AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00028
Edition Number	1
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Open, Randomized, Phase I Study in Subjects with Type 2 Diabetes Mellitus Treated with Metformin to Evaluate the Effect of AZD1656 on the Pharmacokinetics of Pioglitazone and Vice Versa

Study dates: First subject enrolled: 18 February 2010
Last subject last visit: 26 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 conducted at a single center; Profil Institute for Clinical Research Inc., Chula Vista, California, United States.

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 pioglitazone and vice versa	$AUC_{(0-24)}$ and C_{max}	Pharmacokinetic
Secondary	**Secondary**	
To evaluate the effect of AZD1656 on the steady state pharmacokinetics of pioglitazone and vice versa	t_{max}, $t_{1/2}$, and CL/F	Pharmacokinetic
To evaluate the pharmacokinetics of the AZD1656 metabolite AZD5658, when AZD1656 is administered with and without pioglitazone	$AUC_{(0-24)}$, C_{max}, and t_{max}	
To evaluate the pharmacokinetics of the pioglitazone metabolite hydroxy-pioglitazone, when pioglitazone is administered with and without AZD1656, by assessment of $AUC_{(0-24)}$, C_{max} and t_{max}.	$AUC_{(0-24)}$, C_{max}, and t_{max}	
To evaluate the safety of AZD1656 with and without pioglitazone	Adverse events, physical examination, electrocardiogram, pulse, blood pressure, weight, and laboratory variables including 7-point glucose	Safety
Exploratory[a]		
To collect and store DNA samples for potential future research into genes, which may influence drug response (pharmacokinetic profile, drug safety and tolerability) of AZD1656, metformin, and/or pioglitazone	DNA exploratory research	Pharmacogenetics

[a] Results from any genetic research, if performed, will be reported separately from this CSR.

Study design

This was an open label, randomized, 3-period, 2-sequence, crossover, single center, Phase I, drug-drug interaction study in patients with type 2 diabetes mellitus.

Patients were randomized to either Sequence ABC (starting with AZD1656) or Sequence CBA (starting with pioglitazone) comprised of the following treatments: Treatment A was AZD1656 alone; Treatment B was AZD1656 plus pioglitazone; and Treatment C was pioglitazone alone. During the entire study patients kept their metformin treatment unchanged.

Sequence ABC: During study Days 1 to 5 (Period 1) AZD1656 was given alone. Patients started with AZD1656 40 mg twice daily on Day 1 with the dose titrated to 100 mg twice daily on the morning of Day 2, provided fasting plasma glucose was greater than 6.1 mmol/L (110 mg/dL), and no conditions opposed a dose increase. Patients continued with the highest tolerated dose of AZD1656 for the next 3 days. No dose changes of AZD1656 were possible after the morning dose on Day 3; any unacceptable tolerability issues led to discontinuation. From Day 6 to 10 (Period 2) a once-daily dose of 30 mg pioglitazone was added to the treatment with AZD1656. From Day 11 until Day 15 (Period 3), AZD1656 was discontinued and the daily dose of 30 mg pioglitazone was given alone.

Sequence CBA: Patients randomized to this sequence started with pioglitazone and were given a daily dose of 30 mg of pioglitazone alone during study Days 1 to 5 (Period 1). From Day 6 to 10 (Period 2) AZD1656 was added to the treatment with pioglitazone. Starting on Day 6, AZD1656 was titrated in the same way as described above. From Day 11 until Day 15 (Period 3), a daily dose of 100 mg or 40 mg of AZD1656 twice daily, as tolerated in previous period (ie, Days 6 to 10), was given alone.

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 was males and females (of nonchildbearing potential) with type 2 diabetes mellitus aged greater than or equal to 18 years, and with a body mass index of greater than or equal to 19 and less than or equal to 42 kg/m^2.

Twenty-four 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%. This assumed a percent coefficient of variation of 24.0% for $AUC_{(0-24)}$ and 33.7% for C_{max}. The prespecified limits (70% to 143%) represented a 30% relative increase or decrease in the exposure of pioglitazone. Twenty-eight patients were to be enrolled to ensure that 24 patients completed the study.

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

AZD1656 40 mg (2 x 20 mg tablets), lot number 10-000425AZ or 100 mg (2 x 50 mg tablets) tablets, twice daily, lot number 10-000424AZ, manufactured by AstraZeneca;

Pioglitazone 30 mg tablet, once daily, Batch number A16130, manufactured by Takeda Pharmaceuticals.

Duration of treatment

The duration of each patient's participation was about 2 months, including a screening period of 28 days prior to randomization, 3 treatment periods of 5 days each, with no washout between the periods, and a follow-up visit 7 to 10 days after the last dose.

Statistical methods

To assess the effect of pioglitazone on AZD1656 pharmacokinetic parameters [C_{max}, AM dose and $AUC_{(0-24)}$], comparisons of geometric means of test (AZD1656 plus pioglitazone; Treatment B) and reference (AZD1656 alone; Treatment A) were estimated for AZD1656 and its metabolite. To assess the effect of AZD1656 on pioglitazone PK parameters [C_{max} and $AUC_{(0-24)}$], comparisons of geometric means of test (AZD1656 plus pioglitazone; Treatment B) and reference (pioglitazone alone; Treatment C) were estimated for pioglitazone and its metabolite.

