oral dose of AZD7687 or matching placebo (240 mL suspension and water in total) on Day 1 after an overnight fast of at least 10 hours.

Subjects received AZD7687 or placebo (240 mL suspension and water in total) once daily (OD) or twice daily (BID) for 7 days, starting on Day 3. The BID administrations were separated by 12 hours.

AZD7687 was provided as a 0.1 mg/mL and 5 mg/mL frozen oral suspension. The starting dose was 1 mg OD.

Administration of the next dose levels of AZD7687 were based on the review by the SRC of the available safety, pharmacokinetic (PK) and pharmacodynamic (PD) data from the previous cohorts and data from the single ascending dose study.

The actual doses of AZD7687 administered were 1 mg OD (Cohort 1), 5 mg OD (Cohort 2), 20 mg OD (Cohort 3 [with standardised mixed meal] and Cohort 4 [with clinic meal]), 5 mg BID (Cohort 5), 2.5 mg OD (Cohort 6), and 2.5 mg BID (Cohort 7).

Duration of treatment

Each subject received a single dose of AZD7687 or placebo on Day 1 followed by 48 hours of PK sampling (Part A). Repeated dosing commenced on Day 3 with AZD7687 or placebo OD or BID for 7 days. The BID administrations were separated by 12 hours.

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety, tolerability, PK, PD, and applicable exploratory data were summarised descriptively including tables, listings and graphs, as appropriate.

Dose proportionality of AZD7687 and AZ13128940 were analysed following the single dose and multiple dose regimen for primary PK parameters using the power model approach. Least square estimates and 90% confidence intervals (CIs) for slope and intercept are presented.

The time dependency of the PK was evaluated by comparing area under the plasma concentration-time curve during a dosing interval τ ($AUC_{(0-\tau)}$) at steady state (ss) (Day 9) with area under the plasma concentration-time curve from zero to infinity (AUC) (Day 1). Least squares geometric means were used to estimate the ratio $AUC_{(0-\tau),ss}$/AUC and are presented with 90% CI based on an appropriate statistical model. Similarly the maximum plasma (peak) drug concentration (C_{max}) $C_{max,ss}/C_{max}$ were also estimated by calculating ratios of the geometric least square means and are presented with CIs.

For the PD variables of primary interest (the relative change in incremental serum total triacylglycerol [TAG_{total}] AUC), each dose was compared with placebo using 95% CIs using a mixed model. The results were also presented as descriptive statistics.

For all other PD variables, the primary analysis was descriptive, using suitable statistics and graphical presentations of mean values and individual values over time, where appropriate.

Subject population

All enrolled subjects were randomised and were administered AZD7687 or placebo as planned. There were no important protocol deviations and no subjects were excluded from the safety, PK, or PD analyses. The safety analysis included all randomised subjects.

Overall, 42 subjects received AZD7687 and 20 subjects received placebo (OD or BID).

Overall, 13 subjects who received AZD7687 and 6 subjects who received placebo discontinued the investigational product and were withdrawn from the study.

Summary of pharmacokinetic results

A summary of key PK parameters of AZD7687 are presented in Table S1.

Table S1 Geometric mean (%CV) of key AZD7687 PK parameters

Parameter	Study Day	AZD7687 Dose (mg)						
		1 mg OD (N=6)	2.5 mg OD (N= 6)	2.5 mg BID (N= 6)	5 mg OD (N= 6)	5 mg BID (N= 6)	20 mg OD (N= 6)	20 mg OD CM (N= 6)
C_{max} (µmol/l)	Day1	0.160 (21.6)	0.273 (16.0)	0.307 (24.0)	0.495 (22.2)	0.584 (16.8)	2.33 (20.8)	2.28 (25.3)
	Day 9	0.175 (25.3)	0.432 (17.6)	0.484 (21.2)	0.900 (26.3)	NS	3.13 (26.0)[b]	NS
$AUC_{(0-\tau)}$ (µmol*h/L)	Day1	1.16 (24.2)	2.43 (22.9)	1.88 (16.0)	4.43 (26.4)	3.26 (15.3)	24.4 (23.7)	22.7 (20.4)
	Day 9	1.51 (34.2)	3.97 (32.9)	3.68 (19.0)	7.29 (33.9)	NS	30.4 (23.4)[b]	NS
AUC (µmol*h/L)	Day 1	1.45 (33.3)[b]	3.55 (25.5)[b]	3.45 (28.0)	6.00 (31.5)	NC	32.4 (31.4)	31.9 (29.4)
t_{max} (h)[a]	Day 1	0.55 (0.35-1.00)	0.67 (0.33-4.00)	0.67 (0.67-1.00)	0.84 (0.33-4.00)	0.34 (0.33-1.00)	0.87 (0.33-1.50)	0.85 (0.35-4.03)
	Day 9	0.33 (0.33-1.02)	1.01 (0.33-1.53)	0.84 (0.33-2.02)	0.67 (0.35-2.00)	NS	0.67 (0.35-2.00)[b]	NS

Parameter	Study Day	AZD7687 Dose (mg)						
		1 mg OD (N=6)	**2.5 mg OD (N= 6)**	**2.5 mg BID (N= 6)**	**5 mg OD (N= 6)**	**5 mg BID (N= 6)**	**20 mg OD (N= 6)**	**20 mg OD CM (N= 6)**
$t_{1/2}$ (h)	Day 1	10.5 (18.2)	13.5 (16.2)	11.6 (25.7)	13.3 (16.7)	6.84 (6.3)[c]	12.2 (20.9)	14.0 (23.8)
	Day 9	13.8 (21.7)	12.4 (11.7)	12.2 (17.5)	13.6 (12.2)	NS	11.9 (8.4)[b]	NS
CL/F (L/h)	Day 1	1.88 (33.2)	1.91 (25.4)[b]	1.97 (28.2)	2.27 (31.5)	NC	1.68 (31.4)	1.70 (29.4)
	Day 9	1.80 (34.0)	1.71 (32.8)	1.85 (19.1)	1.87 (33.8)	NS	1.79 (23.4)[b]	NS

