AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00029
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A Randomized, Open-label, 3-way Crossover Phase I Study in Type 2 Diabetes Mellitus Patients Treated with Metformin to Evaluate the Pharmacokinetics and Pharmacodynamics of Simvastatin during Coadministration with AZD1656 and to Evaluate the Pharmacokinetics of AZD1656 during Coadministration with Simvastatin

Study dates: First patient enrolled: 18 March 2010
Last patient last visit: 05 August 2010

Phase of development: Clinical pharmacology (I)

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

Study center

The study was conducted at a single center in the United States (Cetero Research Inc., San Antonio, Texas, United States).

Publications

None at the time of writing this clinical study 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 simvastatin (including simvastatin acid) and vice versa by assessment of $AUC_{(0-24)}$ and C_{max}	$AUC_{(0-24)}$ and C_{max}	Pharmacokinetics
Secondary	**Secondary**	
To evaluate the effect of AZD1656 on the steady state pharmacokinetics of simvastatin and simvastatin acid and vice versa by assessment of t_{max}, $t_{1/2}$ and CL/F (only for AZD1656)	t_{max}, $t_{1/2}$, and CL/F	Pharmacokinetics
To evaluate the steady state pharmacokinetics of the AZD1656 metabolite AZD5658 when AZD1656 is administered with and without simvastatin, by assessment of $AUC_{(0-24)}$, C_{max}, and t_{max}	$AUC_{(0-24)}$, C_{max}, and t_{max}	Pharmacokinetics
To evaluate the effect of AZD1656 on the pharmacodynamics of simvastatin by assessment of $AUC_{(0-t)}$ and C_{max} of active 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors	$AUC_{(0-24)}$ and C_{max} (of HMG-CoA reductase inhibitors)	Pharmacodynamics
To evaluate the safety and tolerability of AZD1656 alone and in combination with simvastatin by assessments of adverse events, laboratory variables, electrocardiogram, blood pressure, pulse, results of physical examination, and weight	Adverse events, laboratory variables, electrocardiogram, pulse, blood pressure, pulse, results of physical examination and weight	Safety
Exploratory	**Exploratory**	
To collect and store DNA samples for potential future research into genes, which may influence drug response (pharmacokinetic profile, drug safety, efficacy, and tolerability) of AZD1656, metformin, and/or simvastatin	Not applicable	Pharmacogenetics

$AUC_{(0-24)}$: Area under the concentration-time curve in the plasma from zero (pre dose) until 24 hours post dosing

C_{max}: Maximum concentration in the plasma, obtained directly from the observed concentration versus time data for AZD1656 and AZD5658 based on the morning (AM) dose

CL/F: Apparent oral clearance (L/h), calculated as total daily dose/$AUC_{(0-24)}$ (ie, (20+20 dose)/$AUC_{(0-24)}$; determined for AZ1656 only)

$t_{½}$: Apparent terminal half-life (h), determined as $\ln 2/\lambda_z$ (determined for the second dose for AZD1656 only)

t_{max}: Time of maximum plasma concentration (h), obtained directly from the observed concentration versus time data for AZD1656 and AZD5658 based on the morning (AM) dose

Note: Results from any genetic research, if performed, will be reported separately from this CSR.

Study design

This was an open-label, 3-way crossover, Phase 1, drug-drug interaction study in patients with type 2 diabetes mellitus (T2DM) treated with metformin or metformin and one other oral anti-diabetic (OAD) (dipeptidyl peptidase-4 inhibitor [DPP-4 inhibitor] or sulphonylurea [SU]). Any OADs other than metformin and any prescribed statin drugs were stopped 7 to 10 days before randomization/intake of IP.

Patients were randomized to receive 1 of the 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, and CBA) comprising of Treatment A (AZD1656 20 mg, bid), Treatment B (simvastatin 40 mg, qd) and Treatment C (AZD1656 20 mg, bid + simvastatin 40 mg, qd). Each treatment period lasted for 4 days with no drug-free washout period between each treatment period.

Frequent serial blood samples were drawn during the 24 hours post morning dose on Day 4 in each treatment period to measure and assess the pharmacokinetics of AZD1656, its metabolite AZD5658, simvastatin, and its metabolite simvastatin acid, as appropriate. Blood samples were also drawn for measuring the pharmacodynamics of simvastatin by assessment of active 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors. Safety assessments were made throughout the study and glucose levels were monitored frequently to assure that the patient's blood glucose levels were within the safety range.

Target subject population and sample size

The target population included males and females (of nonchildbearing potential) with T2DM and treated with metformin alone or metformin and one other OAD (DPP-4 inhibitor or SU), aged ≥18 years, and with a body mass index of ≥19 and ≤42 kg/m^2.

