AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00044
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A Randomized, Single-blind, Placebo-controlled, Single-center Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics after Single Ascending Oral Supratherapeutic Doses of AZD1656 in Male Type 2 Diabetes Mellitus Patients

Study dates: First subject enrolled: 22 October 2010
Last subject last visit: 14 January 2011

Phase of development: Clinical pharmacology (I)

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

Study center(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		
To assess the safety and tolerability of AZD1656, following oral administration of single ascending supratherapeutic doses of AZD1656 to patients with type 2 diabetes mellitus in a fasted state	Adverse events, blood pressure, pulse, weight, physical examination, safety laboratory variables, electrocardiograms, telemetry, and 7-point glucose measurements	Safety
Secondary		
To evaluate the pharmacokinetics of AZD1656 and its metabolite AZD5658 following oral administration of single ascending supratherapeutic doses of AZD1656	AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{½\lambda z}$, CL/F (for AZD1656 only)	Pharmacokinetic
To evaluate glucose levels and insulin secretions in type 2 diabetes mellitus patients following oral administration of single ascending supratherapeutic doses of AZD1656	P-glucose and insulin: $AUC_{(0-4)}$, $AUC_{(0-24)}$, $AUC_{(0-4)}/T$, $AUC_{(0-24)}/T$, baseline-adjusted $AUC_{(0-4)}$, $AUC_{(0-24)}$, $AUC_{(0-4)}/T$, and $AUC_{(0-24)}/T$.	Pharmacodynamic
Exploratory[a]		
To explore effects on the electrocardiogram, with main focus on the QTc and on electrocardiogram signal quality in type 2 diabetes mellitus patients without cardiovascular disease, following oral administration of single ascending supratherapeutic doses of AZD1656	paper and digital electrocardiograms, telemetry, blood pressure, and pulse	Pharmacodynamic
To explore adrenaline and cortisol response in relation to plasma glucose levels in type 2 diabetes mellitus patients	Laboratory measurements of: adrenaline, and cortisol Adrenaline and cortisol: $AUC_{(0-6)}$, and $AUC_{(0-6)}/T$	Pharmacodynamic
To collect and store deoxyribonucleic acid samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to AZD1656	Not applicable	Pharmacogenetics

CSP clinical study protocol; dECG digital electrocardiogram; PD pharmacodynamic; PK pharmacokinetic; C_{max} maximum concentration in the plasma; t_{max} time to C_{max}; $AUC_{(0-t)}$ area under the plasma concentration-time curve from zero to the time

of the last measurable concentration; AUC area under the plasma concentration-time curve from zero to infinity; $t_{½\lambda z}$ terminal half-life, CL/F apparent oral clearance; PGX phamacogenetic

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

Study design

This was a Phase I, randomized, single-blind, placebo-controlled, single ascending dose study in type 2 diabetes mellitus male patients.

The starting dose was 150 mg, with 2 dose escalations (300 mg and 450 mg). Administration of the subsequent doses of AZD1656 was based on review of available safety data. After Cohort 2, and if necessary after Cohort 1, pharmacokinetic data from the previous dose was also reviewed. The maximum dose tested was 450 mg AZD1656. The doses were given as single doses staggered in the following way: 2 patients (1 on AZD1656 + 1 on placebo) on the first dosing occasion. The subsequent dosing occasion was 48 hours later, when 6 more patients (5 on AZD1656 + 1 on placebo) were dosed. After each cohort a Safety Review Committee assessed available data to make a decision on the next dose level.

Serial blood samples for pharmacokinetic evaluation were collected up to 48 hours postdose. Blood samples for pharmacodynamic measurements were collected from Day -1 up to 48 hours postdose for the glucose and up to 24 hours postdose for insulin and on Day 1 for adrenaline and cortisol. Glucose infusion rate, volume of glucose infused, and potassium concentrations were measured if glucose was infused due to hypoglycemia. Safety assessments (adverse events, blood pressure, pulse, weight, physical examination, safety laboratory variables, electrocardiogram, telemetry, and 7-point glucose measurements) were performed during the entire study.

