AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00032
Edition Number	1
Date	15 April 2011

A Randomised, Open, Phase I Study in Patients with Type 2 Diabetes Mellitus Treated with Metformin to Evaluate the Effect of AZD1656 on the Pharmacokinetics of Sitagliptin and Vice Versa

Study dates: First subject enrolled: 24 March 2010
Last subject last visit: 17 May 2010

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

The study was performed at 1 centre in Germany (Profil Institut für Stoffwechselforschung GmbH, Neuss).

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 effect of AZD1656 on the steady state pharmacokinetics of sitagliptin and vice versa	$AUC_{(0-24)}$ and C_{max} (C_{max} only for the morning dose)	Pharmacokinetic
Secondary	**Secondary**	
To evaluate the effect of AZD1656 on the steady state pharmacokinetics of sitagliptin and vice versa	t_{max}, $t_{½}$, and CL/F	Pharmacokinetic
To evaluate the pharmacokinetics of the AZD1656 metabolite AZD5658 when AZD1656 is administered with and without sitagliptin	$AUC_{(0-24)}$, C_{max}, t_{max}, and $t_{½}$ (C_{max} and t_{max} only for the morning dose)	Pharmacokinetic
To evaluate the safety of AZD1656 with and without sitagliptin	Adverse events, physical examination, electrocardiogram, pulse, blood pressure, weight, and laboratory variables including 7-point glucose	Safety
Exploratory	**Exploratory**	
To collect and store DNA samples for potential future research into genes which may influence response (pharmacokinetic profile, efficacy, safety, and tolerability) to AZD1656 and/or sitagliptin[a]	Not applicable	Pharmacogenetic

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

Study design

The study was designed as a randomised, open-label, crossover, phase I study in patients with type 2 diabetes mellitus. Treatment during the residential period was divided into 3 treatment periods: days 1 to 5, days 6 to 10 and days 11 to 15. During the entire study period patients kept their metformin treatment unchanged, thus both AZD1656 and sitagliptin were given as an add-on treatment to metformin.

Patients were randomised to start treatment with either AZD1656 or sitagliptin. In the group that started with AZD1656, sitagliptin was added to the treatment with AZD1656 in the 2nd

treatment period and sitagliptin was given alone in the 3rd treatment period. In the group that started with sitagliptin, AZD1656 was added to the treatment with sitagliptin in the 2nd treatment period and AZD1656 was given alone in the 3rd treatment period.

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. The aim was to have 12 evaluable patients; 12 patients were randomised and analysed.

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

AZD1656, 40 mg (as 2 x 20 mg oral tablets, batch no 09-007136AZ) or 100 mg (as 2 x 50 mg oral tablets, batch no 09-007135AZ), twice daily (ie, a total daily dose of 80 mg and 200 mg, respectively), administered for 5 days alone and for 5 days together with sitagliptin

Sitagliptin, oral tablet 100 mg (batch no 10-000567AZ), once daily, administered for 5 days alone and for 5 days together with AZD1656

Duration of treatment

The duration of each patient's participation was about 2 months, including a screening period of 35 days prior to randomisation, 3 treatment periods of 5 days each, with no wash-out between the periods, and a follow-up visit 7 to 10 days after the last dose.

Statistical methods

The analyses of AZD1656 and AZD5658 $AUC_{(0-24)}$ and C_{max} were performed using a linear mixed effects model on the dose-adjusted (to 200 mg for $AUC_{(0-24)}$ and to 100 mg for C_{max}), log-transformed AZD1656 and AZD5658 $AUC_{(0-24)}$ and C_{max} with fixed effects for sequence, period and treatment and random effect for subject nested within sequence. Period in this analysis had values 1 and 2 only depending on the order of the 2 treatments, ie, periods 2 and 3 in the sequence where the 2 treatments were in periods 2 and 3, were modified to 1 and 2. Estimates of the mean difference (AZD1656+sitagliptin – AZD1656 alone) were calculated with 90% confidence intervals. The result was transformed back to the original scale in order to give an estimate of the true ratios (AZD1656+sitagliptin vs AZD1656 alone) and 90% confidence intervals for these ratios.