Twenty-four (24) patients provided at least 90% power to reject both the null hypothesis that the true ratio of the test mean to the reference mean was below 70% and the null hypothesis that the true ratio of test mean to the reference mean was above 143% (ie, that there was a significant drug-drug interaction, in favor of the alternative hypothesis that there is not a significant drug-drug interaction).

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

- AZD1656 20 mg (1 x 20 mg oral tablet) twice daily, manufactured by AstraZeneca Batch number 10-000741AZ
- Simvastatin 40 mg oral tablet, once daily, manufactured by Merck, Batch number Y1614

Duration of treatment

There were 3 treatment periods of 4 days each without a drug-free washout period between each treatment period.

Statistical methods

Plasma concentrations of AZD1656, the metabolite AZD5658, simvastatin, and the metabolite simvastatin acid and the derived pharmacokinetic parameters were summarized by treatment using descriptive statistics. The HMG-CoA reductase activity and derived pharmacodynamic parameters were also summarized.

To assess the effect of AZD1656 on simvastatin and vice versa, the pharmacokinetic parameters of AZD1656, AZD5658, simvastatin, and simvastatin acid were analyzed using linear mixed model on the log-transformed AZD1656, AZD5658, simvastatin, and simvastatin acid $AUC_{(0-24)}$ and C_{max} with fixed effects for sequence, period, and treatment and subject nested within sequence as a random effect. Ratios of geometric means (test/reference) and the associated 90% confidence intervals were presented.

To assess the effect of AZD1656 on the pharmacodynamic of simvastatin, the pharmacodynamic parameters ($AUC_{(0-t)}$ and C_{max}) for active HMG-CoA reductase inhibitors was analyzed using a linear mixed effects model on the log-transformed parameters $AUC_{(0-t)}$ and C_{max} with fixed effects for sequence, period, and treatment and subject nested within sequence as a random effect. Ratios of geometric means (test/reference) and the associated 90% confidence intervals were presented.

All safety variables were summarized using descriptive statistics.

Subject population

Initially 28 patients were randomized to the study. Of these, the plasma samples from 20 patients who completed the study were thawed during transportation from the clinic to the bioanalytical laboratory and were considered unsuitable for analysis. Thus, an additional 18 patients were enrolled increasing the number of enrolled and randomized patients from original 28 to 46 to ensure at least 24 evaluable patients complete the study.

A total of 46 T2DM patients were randomized in this study. The first patient was enrolled on 18 March 2010. The last patient received the last dose of study medication on 26 July 2010, was discharged from the clinic on 27 July 2010 and completed the study on 05 August 2010.

Of the 46 patients randomized, 44 patients completed the study. Two patients discontinued the study:

- Patient E0001027 randomized to the CBA treatment sequence discontinued on 10 May 2010 due to subject's decision. This patient was not part of the pharmacokinetic/pharmacodynamic analysis data set as she was amongst the 20 patients whose pharmacokinetic and pharmacodynamic samples were thawed during shipment.

- Patient E0001056 randomized to the BAC treatment sequence discontinued on 30 July 2010 due to an adverse event of mild upper respiratory tract infection which was not considered to be treatment-related by the Investigator.

The study population consisted of 31 (67.4%) males and 15 (32.6%) females with T2DM, with a mean age of 58±9 years.

Summary of pharmacokinetic results

Of the 28 patients initially randomized, the pharmacokinetic samples of 20 patients were thawed during shipment, hence no pharmacokinetic data is available, as the samples were considered unsuitable for measurement of any pharmacokinetic concentration. However, with the additional 18 patients enrolled and randomized, 26 patients had evaluable data for pharmacokinetic analysis.

$AUC_{(0-24)}$ and C_{max} of simvastatin, simvastatin acid, and AZD1656

The 90% confidence intervals [(99.17%, 116.63%) for $AUC_{(0-24)}$ and (88.22%, 132.63% for C_{max}] for the geometric mean ratios of both $AUC_{(0-24)}$ (107.55%) and C_{max} (108.17%) for simvastatin, when simvastatin was given in combination with AZD1656 versus given alone, were contained entirely within the interval of 70.00 to 143.00%.

Similarly, the 90% confidence intervals [(91.29%, 112.33%) for $AUC_{(0-24)}$ and (95.62%, 120.18%) for C_{max}] for the geometric mean ratios of both $AUC_{(0-24)}$ (101.27%) and C_{max} (107.20%) for simvastatin acid, when simvastatin was given in combination with AZD1656 versus given alone, were contained entirely within the interval of 70.00 to 143.00%.

These results indicate that AZD1656 did not affect the plasma exposures of simvastatin and its metabolite simvastatin acid.

The 90% confidence intervals [(110.14%, 117.18%) for $AUC_{(0-24)}$ and (97.30%, 117.67%) for C_{max}] for the geometric mean ratios of $AUC_{(0-24)}$ (113.61%) and C_{max} (107.00%) for AZD1656, when AZD1656 was given in combination with simvastatin versus given alone, were contained entirely within the interval of 80.00% to 125.00%. These results conclude that simvastatin did not affect the exposure of AZD1656.