The PK parameters of AZD1656, AZD5658, pioglitazone, and hydroxy-pioglitazone were analyzed using analysis of variance model on the log-transformed $AUC_{(0-24)}$ and C_{max} with fixed effects for sequence, period, and treatment and patient nested within sequence as a random effect. Transformed back from the logarithm scale, true geometric means together with confidence intervals (2-sided 95%) for $AUC_{(0-24)}$, and C_{max} were estimated. Also, ratios of test (AZD1656 plus pioglitazone) and reference (AZD1656 alone or pioglitazone alone) geometric means together with corresponding confidence intervals (2-sided 90%) were estimated. No significant drug-drug interaction between AZD1656 and pioglitazone was to be concluded if the two-sided 90% confidence intervals for the ratios of C_{max} and $AUC_{(0-24)}$ were within 70% and 143%.

Safety data were summarized using descriptive statistics.

Subject population

Twenty-eight (28) patients were enrolled and randomized to treatment. However, source data records were lost at the study site for 2 patients. Thus, the number of patients presented is 26.

The first patient was enrolled on 18 February 2010 and the last patient completed on 26 May 2010.

Two patients in the pioglitazone alone group discontinued the study after 1 dose of pioglitazone 300 mg was given in error (scheduled dose was 30 mg). All remaining 24 patients completed the study.

All patients with postdose safety data (26) were analyzed for safety, and all completing patients (24) were included in the pharmacokinetic analyses.

The study population consisted of 11 (42.3%) females and 15 (57.7%) males with type 2 diabetes mellitus, with a mean age of 54 years.

Summary of pharmacokinetic results

AUC(0-24) and Cmax of AZD1656 and Pioglitazone

The 90% confidence interval [(106.23, 123.95) for $AUC_{(0-24)}$ and (93.80, 115.69) confidence interval for C_{max}] for the estimated geometric mean ratio of both $AUC_{(0-24)}$ (114.75%) and C_{max} (104.17%) after repeated administration of pioglitazone in combination with AZD1656 versus pioglitazone alone were contained within the interval 70% to 143%.

Similarly, the 90% confidence interval [(91.45, 95.78) for $AUC_{(0-24)}$ and (94.25, 117.23) confidence interval for C_{max}] for the estimated geometric mean ratio of $AUC_{(0-24)}$ (93.59%) and C_{max} (105.11%) after repeated administration of AZD1656 in combination with pioglitazone versus AZD1656 alone was contained within the interval 70% to 143%.

In fact, the 90% confidence interval for the estimated geometric mean ratio of the combination treatment when compared to the respective single-drug administration were contained within the interval of 80.0% to 125.0%. These results indicate that pioglitazone did not alter the exposure of AZD1656 and vice versa.

Other PK parameters for AZD1656(t_{max}, $t_{1/2}$ and CL/F) and pioglitazone (t_{max}, $t_{1/2}$ and CL/F)

The estimated median t_{max} and the geometric means of $t_{1/2}$ and CL/F of AZD1656 were comparable following repeated administration of AZD1656 alone (1.0 h for t_{max}, 4.65 h for $t_{1/2}$ and 8.04 L/h for CL/F) and when given in combination with pioglitazone (1.27 h for t_{max}, 4.54 h for $t_{1/2}$ and 8.57 L/h for CL/F).

The estimated median t_{max} and the geometric means of $t_{1/2}$ and CL/F of pioglitazone were comparable following repeated administration of pioglitazone alone (3.0 h for t_{max}, 11.5 h for $t_{1/2}$ and 3.61 L/h for CL/F) and when given in combination with AZD1656 (3.5 h for t_{max}, 11.3 h for $t_{1/2}$ and 3.15 L/h for CL/F).

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

The geometric means of $AUC_{(0-24)}$ and C_{max} and the estimated t_{max} of AZD5658 were comparable following repeated administration of AZD1656 alone (7.26 µmol*h/L for $AUC_{(0-24)}$, 0.464 µmol/L for C_{max} and 1.25 h for t_{max}) and when given in combination with pioglitazone (7.96 µmol*h/L for $AUC_{(0-24)}$, 0.529 µmol/L for C_{max} and 1.0 h for t_{max}).

$AUC_{(0-24)}$, C_{max} and t_{max} for hydroxy-pioglitazone

The geometric means of $AUC_{(0-24)}$ and C_{max} and the estimated t_{max} of hydroxy-pioglitazone were comparable following repeated administration of pioglitazone alone (13900 ng*h/mL for for $AUC_{(0-24)}$, 679 ng/mL for C_{max} and 10.0 h for t_{max}) and when given in combination with AZD1656(14000 ng*h/mL for $AUC_{(0-24)}$, 667 ng/mL for C_{max} and 9.0 h for t_{max}).

Summary of safety results

In general, AZD1656 was well tolerated by the patients in this study when administered alone and in combination with pioglitazone. There were no deaths, serious adverse events, discontinuations due to adverse events, or other significant adverse events reported during study conduct. Fifty-seven adverse events were reported in 19 patients in the study. Headache was the commonly reported adverse event in the AZD1656 alone group (3 patients), although more patients in the pioglitazone alone group reported the event (5 patients). The number of AEs was similar across all 3 treatment groups. Dizziness was the most frequently reported AE in the AZD1656 plus pioglitazone group (3 patients). One patient (AZD1656 plus pioglitazone) reported an AE of muscle tightness that was assessed by the Investigator as severe in intensity. Two patients (1 each in the AZD1656 alone and pioglitazone alone groups) reported AEs of headache that were assessed as moderate in intensity, and the rest (19 patients, 54 adverse events) were assessed as mild in intensity.

Hypoglycemia was reported by 2 (8.3%) different patients in the AZD1656 alone group (Treatment A) and 2 (8.3%) different patients in the AZD1656 plus pioglitazone group, but not by any patients in the pioglitazone alone group.

Two patients were discontinued due to an unintended overdose of pioglitazone on Day 1 of the study.

There were no clinically relevant changes in clinical laboratory, vital sign, ECG, weight, or physical examination findings.