Drug Product	PPAR alpha gamma	**SYNOPSIS**	
Drug Substance	AZD6610		
Study Code	D4350C00005		
Edition Number	1		
Date	06 March 2008		

A 4-Week Dose-Ranging Study to Evaluate Antidyslipidemic Effects, Other Pharmacodynamic Effects, Safety, and Tolerability of AZD6610 with Concomitant Open-Label Simvastatin Therapy in Patients with Elevated Triglycerides, Elevated Low Density Lipid Cholesterol and Abdominal Obesity: a Randomized, Double-Blind, Placebo-Controlled, Multi-Centre, Parallel-Group Study with Fenofibrate as Reference Treatment

International co-ordinating investigator

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Study centre(s)

The study was performed at 16 centres in Norway and 29 centres in the USA.

Publications

There were at the time of writing this report no publications based on the results of this study.

Study dates		**Phase of development**
First subject enrolled	18 September 2006	Therapeutic exploratory (II)
Last subject completed	21 May 2007	

Objectives

The primary objective of this study was to compare two different doses of AZD6610 with placebo when administered to patients treated with simvastatin, by evaluation of the effect on non-HDL-C.

The secondary objectives of the study were:

- to compare 2 different doses of AZD6610 with placebo when administered to patients treated with simvastatin, by evaluation of the effect on plasma triglycerides

(P-TG), total cholesterol (TC), low density lipoprotein (LDL) cholesterol (LDL-C), high density lipoprotein (HDL) cholesterol (HDL-C), free fatty acids (FFA), apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo B), Apo B/Apo A-I ratio, apolipoprotein C-III (Apo C-III), glucose, haemoglobin A1c (HbA1c), insulin, homeostatic model assessment (HOMA) index, adiponectin, high-sensitivity C-reactive protein (hs-CRP), waist circumference and waist-hip ratio (WHR).

- to evaluate the safety and tolerability of 2 different doses of AZD6610 in relation to placebo when administered to patients treated with simvastatin, by assessment of adverse events (AEs) occurring during the study, laboratory variables, blood pressure (BP), pulse, body weight, electrocardiography (ECG) and physical examination

- to obtain and evaluate trough plasma concentrations of AZD6610 (S-enantiomer) and its metabolite AR-H045191XX (R-enantiomer) in patients with elevated triglycerides (TG), elevated LDL-C and abdominal obesity treated with simvastatin

- to compare fenofibrate with placebo and with 2 different doses of AZD6610 when administered to patients treated with simvastatin, by evaluation of the effect on pharmacodynamic (PD) and safety variables.

Study design

This was a randomized, double-blind, placebo-controlled, multi-centre dose ranging study with 4 parallel groups, 2 doses of AZD6610, a reference treatment (open label fenofibrate) and placebo, to evaluate the antidyslipidaemic and other pharmacodynamic effects, safety and tolerability of AZD6610, with concomitant open label simvastatin therapy, when given to patients with elevated triglycerides, elevated LDL-C and abdominal obesity for a period of 4 weeks.

Target subject population and sample size

Male and female (postmenopausal or bilaterally oophorectomised or hysterectomised) patients, aged between 30 and 70 years inclusive, with abdominal obesity, dyslipidaemia (elevated TG and LDL-C), and on statin treatment.

A sample size of 120 patients was calculated to give sufficient statistical power to detect a difference of 15% in non-HDL-cholesterol. A total of 150 patients were given randomized treatment: placebo (43), AZD6610 2 mg (41), AZD6610 10 mg (32), and fenofibrate (34).