The AZD7687 was rapidly absorbed with maximum concentration (t_{max}) reached within 1 hour at all dose levels on both Day 1 and Day 9. The geometric mean AZD7687 terminal half-life ($t_{1/2}$) ranged from 10.5 to 14 hours on Day 1 and 11.9 to 13.8 hours on Day 9. The oral clearance of drug from plasma (CL/F) was similar across the dose groups and similar between Day 1 and Day 9.

At dose levels where quantifiable plasma concentrations for AZD7687 glucuronide exists the exposure was low in relation to that of AZD7687 and t_{max} concentration was reached within 1 hour.

The geometric mean AZD7687 renal clearance (CL_r) was low in all the dose groups (where it could be estimated) and ranged from 0.00154 L/h to 0.00218 L/h on Day 1 and 0.0015 to 0.00363 L/h on Day 9. Only about 0.1% of the administered AZD7687 dose was excreted unchanged in the urine both on Day 1 and Day 9.

Steady state plasma concentrations of AZD7687 seem to have been reached after 7 days of repeated dosing. There is no indication of any time dependency in the PK.

The AZD7687 exposure in terms of both C_{max} and AUC increased proportionally with dose on Day 1 as well as Day 9.

Summary of pharmacodynamic results

A summary of key PD parameters for serum triacylglycerol (TAG) are presented in Table S2.

Table S2 Mean (SD) of key PD parameters for serum TAG

Dose group	Day -2	Day 3		Day 8	
	$AUC_{incremental}$	$AUC_{incremental}$	Change in $AUC_{incremental}$	$AUC_{incremental}$	Change in $AUC_{incremental}$
Placebo (N=14)	2.00 (1.69)	3.39 (3.18)[b]	1.22 (2.53)[b]	3.87 (4.2)	1.87 (3.64)
1 mg OD AZD7687 (N=6)	1.33 (0.726)	3.36 (2.41)	2.03 (2.42)	2.48 (1.89)	1.15 (1.95)
2.5 mg OD AZD7687 (N=6)	1.36 (1.29)	NA	NA	1.78 (2.64)	0.423 (1.25)
2.5 mg BID AZD7687 (N=6)	2.93 (1.45)	NA	NA	0.295 (1.68)	-2.63 (1.72)
5 mg OD AZD7687 (N=6)	2.95 (1.83)	2.30 (1.93)	-0.652 (1.84)	1.44 (1.39)	-1.51 (2.15)
20 mg OD AZD7687 (N=6)	4.63 (4.89)	0.508 (1.82)	-4.12 (4.90)	-0.902 (3.07)[a]	-5.11 (4.23)[a]

a N=5;
b N=8.
Note: 20 mg OD clinic meal and 5 mg BID dose groups are not included in the calculations.

There was a dose-dependent decrease in the mean TAG difference in area under the TAG concentration-time curve and area of rectangle with height = pre-meal TAG value and width = 8 hours ($AUC_{incremental}$) on Day 3 and Day 8 when compared to the placebo. The magnitude of negative change in the incremental TAG AUC increased with increasing AZD7687 doses on Day 3 as well as Day 8. For the doses where both Day 3 and Day 8 TAG levels were measured, the magnitude of negative change in the incremental TAG AUC was greater on Day 8 as compared to Day 3.

Summary of safety results

There were no deaths, serious adverse events (SAEs), or other significant adverse events (OAEs) in the study.

Overall, 13 subjects who received AZD7687 and 6 subjects who received placebo discontinued the investigational product and were withdrawn from the study. In total, 11 subjects (all on active treatment) were withdrawn due to AEs and 8 subjects (2 subjects on active treatment and 6 subjects on placebo) were withdrawn due to the sponsor's decision. The sponsor decided to discontinue the remaining subjects in Cohorts 4 and 5 after most of the subjects on active treatment in these cohorts were discontinued due to AEs.

Adverse events (AEs) for which the investigational product was permanently discontinued and the subjects withdrawn from the study were diarrhoea, nausea, vomiting, abdominal pain, and decreased appetite.

All 11 subjects who withdrew from the study due to AEs received either 5 mg BID (Cohort 5: 5 subjects) or 20 mg OD (Cohort 3: 1 subject, Cohort 4: 5 subjects). Gastrointestinal symptoms were pronounced at the 20 mg OD and 5 mg BID doses, present albeit tolerated at the 5 mg OD dose, and absent at the 1 mg OD dose.

Two subjects each reported 1 severe AE of abdominal pain (20 mg OD [Cohort 4]).

The majority of AEs with an onset up to 24 hours after the last administration of investigational product were assessed by the investigator to have a causal relationship to the investigational product.

Laboratory values above and below the predefined reference ranges were reported for clinical chemistry, haematology, and faecal variables. Laboratory values above the predefined reference ranges were reported for urinalysis variables. No clinically significant changes in liver function tests were observed in any of the subjects.

No trends in the mean change from baseline values were observed over time and between doses for vital signs. All electrocardiograms (ECGs) were judged to be normal and no changes were judged to be clinically significant. No clinically significant physical examination findings were reported.