Other pharmacokinetic parameters of simvastatin, simvastatin acid, and AZD1656

The estimated median t_{max} and mean $t_{1/2}$ of simvastatin were comparable following repeated administration of simvastatin alone (0.75 h for t_{max} and 5.55 h for $t_{1/2}$ respectively) and when given in combination with AZD1656 (1.00 h for t_{max} and 6.01 h for $t_{1/2}$ respectively).

The estimated median t_{max} and mean $t_{1/2}$ of simvastatin acid were comparable following repeated administration of simvastatin alone (3.00 h for t_{max} and 5.52 h for $t_{1/2}$ respectively) and when given in combination with AZD1656 (3.00 h for t_{max} and 5.46 h for $t_{1/2}$ respectively).

The estimated median t_{max}, mean $t_{1/2}$ and CL/F of AZD1656 were comparable following repeated administration of AZD1656 alone (0.75 h for t_{max}, 4.63 h for $t_{1/2}$ and 9.56 L/h for CL/F respectively) and when given in combination with simvastatin (0.75 h for t_{max}, 5.04 h for $t_{1/2}$ and 8.36 L/h for CL/F respectively).

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

The geometric mean $AUC_{(0-24)}$ and C_{max} and estimated median t_{max} of AZD5658 were comparable following repeated administration of AZD1656 alone (1.32 µmol*h/L for $AUC_{(0-24)}$, 0.114 µmol/L for C_{max} and 0.75 h for t_{max}) and when given in combination with simvastatin (1.46 µmol*h/L for $AUC_{(0-24)}$, 0.120 µmol/L for C_{max} and 0.75 h for t_{max}).

Summary of pharmacodynamic results

Of the 28 patients initially randomized, the pharmacokinetic samples of 20 patients were thawed during shipment. The pharmacodynamic samples of these 20 patients were therefore decided to be destroyed once the pharmacokinetic samples were thawed hence no pharmacodynamic data is available. However, with the additional 18 patients enrolled and randomized, 26 patients had evaluable data for pharmacodynamic analysis.

The geometric mean ratios for $AUC_{(0-t)}$ (100.22%) and C_{max} (99.02%) of active HMG-CoA reductase inhibitors, following administration of simvastatin in combination with AZD1656 versus simvastatin alone, indicate that AZD1656 did not affect the exposure of the active HMG-CoA-reductase inhibitors.

$AUC_{(0-t)}$, and C_{max} of active HMG-CoA reductase inhibitors

The geometric mean $AUC_{(0-t)}$ and C_{max}, and estimated median t_{max} of active HMG-CoA reductase inhibitors were comparable following administration of simvastatin alone (220 nEq*h/mL for $AUC_{(0-t)}$, 58.6 nEq/mL for C_{max} and 1.0 h for t_{max}) and when given in combination with AZD1656 (223 nEq*h/mL for $AUC_{(0-t)}$, 58.4 nEq/mL for C_{max} and 1.0 h for t_{max}).

Summary of safety results

All 46 randomized subjects were included in the safety analyses. There were no deaths, serious adverse events, or other significant AEs in this study. There were no AEs of hypoglycemia in the study. One patient, E0001056, randomized to the BAC treatment sequence discontinued (during Treatment C [AZD1656 20 mg, bid + simvastatin 40 mg, qd], Day 1) due to an AE of mild upper respiratory tract infection which was not considered to be treatment-related by the Investigator.

A total of 79 AEs were reported by 34 (73.9%) patients during the study. The most common AEs were headache, constipation and diarrhea. A higher number of AEs (21 [45.7%]) was reported during Treatment A (AZD1656 20 mg, bid) compared with Treatment B (15 [32.6%]) and Treatment C (19 [41.3%]). The number of patients reporting AEs during Treatment A (AZD1656 20 mg, bid) was comparable with patients reporting AEs during Treatment C (AZD1656 20 mg, bid + simvastatin 40 mg, qd).

There were 2 patients who experienced AEs assessed by the Investigator as moderate in intensity: rash pruritic (Treatment B [simvastatin 40 mg, qd]) and abdominal distension (Treatment C [AZD1656 20 mg, bid + simvastatin 40 mg, qd]) both of which were judged by the Investigator as causally related. All other adverse events were assessed as mild in intensity.

Overall, 22 (47.8%) patients reported 35 AEs that were judged by the Investigator as causally related. The number of causally related AEs was similar across Treatment A (AZD1656 20 mg, bid) and Treatment C (AZD1656 20 mg, bid + simvastatin 40 mg, qd).

There were no clinically significant changes in clinical laboratory, ECG, vital signs, examination findings, or body weight.