Investigational product and comparators: dosage, mode of administration and batch numbers

Tablets of AZD6610 0.5 mg and 2.5 mg and matching placebo were used to get the appropriate doses 2 mg and 10 mg of AZD6610. Capsules of commercial fenofibrate 145 mg were used (the first patients, 16% of the fenofibrate dose group, used capsules of commercial fenofibrate 160 mg and matching placebo). Tablets of commercial simvastatin 20 mg were

used in addition to the investigational drugs. The batch numbers were: AZD6610 0.5 mg, H1817-01-02-0; AZD6610 2.5 mg, H1827-01-02-01; AZD6610 placebo, H1819-01-02-03; fenofibrate 145 mg, H1809-01-01-01; fenofibrate 160 mg, H1676-01-01-05; fenofibrate placebo, H1684-01-01-02.

The investigational products AZD6610, AZD6610 placebo and fenofibrate were taken orally once daily in the morning. The additional drug simvastatin was taken orally, with or without food, once every evening.

Duration of treatment

There was a 4-week run-in on simvastatin, a 4-week treatment period on investigational drugs and simvastatin, and a 2-week follow-up period on simvastatin.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Primary: Change from baseline to end of treatment in non-HDL-C. Secondary: Change from baseline to end of treatment in P-TG, total cholesterol, LDL-C, HDL-C, FFA, Apo A-I, Apo B, Apo B/Apo A-I ratio, Apo C-III, glucose, HbA1c, insulin, HOMA index, adiponectin, hs-CRP, waist circumference, and waist-hip ratio. Pharmacokinetic: Trough plasma concentration of AZD6610 (S-enantiomer) and its metabolite AR-H045191XX (R-enantiomer) at 1, 2, 3 and 4 weeks of treatment.

Safety

AEs, haematology, clinical chemistry, urinalysis, BP, pulse, body weight, ECG and physical examination.

Statistical methods

The primary variable, the secondary efficacy laboratory variables, and the haematology and clinical chemistry variables were analysed in a linear model using a fixed-effect analysis of covariance (ANCOVA) with treatment and country as factors and baseline value as a covariate. The results were stated as p-values (0.05 significance level), estimates and 2-sided confidence intervals. A Per Protocol (PP) analysis was performed on the primary variable. Descriptive statistics were presented for all variables. AEs were summarized.

Subject population

Table S1 Subject population and disposition

Demographic or baseline characteristics		Treatment group			
		Placebo	**AZD6610 2 mg**	**AZD6610 10mg**	**Fenofibrate 160/145 mg**
Population					
N randomized treatment (N planned)		43 (30)	41 (30)	32 (30)	34 (30)
Demographic characteristics					
Sex	Male	28 (66.7%)	17 (41.5%)	17 (53.1%)	21 (61.8%)
(n and % of subjects)	Female	14 (33.3%)	24 (58.5%)	15 (46.9%)	13 (38.2%)
Age (years)	Mean (SD)	55.4 (8.9)	56.2 (9.1)	55.8 (7.6)	53.9 (87.6)
	Range	31 to 69	39 to 70	42 to 70	33 to 65
Race	Caucasian	38 (90.5%)	37 (90.2%)	29 (90.6%)	29 (85.3%)
(n and % of subjects)	Black	2 (4.8%)	1 (2.4%)	1 (3.1%)	-
	Oriental	1 (2.4%)	-	-	1 (2.9%)
	Other	1 (2.4%)	3 (7.3%)	2 (6.3%)	4 (11.8%)
Baseline characteristics					
Weight (kg)	Mean (SD)	92.3 (16.0)	89.1 (14.5)	87.0 (19.4)	87.1 (14.8)
BMI (kg/cm2)	Mean (SD)	30.7 (4.2)	30.8 (4.2)	29.9 (5.2)	29.5 (3.6)
Waist circumference (cm)	Mean (SD)	104.0 (11.0)	101.4 (11.3)	101.0 (11.6)	101.7 (9.4)
P-Triglycerides (mmol/L)	Mean (SD)	2.24 (1.16)	2.61 (1.33)	2.46 (1.07)	2.39 (1.15)
P-LDL-Cholesterol (mmol/L)	Mean (SD)	2.67 (0.74)	2.90 (0.74)	2.87 (0.80)	2.83 (0.74)
P-Glucose (mmol/L)	Mean (SD)	5.81 (0.91)	5.68 (0.76)	5.51 (0.64)	5.72 (0.65)
Disposition					
N (%) of subjects who	completed	36 (84%)	38 (93%)	25 (78%)	29 (85%)
	discontinued	7 (16%)	3 (7%)	7 (22%)	5 (15%)
N analysed for safetya		43	41	32	34
N analysed for efficacy (ITT)		42	41	32	34
N analysed for efficacy (PP)		27	21	22	19

