AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00030
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A Randomised, Open, Placebo controlled, Two-way Crossover Phase I Study in Type 2 Diabetes Mellitus Patients Treated with Metformin to Evaluate the Effect of Gemfibrozil on the Pharmacokinetics and Pharmacodynamics of a Single Dose of AZD1656

Study dates: First subject enrolled: 15 March 2010
Last subject last visit: 3 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 evaluate the pharmacokinetics of a single dose of AZD1656 when administered with placebo or following repeated dosing of gemfibrozil	AUC and C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To evaluate the pharmacokinetics of AZD1656 when administered with placebo or following repeated dosing of gemfibrozil	$AUC_{(0-t)}$, t_{max}, $t_{½}$, CL/F, and V_z/F	Pharmacokinetic
To evaluate the pharmacokinetics of the AZD1656 metabolite AZD5658 when AZD1656 is administered with placebo or following repeated dosing of gemfibrozil	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, and $t_{½}$	Pharmacokinetic
To evaluate the safety of AZD1656 when administered with placebo or following repeated dosing of gemfibrozil	Electrocardiogram, weight, pulse, blood pressure, laboratory variables including 24-h plasma glucose, physical examination, and adverse events	Safety
To evaluate the pharmacodynamic effects (glucose and insulin) of AZD1656 when administered with placebo or following repeated dosing of gemfibrozil	Glucose ($AUC_{(0-4)}$ and $AUC_{(0-24)}$) and insulin ($AUC_{(0-4)}$)	Pharmacodynamic
Exploratory		
To collect and store deoxyribonucleic acid samples for potential future research into genes which may influence response (pharmacokinetic profile, efficacy, safety and tolerability) to AZD1656, metformin and/or gemfibrozil[a]	Not applicable	Pharmacogenetic

a Results from any genetic research, if performed, will be reported separately from this report.

Study design

In this randomised, open, placebo controlled, two-way crossover, drug-drug interaction Phase I study, the pharmacokinetics, pharmacodynamics, and safety of a single dose of AZD1656 were assessed by adding AZD1656 to the dosing of gemfibrozil or placebo.

In each treatment period, patients were administered gemfibrozil or placebo twice daily on days 1 to 5. One (1) h after gemfibrozil or placebo administration on day 4, patients received a single dose of AZD1656 together with breakfast.

Target subject population and sample size

The target population was males and females of non child-bearing potential with type 2 diabetes mellitus aged ≥18 years and ≤75 years, and with a body mass index of ≥19 and ≤42 kg/m^2. Eligible patients kept their metformin treatment during the study. To estimate the effect of gemfibrozil on the PK of AZD1656 with a 95% confidence interval, 12 evaluable patients was considered to be sufficient. Twelve (12) patients were randomised and analysed.

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

AZD1656, oral tablet 20 mg (AstraZeneca, batch no 09-007136AZ), administered as a single dose together with gemfibrozil/placebo

Gemfibrozil, oral tablet 600 mg (Pfizer, batch no 10-000566AZ), twice daily, administered for 5 days

Placebo, oral tablet (AstraZeneca, batch no 09-003942AZ), twice daily, administered for 5 days

Duration of treatment

The duration of each patient's participation was about 2 months, including a screening period of 35 days prior to randomisation, 2 treatment periods of 5 days each separated by a wash-out period of 5 to 9 days, and a follow-up visit 7 to 10 days after the last dose.

Statistical methods

The primary analyses of AZD1656 AUC and C_{max} were performed using a linear mixed effects model on the log-transformed AZD1656 AUC and C_{max} with fixed effects for sequence, period and treatment and random effect for subject nested within sequence. Estimates of the mean difference (AZD1656+gemfibrozil – AZD1656+placebo) were calculated with 95% confidence intervals. The result was transformed back to the original scale and multiplied by 100 in order to give an estimate of the true ratios (AZD1656+gemfibrozil vs AZD1656+placebo) in percent and 95% confidence intervals for these ratios. In addition, for descriptive purposes, 90% confidence intervals were estimated in accordance with above.

The analyses of glucose $AUC_{(0-4)}/4$ and $AUC_{(0-24)}/24$, and insulin $AUC_{(0-4)}/4$ were performed using a linear mixed effects model on the log-transformed glucose $AUC_{(0-4)}/4$ and $AUC_{(0-24)}/24$, and insulin $AUC_{(0-4)}/4$ with fixed effects for sequence, period and treatment and random effect for subject nested within sequence. Estimates of the mean difference (AZD1656+gemfibrozil – AZD1656+placebo) were calculated with 95% CIs. The result was transformed back to the original scale in order to give an estimate of the true ratios (AZD1656+gemfibrozil vs AZD1656+placebo) and 95% CIs for these ratios.