No relevant effects on the pharmacokinetics of AZD1656 after co-administration with sitagliptin were concluded if the two-sided 90% confidence intervals for the ratios of $AUC_{(0-24)}$ and C_{max} were within 0.8 and 1.25 (80.00% and 125.00%).

A similar statistical analysis was performed for sitagliptin to evaluate the effects of AZD1656 co-administration on sitagliptin pharmacokinetics.

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

All safety variables were presented descriptively.

Subject population

A total of 12 patients (6 males and 6 females), aged 47 to 70 years, were included in the study. All patients completed the study. Their mean (±standard deviation) weight and body mass index were 86.9 (± 18.4) kg and 28.8 (± 4.5) kg/m^2, respectively.

Summary of pharmacokinetic results

$AUC_{(0-24)}$ and C_{max} of sitagliptin and AZD1656

AZD1656 did not affect the plasma exposure of sitagliptin at steady state in terms of $AUC_{(0-24)}$ whereas an increase in C_{max} cannot be excluded as the upper 90% confidence interval was just above 125.00%. The estimated geometric mean ratios for sitagliptin with AZD1656 vs sitagliptin alone (90% confidence interval) of $AUC_{(0-24)}$ and C_{max} were 105.16% (101.10% to 109.37%) and 110.79% (97.91% to 125.38%), respectively. The upper 90% confidence interval being very close to 125.00%, and the small increase in the estimated geometric mean suggest that the indicated increase in C_{max} is not clinically relevant.

Sitagliptin did not affect the plasma exposure ($AUC_{(0-24)}$ and C_{max}) of AZD1656 at steady state. The estimated geometric mean ratios for AZD1656 with sitagliptin vs AZD1656 alone (90% confidence interval) of $AUC_{(0-24)}$ and C_{max} were 99.08% (96.90% to 101.32%) and 107.15% (97.80% to 117.39%), respectively.

Other PK parameters (t_{max}, $t_{½}$ and CL/F) of sitagliptin and AZD1656

Median t_{max}, geometric mean $t_{½}$ and geometric mean CL/F of sitagliptin were comparable after repeated administration of sitagliptin alone (0.63 h, 12.0 h and 33.3 L/h, respectively) and with AZD1656 (0.50 h, 11.9 h and 31.6 L/h, respectively).

Median t_{max}, geometric mean $t_{½}$ and geometric mean CL/F of AZD1656 were comparable after repeated administration of AZD1656 alone (0.50 h, 4.42 h and 8.17 L/h, respectively) and in combination with sitagliptin (0.50 h, 4.36 h and 8.24 L/h, respectively).

$AUC_{(0-24)}$, C_{max}, t_{max} and $t_{½}$ of AZD5658

Sitagliptin did not affect the plasma exposure ($AUC_{(0-24)}$ and C_{max}) of the AZD1656 metabolite AZD5658 at steady state. The estimated geometric mean ratios for AZD5658 with sitagliptin vs AZD1656 alone (90% confidence interval) of $AUC_{(0-24)}$ and C_{max} were 97.79% (91.25% to 104.81%) and 105.32% (97.19% to 114.13%), respectively. Median t_{max} was comparable when AZD1656 was administered alone (0.75 h) and in combination with sitagliptin (0.50 h). Due to a small number of reported values, the effect of sitagliptin on $t_{½}$ of AZD5658 could not be evaluated.

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. Few adverse events were reported (8 events by 6 patients) and all were of mild (6 events) or moderate (2 events) intensity.

Treatment with AZD1656 alone and in combination with sitagliptin decreased glucose levels. There were no clinically significant findings in vital signs, electrocardiogram, weight or physical examination.