Target subject population and sample size

Male type 2 diabetic patients without known cardiovascular disease, with the exception of Grade 1 hypertension without secondary organ involvement, 20 to 60 years (inclusive) of age with body mass index of greater than or equal to 19 and less than or equal to 35 kg/m^2, and a glycosylated hemoglobin type A1c less than 11%. Patients were to have been treated with 1 or 2 oral antidiabetic drugs as therapy for type 2 diabetes mellitus for at least 30 days prior to enrollment and had no change in the dose of these drugs during this period. The antidiabetic treatment(s) were to be washed out 7 days before randomization. Patients should not have been treated with glitazones within 6 months prior to enrollment.

Eighty patients were enrolled with 24 patients randomized. All 24 randomized patients completed this study.

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

AZD1656 (50-mg tablets), batch number/lot number 09-007135AZ/WK90574.003 was manufactured by AstraZeneca and administered orally in doses of 150 mg, 300 mg, and

450 mg. Placebo (film-coated tablet to match AZD1656), batch number/lot number 09003942AZ/WK90574.004 was manufactured by AstraZeneca and administered orally.

Duration of treatment

Each patient received a single oral dose of AZD1656 or placebo on Day 1.

Statistical methods

No formal statistical hypothesis testing was performed.

The analyses of safety, tolerability, pharmacokinetic, and pharmacodynamic data were summarized descriptively including tables, listings, and graphs, as appropriate.

Dose proportionality of AZD1656 pharmacokinetics was assessed graphically and analyzed using the power model approach with the logarithm of pharmacokinetic parameters AUC and C_{max} as the dependent variable and the logarithm of the dose as the independent variable. The α and β coefficients (log [AUC or C_{max}] = α + β log dose) together with confidence intervals (2-sided 95%) were estimated and presented for AUC and C_{max}.

Pharmacodynamic data were presented by dose group.

For insulin and glucose, an analysis of variance model was performed on delta ln-transformed AUC values (Day 1 ln AUC minus Day -1 ln AUC) for $AUC_{(0-4)}$/T and $AUC_{(0-24)}$/T with treatment group as a fixed effect. Geometric least-squares means, along with corresponding 95% confidence intervals, geometric least-squares means differences, associated 95% confidence intervals, and p-values were presented for treatment comparisons (each active versus placebo and each active versus each active). Results were transformed back to original value.

Subject population

A total of 24 patients were enrolled, randomized, and received investigational product. The first patient was enrolled on 22 October 2010 and the last patient completed on 14 January 2011. All 24 patients completed the study and were analyzed for safety and the pharmacokinetics of AZD1656 and its metabolite, AZD5658, as well and in the pharmacodynamic evaluation of glucose levels and insulin secretions.

The study population consisted of 24 males with type 2 diabetes mellitus, with a mean age of 50 years.

Summary of pharmacokinetic results

The PK parameters (t_{max}, $t_{1/2}$ and CL/F) for AZD1656 were generally similar across the 150- to 450 mg dose groups. The estimated median t_{max}, geometric mean $t_{1/2,}$ and geometric mean CL/F for AZD1656 was 2.75 hours, 4.45 hours and 8.56 L/h for the 150-mg dose group, 2.75 hours, 4.72 hours and 8.64 L/h for the 300-mg dose group and 2.50 hours, 5.64 hours and 10.2 hours for the 450-mg dose group, respectively.

The PK parameters (t_{max} and $t_{1/2}$) for AZD5658 were generally similar across the 150- to 450 mg dose groups. The estimated median t_{max} and the geometric mean $t_{1/2}$ for AZD5658 were 3.0 hours and 15.0 hours for the 150-mg dose group, 3.25 hours and 12.6 hours for the 300-mg dose group and 2.5 hours and 13.2 hours for the 450-mg dose group, respectively.