Plasma concentrations of AZD1656 and the metabolite AZD5658 and derived pharmacokinetic parameters were summarised by treatment using descriptive statistics.

All safety variables were presented descriptively.

Subject population

A total of 30 patients were enrolled in the study. Twelve (12; 7 males and 5 females) patients with type 2 diabetes mellitus treated with metformin, aged 49 to 70 years, were included. All patients completed the study. Their mean (±standard deviation) weight and body mass index were 82.0 (±7.1) kg and 28.3 (±3.8) kg/m^2, respectively. Their mean (±standard deviation) haemoglobin A1c and fasting plasma glucose were 7.97% (±1.05%) and 8.77 (±1.51) mmol/L (157.8 [±27.23] mg/dL), respectively, at the pre-entry visit.

Summary of pharmacokinetic results

AUC and C_{max} of AZD1656

There was a statistically significant increase in AUC but not in C_{max} of AZD1656 when AZD1656 was administered with gemfibrozil compared to when administered with placebo. Gemfibrozil increased AUC of AZD1656 2.7-fold. The estimated geometric ratios for AZD1656 with gemfibrozil vs AZD1656 with placebo (95% confidence interval) of AUC and C_{max} were 271.19% (244.31% to 301.03%) and 120.87% (94.35% to 154.82%), respectively.

Other PK parameters ($AUC_{(0-t)}$, t_{max}, $t_{½}$, CL/F and V_z/F) of AZD1656

Geometric mean $AUC_{(0-t)}$ was higher whereas median t_{max} was comparable when AZD1656 was administered with gemfibrozil (12.4 h*µmol/L and 0.75 h, respectively) compared to when administered with placebo (4.60 h*µmol/L and 0.67 h, respectively).

Geometric mean $t_{½}$ was 2 times longer when AZD1656 was administered with gemfibrozil (8.01 h) compared to when administered with placebo (3.99 h). This is in line with the geometric means of CL/F and V_z/F, which were 63% and 26% lower, respectively, when AZD1656 was administered with gemfibrozil (3.31 L/h and 38.2 L, respectively) compared to when administered with placebo (8.98 L/h and 51.7 L, respectively).

AUC, $AUC_{(0-t)}$, C_{max}, t_{max} and $t_{½}$ of AZD5658

Due to sparse measurable plasma concentration data, especially when AZD1656 was administered with gemfibrozil, the PK results for AZD5658 should be interpreted with caution.

The geometric means of $AUC_{(0-t)}$ and C_{max} of AZD5658 were markedly lower when AZD1656 was administered with gemfibrozil (0.0154 h*µmol/L and 0.0107µmol/L, respectively) compared to when administered with placebo (0.428 h*µmol/L and 0.0760 µmol/L, respectively). Median t_{max} was comparable when AZD1656 was administered with gemfibrozil (0.77 h) and placebo (0.75 h).

Due to the small number of reported values, the effect of gemfibrozil on AUC and $t_{½}$ of AZD5658 could not be evaluated.

Summary of pharmacodynamic results

There was no statistically significant change in plasma glucose during the 4- or 24-h period or in plasma insulin during the 4-h period after administration of AZD1656 with gemfibrozil compared to placebo. The estimated geometric ratios for AZD1656 with gemfibrozil vs AZD1656 with placebo (95% confidence interval) were 104.17% (89.19% to 121.67%) and 100.30% (90.93 to 110.64%), respectively for $AUC_{(0-4)}/4$ and $AUC_{(0-24)}/24$ of plasma glucose and 105.83% (87.42% to 128.12%) for $AUC_{(0-4)}/4$ of plasma insulin.

Summary of pharmacokinetic/pharmacodynamic relationships

There was a statistically significant 2.7-fold increase in AUC of AZD1656 and marked decreases in geometric means of $AUC_{(0-t)}$ and C_{max} of the active metabolite AZD5658 when a single dose of 20 mg AZD1656 was administered with gemfibrozil compared to when administered with placebo. The observed changes in exposure to AZD1656 and AZD5658 did not result in any statistically significant changes in plasma glucose ($AUC_{(0-4)}/4$ or $AUC_{(0-24)}/24$) or plasma insulin ($AUC_{(0-4)}/4$).

Summary of safety results

There were no serious adverse events, no other significant adverse events and no discontinuations of investigational product due to adverse events in the study. All adverse events were of mild or moderate intensity.

There were no clinically relevant findings in safety laboratory variables, vital signs, electrocardiogram, weight or physical examination.