AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00018
Edition Number	1
Date	4 September 2009

A Randomised, open, two-way Cross-over, Phase I Study to Evaluate the Response to Glucagon versus the spontaneous counter-regulatory response in T2DM Patients treated with AZD1656 and Metformin during hypoglycemia

Study dates: First subject enrolled: 03 February 2009
Last subject completed: 22 April 2009

Phase of development: Clinical pharmacology (I)

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

Study centre

The study was conducted at 1 centre, the Profil Institute for Clinical Research Inc., 855 3rd Avenue, Suite 4400, Chula Vista, CA 91911, USA.

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of the study was to compare the recovery from hypoglycaemia in a fasting state induced by a single oral dose of AZD1656 in T2DM patients on metformin treatment as induced by treatment with intramuscular glucagon versus spontaneous counter regulatory (CR) response. The recovery from hypoglycaemia was primarily assessed by the difference in plasma glucose levels between glucagon treatment and the control situation. As secondary pharmacodynamic variables time to recovery was measured.

Secondary objectives

The secondary objectives of the study were:

1. To describe safety and tolerability of AZD1656 in T2DM patients.

2. To evaluate pharmacokinetic (PK) properties of AZD1656.

3. To assess the response in glucose, C-peptide and insulin during hypoglycaemia in T2DM patients.

Exploratory objectives

1. To assess the CR response (norepinephrine, epinephrine, glucagon, cortisol and growth hormone) during hypoglycaemia in T2DM patients treated with metformin.

2. To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence drug response ie, distribution, safety, tolerability and efficacy of AZD1656 treatment.

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

Study design

This was a randomised, open, two-way cross-over phase I study, conducted in 1 centre. Eight (8) days before start of treatment with AZD1656, the enrolled subjects were switched to metformin tablets provided by the centre, but kept their regular treatment regimen. At the residential visit 3, AZD1656 was administered for 8 consecutive days. On day 1, subjects entered a 2-day titration phase starting with 40 mg AZD1656 bid on the first and 80 mg bid, if

tolerated, on the second day. Thereafter, the tolerated dose (40 or 80 mg bid), was maintained for 2 more days. On day 5 and day 8, each subject received, the total daily AZD1656 dose (80 mg or 160 mg) as a single dose in the morning after an overnight fast. Thereafter, plasma glucose (PG) was controlled over 3 hours at decreasing levels in a stepwise fashion by means of a hypoglycaemic clamp setting. After having reached the target PG nadir of 2.7 mmol/L for 30 minutes, the clamp was released at 3 hours post AZD1656 dosing. At the same time subjects either received an intramuscular (im) injection of 1 mg glucagon or were subjected to spontaneous recovery from hypoglycaemia. To avoid prolonged hypoglycaemia, a reversed clamp was applied from 4 to 6 hours post-dose to secure stepwise increasing minimum PG levels. On the two days between the clamps (day 6 and day 7) AZD1656 was maintained at the same bid dose as on day 3 and day 4.

Target subject population and sample size

Men and non-fertile women with T2DM treated with metformin participated in the study, and approximately 10 subjects were estimated to be randomized to achieve the goal of 8 subjects with evaluable data.

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

- AZD1656 oral suspension 25 mg/mL, batch number: 09-000729AZ

Duration of treatment

The IP was administered for 8 consecutive days: twice daily on 6 days and as a single dose on 2 days (ie, the clamp days).

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

Primary PD variables: PG level 20 minutes post release of the hypoglycaemic clamp, time (min) from release of the hypoglycaemic clamp to the time point where two consecutive PG levels are ≥3.5 mmol/L ($t_{3.5\ mmol/L}$), time (min) from release of the hypoglycaemic clamp to the time point where two consecutive PG levels are ≥5.0 mmol/L ($t_{5\ mmol/L}$).

Secondary PD variables: AUC_{0-6} of C-peptide, insulin and glucose in plasma.

Exploratory PD variables: AUC_{0-6} of norepinephrine, epinephrine, glucagon, cortisol and growth hormone in plasma.

PK variables: AZD1656 and metabolite AZ12555623 concentration in plasma: AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$ (only AZD1656), CL/F (only AZD1656), quotient AZ12555623/AZD1656 for AUC_{0-24} and C_{max}.

Criteria for evaluation - safety (main variables)

Adverse events (AEs), safety laboratory tests, 7-point PG profiles, physical examination, electrocardiogram (EGG), vital signs, weight.

Statistical methods

The primary and secondary PD variables were, after log-transformation, analysed with a mixed-effects ANOVA model, where treatment, period and sequence were taken as fixed effects and subject within sequence as a random effect. An exception was the analysis of the primary variable PG 20 min post clamp release, where no log-transformation was made. Within the model, LS-means per treatment and the difference between the means were determined and analysed using Fisher's Least Significance Difference test (LSD). The individual differences between the two treatments for $t_{3.5\ mmol/L}$ and $t_{5\ mmol/L}$, respectively, were analysed by using a two-sided pairwise Wilcoxon's Signed Rank test. In addition, the shift estimate of Hodges and Lehmann was derived for the differences, together with a 95% confidence interval. PK variables were analysed in the same ANOVA model as used in the PD analysis, and for differences in t_{max} the same non-parametric method was used. All statistical tests were two-sided with the significance level 0.05. No alpha-adjustment was made. Safety variables were summarised by means of descriptive statistics.