[a] Number of subjects who took at least 1 dose of study treatment and for whom subsequent study information was available.

N=Number, ITT=Intention To Treat, PP=Per Protocol

Efficacy and pharmacokinetic (PK) results

There was an effect on the lipid variables of AZD6610. The primary efficacy variable non-HDL-C was significantly reduced in both dose groups in the ITT and PP analyses. Also the secondary variables TG, cholesterol, Apo B/Apo A-I ratio and Apo C-III were significantly reduced compared to placebo in both dose groups, while there was no statistically significant effect on HDL-C and LDL-C.

There was no detectable effect in the 2 mg AZD6610 dose group on insulin/glucose metabolism. In the 10 mg dose group, glucose was significantly decreased compared to placebo, and adiponectin was significantly increased.

There was no effect on FFA or the inflammation marker hs-CRP in neither of the AZD6610 dose groups.

Table S2 Change from baseline to end of treatment (%) compared to placebo in efficacy laboratory variables

	AZD6610 2 mg ITT: n=41; PP: n=21			**AZD6610 10 mg ITT: n=32; PP: n=22**		
	Mean change	**95% confidence interval**	**Statistical significance**	**Mean change (%**	**95% confidence interval**	**Statistical significance**
Non-HDL-C (ITT)	-10	-17 ; -3	p=0.007	-11	-18 ; -4	p=0.005
Non-HDL-C (PP)	-13	-22 ; -3	p=0.012	-12	-21 ; -3	p=0.013
TG	-27	-38 ; -14	p<0.001	-37	-47 ; -25	p<0.001
Cholesterol	-6	-11 ; 0	p=0.038	-7	-13 ; -2	p=0.012
HDL-C	4	-2 ; 10	n.s.	5	-1 ; 12	n.s.
LDL-C	-1	-9 ; 8	n.s.	1	-8 ; 11	n.s.
Apo A-I	1	-4 ; 5	n.s.	4	-1 ; 9	n.s.
Apo B	-7	-13 ; -1	n.s.	-8	-15 ; -2	n.s.
Apo B/Apo A-I	-8	-15 ; -1	p=0.034	-12	-19 ; -2	p=0.001
Apo C-III	-14	-24 ; -2	p=0.022	-22	-32 ; -11	p<0.001
FFA	-5	-19 ; 12	n.s.	-1	-17 ; 17	n.s.
Glucose	-2	-4 ; 6	n.s.	-6	-8 ; 2	p=0.023
HbA1c	1	-1 ; 3	n.s.	0	-2 ; 2	n.s.
Insulin	3	-20 ; 32	n.s.	-22	-40 ; 1	n.s.
HOMA	1	-23 ; 32	n.s.	-23	-42 ; 3	n.s.
Adiponectin	6	-3 ; 15	n.s.	19	8 ; 30	p<0.001
hs-CRP	-19	-44 ; 16	n.s.	-9	-38 ; 33	n.s.

The waist circumference and the waist/hip ratio did not change during the study.

The mean trough plasma concentrations of AZD6610 (S-enantiomer) and the metabolite AR-H045191XX (R-enantiomer) were similar.

In the fenofibrate treatment group there was a statistically significant reduction of TG, FFA and Apo C and increase of HDL-C from baseline to end of treatment compared with placebo. FFA was statistically significantly reduced in comparison with both doses of AZD6610. Adiponectin was statistically significantly increased in the AZD6610 10 mg group compared with the fenofibrate group.

