AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00017
Edition Number	1
Date	09 October 2009

A Randomised, Two Way Cross-over, Single-Blind, Phase I Study to Evaluate 24-hour Glucose Profiles in Patients with T2DM when Dosed OD and BD on Top of Metformin for Four Days with AZD1656

Study dates:	First subject enrolled: 30 January 2009 Last subject completed: 02 May 2009
Phase of development:	Phase 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 1 centre: Healthcare Discoveries, LLC (d/b/a ICON Development Solutions, LLC), San Antonio, Texas, USA.

Publications

None at the time of writing this report.

Objectives

The primary objective was to compare the 24-hour glucose profiles in type 2 diabetes mellitus (T2DM) patients treated with metformin following once daily (OD) and twice daily (BD) oral dosing, respectively, of AZD1656 during 4 days.

Secondary objectives

To describe the safety and tolerability of AZD1656 in T2DM patients treated with metformin after OD and BD oral dosing

To evaluate the pharmacokinetics (PK) of AZD1656 and the metabolite, AZ12555623, after OD and BD oral dosing in T2DM patients treated with metformin

To evaluate S-insulin and C-peptide 24-hour profiles and fasting plasma glucose (FPG) after OD and BD oral dosing of AZD1656 in T2DM patients treated with metformin.

Exploratory objective

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

Study design

This was a randomised, 2-way cross-over, single-blind study designed to evaluate 2 different oral dosing regimens of AZD1656 (OD versus BD) in 12 T2DM patients (henceforth called subjects). To ensure blinding between dosing regimens, subjects were administered a placebo suspension at the evening administration during the OD regimen. All subjects were treated with metformin from at least 1 month before enrollment and throughout the study. In total, 36 subjects were enrolled, 12 were randomised, and 11 completed the study.

A pre-entry screening visit took place within 28 days of study Day 1. Eligible subjects came back to receive metformin at the dispensation visit. During a 10-day in-patient period, subjects were given AZD1656 80 mg OD for 4 days and 40 mg BD for 4 days in a randomised order, (OD > BD or BD > OD) in addition to their metformin treatment. A follow-up visit was conducted 7 to 10 days after the last dose.

Target population and sample size

Male and female T2DM subjects treated with metformin as a single pharmacological anti-diabetic treatment, 30 to 75 years of age, and with a body mass index ≥19 and ≤40 kg/m^2.

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

The details of the investigational products are given in Table S1.

Table S1 Details of investigational product and other study treatments

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD1656	Oral suspension 25 mg/mL	AstraZeneca R&D	H 2001-01-01	09-000792
AZD1656 Placebo	Oral suspension	AstraZeneca R&D	H 2002-01-01	09-000791

Duration of treatment

AZD1656 oral suspension was administered in 2 different dosing regimens, 80 mg OD (in the morning) for 4 days, and 40 mg BD (once in the morning and 9 hours later) for 4 days.

Criteria for evaluation (main variables)

Primary PD variable: area under the effect curve (AUEC) divided by time (AUEC/T) for 24-hour glucose profiles.

Secondary PD variables: AUEC/T for 24-hour S-insulin and C-peptide profiles, and FPG.

Secondary PK variables: Area under the plasma concentration time curve from time zero to 24 hours (AUC_{0-24}), maximum concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), apparent terminal half-life ($t_{½}$), and oral clearance (CL/F) for AZD1656, and AUC_{0-24}, C_{max} and t_{max} for AZ12555623. PK variables were calculated for Days 4 and 8 by non-compartmental analysis.

Safety: assessment of AEs during the study; blood pressure; pulse; safety laboratory variables (including P-glucose); and electrocardiograms (ECG).

Statistical methods

All main variables were presented with descriptive statistics for all subjects. A mixed effect analysis of variance (ANOVA) model was performed on primary and secondary PD variables. A pairwise comparison was made between baseline (BL), OD, and BD, and statistical estimates were presented.

Subject population

In total, 36 subjects were enrolled, and 6 white males and 6 white female subjects were randomised into the study at 1 study site. Eleven (11) of the 12 randomised subjects completed the study. Subjects received 2 different dosing regimens: 80 mg once in the morning for 4 days, and 40 mg BD (once in the morning and once 9 hours later) for 4 days during the planned treatment visit. Subject E0001005 voluntarily withdrew consent to continue study participation after receiving the first 3 days of the 80 mg OD regimen. This female subject had only 1 predose sample collected for the PK analysis and only 3 full days of collections for pharmacodynamic (PD) analysis; therefore, the subject was included in the safety analysis set, but not in the PK or PD analysis sets.

Summary of PK results

AZD1656 was absorbed following both the 40 mg BD and 80 mg OD regimens. The 80 mg OD regimen demonstrated a higher C_{max} than the 40 mg BD regimen. AZD1656 is metabolised to the metabolite AZ12555623, and its t_{max} occurred at approximately the same time as the t_{max} for AZD1656. The majority of AZD1656 plasma concentrations versus time profiles showed a single peak following the 80 mg OD and 2 peaks following 40 mg BD. Most subjects had AZ12555623 plasma concentration versus time profiles with 2 peaks; however, 1 subject (Subject E0001022) did not show a second peak at the time of the second dose. Moreover, for both Subjects E0001028 and E0001034, plasma concentration profiles for AZ12555623 showed 2 peaks following the 80 mg OD dosing.

Summary of PD results

For the primary study endpoint (P-glucose AUEC/T), the 95% confidence interval (CI) of the geometric mean ratio (GMR) for 40 mg BD/BL and 80 mg OD/BL comparisons did not include 1, suggesting that AZD1656 dosing affected 24-hour glucose profiles. However, for C-peptide and S-insulin levels, the GMRs for 40 mg BD/BL and 80 mg OD/BL comparisons were close to 1 and the corresponding 95% CIs included 1, suggesting that AZD1656 dosing did not affect the endogenous production of C-peptide nor S-insulin. The 95% CIs for the GMRs of P-glucose, S-insulin, and C-peptide AUEC/T 40 mg BD/80 mg OD comparison included 1 and the GMRs were close to 1, indicating that both the 40 mg BD and 80 mg OD regimens resulted in a similar effect on P-glucose, S-insulin, and C-peptide levels.

Summary of safety results

There were no deaths, SAEs, discontinuations of IP due to AEs, or other significant AEs in the study. There was no difference in the occurrence of AEs between the 2 treatment regimens. All AEs were evaluated as mild. There were no clinically relevant trends in clinical laboratory results, ECGs, or vital signs. A number of subjects had glucose levels in this study that were low, and 2 subjects had 6 low plasma glucose levels reported as AE; however, all these AEs were of mild severity.

Overall, the treatment regimens were similar with regard to efficacy and safety. Of note, there was a trend towards lower glucose levels with the BD dosing regimen, eg, the estimated geometric means of FPG following 80 mg OD and 40 mg BD oral regimens were 6.60 mmol/L and 6.36 mmol/L, respectively. However, these differences did not achieve statistical significance. Moreover, the higher C_{max} of AZD1656 following the 80 mg OD regimen indicates a higher risk for hypoglycaemia, although the events were few in this study, and no firm conclusions of a difference can be drawn from the 2 subjects who had 6 AEs of low plasma glucose reported during the in-patient period.