In all PD analyses, AUCs were standardised to 1 hour. For evaluation of AUC_{0-24} and C_{max} of AZD1656 and metabolite AZ12555623 doses were normalised to 100 mg (AUC_{0-24}) and 50 mg (C_{max}).

Subject population

In total 42 subjects were enrolled, 11 started the AZD1656 treatment before randomisation, and 3 discontinued before randomisation. The remaining 8 subjects (7 men and 1 woman, mean (±SD) age 58.6±11.7 years and BMI 28.08±3.84) were randomised to one of the two treatment sequences. Due to the outcome of the dose titration, 3 subjects received 40 mg AZD1656 bid and 5 subjects 80 mg bid during the maintenance period and received a single dose of 80 mg or 160 mg AZD1656, respectively, on day 5 and day 8. All subjects received metformin bid; administered total daily doses ranged from 1000 to 2250 mg. All subjects randomised to treatment completed the study. The safety analysis set comprised 11 subjects (ie, all subjects who had received at least one dose of AZD15656) and the PD and the PK analysis set consisted of 8 subjects (ie, all randomised subjects).

Summary of pharmacodynamic results

Mean PG at 20 minutes after release of the hypoglycaemic clamp was lower for AZD1656 alone compared to AZD1656+glucagon (estimate -37%, 95% CI [-49% to -25%], $p<0.001$). Median $t_{3.5\ mmol/L}$ (calculated from clamp release) as well as median $t_{5\ mmol/L}$ was longer for AZD1656 alone than for AZD1656+glucagon (37 vs 10 min and 122 vs 23 min, $p=0.008$ for both comparisons).

Geometric mean AUC_{0-6}s of C-peptide and insulin were smaller (estimate C-peptide -16%, 95% CI [-27% to -4%], $p=0.017$; estimate insulin -19%, 95% CI [-30% to -7%], $p=0.010$) for the AZD1656 alone compared to the AZD1656+glucagon treatment. Geometric mean PG AUC_{0-6}, as determined from bedside measurements with the YSI analyser, was also smaller (estimate -22%, 95% CI [-26% to -18%], $p<0.001$) for AZD1656 alone than for the AZD1656+glucagon treatment.

Geometric mean AUC_{0-6}s of norepinephrine, epinephrine and cortisol were similar for both treatments. Geometric mean glucagon AUC_{0-6} was distinctly smaller (estimate -72%, 95% CI [-75% to -67%], $p<0.001$) for AZD1656 alone compared to the AZD1656+glucagon treatment. Geometric mean growth hormone AUC_{0-6} was moderately smaller (estimate -18%, 95% CI [-29% to -7%], $p<0.010$) for AZD1656 alone than for the AZD1656+glucagon treatment.

Summary of pharmacokinetic results

AZD1656 was rapidly absorbed (C_{max} reached within 1 hour for most subjects, median t_{max}=1 h) and rapidly eliminated with a geometric mean terminal elimination half-life of about 4 hours. The geometric mean apparent oral clearance (CL/F) of AZD1656 was 8-9 L/h. There was no statistically significant difference in any of the analysed AZD1656 PK parameters between the two treatments.

AZ12555623 concentrations peaked slightly later than the parent compound AZD1656 (C_{max} reached within 1.5 hours for most subjects, median t_{max}=1.5 h). There was no statistically significant difference in any of the analysed AZ12555623 PK parameters between the two treatments.

Geometric mean ratios were 0.16 (AZD1656) and 0.17 (AZD1656+glucagon) for AUC_{0-24} and 0.10 and 0.11 for C_{max}, respectively. Thus the exposure to the metabolite was about 1/6 that to AZD1656, based on AUC_{0-24}, and about 1/10, based on C_{max}. There was no statistically significant difference in any of the analysed AZ12555623/AZD1656 ratios between the two treatments.

Summary of safety results

Five (5) subjects (45.5%) experienced at least one AE during the titration/maintenance period of the study. One (1) subject experienced at least 1 adverse event (AE) during the clamp period with AZD1656 alone and 3 during the clamp period with AZD1656+ glucagon. One (1) subject experienced at least 1 AE during the recovery period (ie, the 2 days between the 2 clamp sessions) and 2 subjects during the follow-up period. There were no deaths, premature discontinuations due to adverse events (DAEs) or other significant adverse events (OAEs). One (1) serious adverse event (SAE) was reported during the clamp period with AZD1656+glucagon (short episode of ventricular tachycardia, captured by telemetry 49 minutes after glucagon injection and release of the clamp and assessed as mild and possibly related to the IP by the investigator). In total 13 AEs were reported during the entire study and in their majority they were of mild intensity. The most frequent AE was headache, reported by 3 subjects during the titration/maintenance period and by 1 subject during the AZD1656+glucagon clamp session.

There were no clinically relevant changes or trends observed in laboratory variables, vital signs, weight, 7-point PG profiles, 12-lead ECG or physical examination findings.