AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00015
Edition Number	1
Date	18 October 2010

A Randomised, Single-Blind, Placebo-Controlled, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics after Multiple Oral Doses of AZD1656 in Subjects with T2DM Treated with Metformin

Study dates: First patient enrolled: 13 October 2008
Last patient last visit: 07 January 2010

Phase of development: Clinical pharmacology (I)

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

Study centres

This study was conducted at 2 study centres: ICON Development Solutions, LLC, San Antonio, TX, USA and Veeda Clinical Research Pvt. Ltd, Ahmedabad, Gujarat, India.

Publications

None at the time of writing this report.

Primary objective

To assess the safety and tolerability after oral repeated doses of AZD1656 in patients with Type 2 Diabetes Mellitus (T2DM) treated with metformin.

Secondary objectives

- To evaluate pharmacokinetics (PK) of AZD1656 after repeated oral doses in patients with T2DM treated with metformin by calculation of area under the plasma concentration curve (AUC_{0-24}), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}) and elimination half-life ($t_{1/2}$)

- To evaluate PK of metformin after repeated oral doses with AZD1656 in patients with T2DM by calculation of area under the plasma concentration curve (AUC_{0-9}), C_{max}, t_{max} and $t_{1/2}$

- To evaluate glucose and endogenous insulin levels and insulin secretion after administration of repeated oral doses of AZD1656 in patients with T2DM treated with metformin

Study design

This was a randomised, single-blind, placebo-controlled, phase I study in 26 (17 AZD1656 + 9 placebo) T2DM patients treated with metformin alone or metformin and 1 other anti-diabetic drug. All patients continued their background metformin treatment (unchanged daily dose) during the treatment period; any oral anti-diabetic drug other than metformin was stopped 8 days before the start of treatment with investigational product (IP).

Target patient population and sample size

The target patient population included male or female patients of non-childbearing potential diagnosed with T2DM. The sample size was not based on statistical considerations. The number of patients included was considered sufficient for an initial evaluation of tolerability and safety during titration of AZD1656 on top of metformin.

Investigational product: dosage, mode of administration and batch numbers

The details of the IP are given in Table S1.

Table S1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form and strength	Manufacturer	Batch number[a]
AZD1656	Oral suspension 2 mg/mL	AstraZeneca R&D	H 2000-01-01
AZD1656	Oral suspension 25 mg/mL	AstraZeneca R&D	H 2001-01-01
AZD1656	Oral suspension Placebo	AstraZeneca R&D	H 2002-01-01
Metformin[b]	Oral administration 500 mg tablet as metformin hydrochloride (Glucophage®)	Merck Sante, France or Inpac AB, Sweden	H 1605-01-01-11

[a] Batch numbers are not required for non-investigational product/test drug.
[b] Information pertains to metformin provided at the India site.

The dose was titrated in each patient based on glucose response. The starting dose of AZD1656 was 5 mg bd with the possibility of increases to 12.5 mg bd and 25 mg bd, to a maximum dose of 50 mg bd.

Eleven (11) of the 17 patients treated with AZD1656 received 50 mg bd and 6 patients received the lower doses, 2 patients in each dose level.

Duration of treatment

Each patient was treated with AZD1656 or placebo bd for 10 days including 4 days of dose titration and 6 days of dose maintenance.

Criteria for evaluation (main variables)

Adverse events (AEs), blood pressure (BP), pulse, weight, physical examination, plasma glucose, safety laboratory variables and electrocardiogram (ECG).

AZD1656, AZD5658[1]: AUC_{0-24}, C_{max}, t_{max} and $t_{1/2}$

Metformin: AUC_{0-9}, C_{max}, t_{max} and $t_{1/2}$

24-hour P-glucose, 24-hour S-insulin, and 24-hour S-C-peptide (Days -1, 5 and 10): AUC_{0-24}

[1] Two different development codes (AZD5658 and AZ12555623) are used for the same active metabolite to AZD1656 as a consequence of changes in AstraZeneca's internal system of substance coding. In this document, the metabolite is referred to as AZD5658.

Statistical methods

No formal statistical analysis of the safety parameters was performed. Patient listings and summary statistics including mean, median, standard deviation (SD), minimum and maximum and graphs were used, as appropriate.

The $AUC_{0-24}/24$ of 24-hour P-glucose, S-insulin, and S-C-peptide were used to address the secondary objective of evaluating glucose, endogenous insulin levels, and insulin secretion after administration of repeated oral doses of AZD1656 in patients with T2DM treated with metformin.

All PD parameters were $\log_e$-transformed prior to statistical analysis. The response variable was the difference between the $\log_e$-transformed $AUC_{(0\ 24)}/24$ value during IP treatment and the $\log_e$-transformed $AUC_{0-24}/24$ baseline value (Day -1), and were compared between Test Treatment (AZD1656) and Reference Treatment (Placebo) on Days 5 and 10 using a mixed effects analysis of covariance.