The statistical assessment of dose-proportionality of AZD1656 and AZD5658 following single dose oral administration of 150 mg, 300 mg, and 450 mg AZD1656 is presented in Table S2.

Table S2 Statistical analysis of dose proportionality of AZD1656 and AZD5658

Analyte	Parameter (unit)	n[a]	Slope Estimate (95%CI)	Intercept Estimate (95%CI)	Coefficient of determination
AZD1656	AUC (µmol*h/L)	18	0.86 (0.59, 1.12)	-0.67 (-2.15, 0.81)	0.7484
	C_{max} (µmol/L)	18	0.68 (0.33, 1.03)	-1.63 (-3.62, 0.35)	0.5116
AZD5658	AUC (µmol*h/L)	16	1.01 (0.50, 1.52)	-3.61 (-6.51, -0.71)	0.5589
	C_{max} (µmol/L)	18	0.90 (0.42, 1.39)	-5.31 (-8.03, -2.6)	0.4950

[a] The 'n' represents number of observations used in the model.
Source: Table 11.2.1.5.

The proportionality test does not reject that C_{max} and AUC of AZD1656 and AZD5658 are dose proportional for the 150 mg to 450 mg dose range. However, caution should be taken in the interpretation of the results as the study was not formally powered to perform hypothesis testing.

Summary of pharmacodynamic results

The glucose levels decreased in response to all doses of AZD1656. The reduction from baseline ranged from approximately 17% to 21% for $AUC_{(0-4)}/T$ and about 8% to 18% for $AUC_{(0-24)}/T$ across all the dose groups. The maximum decrease in mean glucose levels at a single time point post AZD1656 administration and across all dose groups was 4.28 mmol/L (77 mg/dL) at 5.5 hours for the 300-mg dose group. Statistical analysis of $AUC_{(0-4)}/T$ data suggests that there is a decrease in glucose levels from baseline following all doses of AZD1656 when compared to placebo; however, no specific trend in this response was observed when data was compared between the 150- to 450 mg dose groups. Similar results were observed for $AUC_{(0-24)}/T$.

The statistical analysis for $AUC_{(0-4)}/T$ suggests that there is an increase in insulin response with the 300-mg and 450-mg dose groups when compared to baseline and the increase was significant when 450-mg dose group was compared to placebo, however, no specific trend in the response was observed between the 150 to 450 mg dose groups. For $AUC_{(0-24)}/T$, the

increase in levels was significant for the the 300-mg and 450-mg dose groups when compared to the 150-mg dose group. Three patients (E0001019, E0001040 and E0001058) who received glucose infusion due to hypoglycemic events had high levels of insulin that could have contributed to the variability in the insulin data.

Similarly, for adrenaline and cortisol, the average response as measured by $AUC_{(0-6)}/T$ was similar between the dose groups with no particular trend being observed for the 150 to 450-mg dose groups. The 3 patients who received glucose infusion did not appear to have higher cortisol or adrenaline response when compared to the rest of the patients in their respective dose groups.

Summary of safety results

In general, AZD1656 given as 150-mg, 300-mg, and 450-mg single doses was well tolerated by the patients in this study. There were no deaths, serious adverse events, discontinuations due to adverse events, or any other significant adverse events during the study. Eleven adverse events were reported in 7 patients during the study and no single adverse event was reported by more than 1 patient. There were more adverse events reported in the patients receiving AZD1656 (6 patients, 33%) than those receiving placebo (1 patient, 16.7%). All adverse events were assessed as mild in intensity. Two patients (450 mg) reported 3 adverse events that were judged by the Investigator to be causally related to investigational product.

Three patients (1 in each of the 150-, 300-, and 450-mg groups) received glucose infusions for hypoglycemic events. The patients in the 300 mg and 450 mg groups were symptomatic; the patient in the 150-mg group was asymptomatic with a plasma glucose of 3.8 mmol/L (68.5 mg/dL).

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