Safety results

Table S3 Number (%) of subjects who had at least one adverse event in any category.

Category of adverse event	Number (%) of subjects who had an adverse event in each categorya			
	Placebo n=43	AZD6610 2 mg n=41	AZD6610 10 mg n=32	Fenofibrate 160/145 mg n=34
Any adverse events	22 (52)	17 (41)	10 (31)	16 (47)
Serious adverse events	1 (2)	1 (2)	0 (0)	-
Serious adverse events not leading to death	1 (2)	1 (2)	0 (0)	-
Discontinuations of study treatment due to adverse events	3 (7)	4 (10)	2 (6)	2 (6)

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Table S4 Number (%) of subjects adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Placebo n (%)	AZD6610 2mg n (%)	AZD6610 10 mg n (%)	Fenofibrate 160/145 mg n (%)
Nasopharyngitis	3 (7%)	1 (2%)	3 (9%)	3 (9%)
Back pain	2 (5%)	1 (2%)	1 (3%)	1 (3%)
Bronchitis	1 (2%)	-	1 (3%)	2 (6%)
Diarrhoea	1 (2%)	1 (2%)	-	2 (6%)
Nausea	2 (5%)	1 (2%)	-	1 (3%)
Dizziness	2 (5%)	1 (2%)	-	1 (3%)
Sinusitis	1 (2%)	-	1 (3%)	1 (3%)
Arthralgia	1 (2%)	1 (2%)	-	1 (3%)
Muscle spasms	2 (5%)	1 (2%)	-	-
Headache	3 (7%)	-	-	-
Myalgia	-	-	-	2 (6%)
Gamma-glutamyl transferase increased	-	1 (2%)	-	1 (3%)
Urinary tract infection	-	2 (5%)	-	-
Abdominal pain	1 (2%)	1 (2%)	-	-
Cough	1 (2%)	1 (2%)	-	-

Overall, AZD6610 was well tolerated and the proportion of patients with reported adverse events as well as patients with adverse events leading to discontinuation was similar as for placebo. Serious adverse events (SAEs) were rare, only 2 were reported after randomisation (1 in the placebo group and 1 in the AZD6610 2 mg dose group), which were judged by the principal investigator to have no causal relationship to the randomized treatment. One (1) more SAE occurred during the run-in period, and the patient was subsequently not

randomized. There were no deaths during the study. There was a reduction compared to placebo in the particle concentration of erythrocytes (Ery) and reticulocytes, and of B-haemoglobin. There was also a decrease in the particle concentration of neutrophiles, resulting in a reduction of the particle concentration of leucocytes. The changes were small but statistically significant for the 10 mg AZD6610 dose group and also for the 2 mg dose group regarding particle concentration of reticulocytes. The changes in the haematology variables were smaller in fenofibrate group, and statistically significant only for the reticulocytes. Liver function variables ALAT, ALP and gamma-GT were statistically significantly decreased compared to placebo in both AZD6610 dose groups and bilirubin in the 10 mg dose group. The decrease was more pronounced in the 10 mg dose group. In the fenofibrate group there were statistically significant changes compared to placebo of the hepatic variables only for ALP and bilirubin. There was an increase in serum creatinine in both the 2 mg and 10 mg AZD6610 dose group (4% and 6%, respectively) that was statistically significant in the 10 mg dose group ($p=0.070$ and $p=0.004$, respectively). The fenofibrate group showed an 11% increase in S-creatinine compared to placebo that was statistically significant ($p<0.001$). The urine haemoglobin test was positive in only a few of the patients treated with AZD6610 (1 patient in the 2 mg and 2 patients in the 10 mg dose group had U-Hb ++ or higher) and fenofibrate (1 patient had U-Hb ++ or higher).

Date of the report
06 March 2008