Patient population

In total, 70 patients were enrolled, 47 met eligibility criteria at screening, 26 were randomised (19 males and 7 female patients at 2 study sites), and 23 of the 26 randomised patients completed the study.

Summary of pharmacokinetic results

The geometric mean dose-adjusted values for C_{max} and AUC_{0-24} of AZD1656 were 4.514 µmol/L and 44.39 µmol*h/L, respectively. The inter-individual variability in dose-adjusted exposure (AUC_{0-24} and C_{max}) of AZD1656 was moderate with a coefficient of variation of approximately 40%. The apparent terminal half-life ($t_{1/2}$) of AZD1656 was approximately 5 hours.

The geometric mean dose-adjusted values for C_{max} and AUC_{0-24} of AZD5658 were 0.5440 µmol/L and 6.774 µmol*h/L, respectively. The inter-individual variability in dose adjusted exposure (AUC_{0-24} and C_{max}) of AZD5658 was higher than that of AZD1656 with a coefficient of variation of approximately 80% for AUC_{0-24} and 65% for C_{max}. Due to the nature of the AZD5658 profiles as collected in this study, the criteria for $t_{1/2}$ calculation were met for only 3 patients.

The apparent terminal half-life ($t_{1/2}$) of metformin was approximately 4.0 hours for both AZD1656-treated and placebo patients. The exposure (AUC_{0-9} and C_{max}) of metformin was similar on Day -1 and Day 10 for placebo patients as well as for the AZD1656-treated patients. When comparing the C_{max} and AUC_{0-9} of metformin on Day 10 (AZD1656 + metformin) with Day -1 (metformin alone), the corresponding 90% CIs of the geometric mean ratio (GMR) included 1 (GMR [90% CI] for AUC_{0-9}: 0.981 [0.890 – 1.082]; C_{max}: 0.980 [0.885 – 1.086]), confirming that repeated doses of AZD1656 did not have a statistically significant impact on the C_{max} and AUC_{0-9} of metformin.

Summary of pharmacodynamic results

At baseline (Day -1), the arithmetic mean 24-hour P-glucose ($AUC_{0-24}/24$) for the AZD1656 group was 9.029 (± 1.336) mmol/L and 9.700 (± 2.570) mmol/L in the placebo group. For 24-hour P-glucose, a statistically significant reduction was observed in the AZD1656 group on both Days 5 (GMR [95% CI]: 0.774 [0.707 – 0.847]) and 10 (0.797 [0.728 – 0.872]) compared to Day -1. The AZD1656 group had a nearly 20% reduction in P-glucose as compared to the placebo group at Day 5 (0.806 [0.691 – 0.939]), but differences between groups were not statistically significant at Day 10 (0.879 ([0.753 – 1.024]).

At baseline (Day -1), the arithmetic mean 24-hour S-insulin ($AUC_{0-24}/24$) for the AZD1656 group was 20.845 (± 8.673) µIU/mL and 23.111 (± 12.283) µIU/mL in the placebo group. For 24-hour S-insulin, a statistically significant reduction was observed in the AZD1656 group on Day 10 compared to Day -1 (GMR [95% CI]: 1.220 [1.020 – 1.458]). However, there were no changes in S-insulin levels on Day 5 when compared with Day -1. No statistically significant differences were seen within the placebo group or when comparing the treatment groups at Days 5 and 10.

At baseline (Day -1), the arithmetic mean 24-hour S-C-peptide ($AUC_{0-24}/24$) for the AZD1656 group was 4.833 (± 2.163) ng/mL and 4.880 (± 1.577) ng/mL in the placebo group. No statistically significant differences were observed for either treatment group when comparing results on Day 5 and Day 10 with Day -1. There were also no significant differences between treatment groups on Day 5 or Day 10.

The arithmetic pre-treatment fasting P-glucose for the AZD1656 group was 8.76 (±2.06) mmol/L and 8.32 (±1.23) mmol/L in the placebo group. For fasting P-glucose, a statistically significant reduction was observed in the AZD1656 group at end-of-treatment compared to pre-treatment (GMR [95% CI]:0.823 [0.748 – 0.905]). There were no statistically significant differences between pre-treatment and end-of-treatment for placebo patients or between treatment groups.

Summary of pharmacokinetic/pharmacodynamic relationships

Not evaluated.

Summary of safety results

No deaths, serious AEs, or other significant AEs were reported. No clinically relevant trends were observed in clinical laboratory results, ECGs, or vital signs. The most common AEs were application site rash and headache. No patients met the discontinuation criteria for a hypoglycaemic event.

One patient in the AZD1656 treatment group experienced an AE that led to discontinuation of IP on Day 9 when the patient fulfilled the study-specific discontinuation criterion for hyperglycaemia. This patient was incorrectly randomised with a fasting P-glucose above the eligibility limit.