AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00010
Edition Number	1
Date	02 March 2010

A Randomised, Open, Single-Dose, Single-Centre, Cross-Over, Phase I Study in Type 1 Diabetes Mellitus Patients to Estimate the Extent and Rate of Absorption of AZD1656 After Administration of a Tablet Formulation in the Fasting State and Just Before Food in Comparison with an Oral Suspension of AZD1656 in the Fasting State and an Exploratory Part to Evaluate the Glucokinase Effect in the Liver

Study dates: First patient enrolled: 29 December 2008
Last patient completed: 30 September 2009

Phase of development: Clinical 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, San Antonio, Texas, USA

Publications

There were no publications at the time of writing this report.

Objectives

The primary objective was to measure the extent and rate of absorption of AZD1656 administered as an immediate release (IR) tablet fasting and just before food and as an oral suspension in the fasting state in type 1 diabetes (T1DM) patients.

The secondary objective was to study/describe the safety and tolerability of AZD1656 administered as an IR tablet formulation and an oral suspension of AZD1656 by assessment of adverse events (AEs), blood pressure (BP), pulse, electrocardiogram (ECG), and laboratory variables in T1DM patients.

Exploratory objectives:

To explore the effect of glucokinase (GK) activation in the liver in T1DM patients

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

Study design

This was a randomised, open, single-centre, crossover study designed to compare the extent and rate of absorption of AZD1656 after administration as a tablet and an oral suspension in the fasting state and after administration of a tablet just prior to a standard meal (American Diabetes Association guidelines: 50% to 60% of calorie intake to come from carbohydrates, 15% to 20% from protein and 20% to 25% from fat).

In total, 12 evaluable patients were given either a tablet formulation of AZD1656 administered in the fasting state or just prior to food, or AZD1656 as a suspension administered in the fasting state. All 11 completed patients received all 3 treatments in a cross-over design with at least 72 hours of wash-out after the treatment periods. Eleven (11) patients also participated in a fourth exploratory visit when no investigational product (IP) was given to assess how the glucokinase activator (GKA) affected the liver.

Target population and sample size

Healthy male and female patients aged between 20 years to 45 years with T1DM. No formal determination of sample size was done.

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	Batch number
AZD1656	Tablets 45 mg	AstraZeneca R&D	H2001-01-01-03
AZD1656	Oral suspension 25 mg/mL	AstraZeneca R&D	J2080-01-01-01

Duration of treatment

Single dose.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{½}$, λ_z, and CL/F for AZD1656 and AUC, AUC_{0-t}, C_{max}, t_{max}, $t_{½}$, and λ_z for the primary metabolite, AZD12555623.

$AUEC_{0-4}$, $C_{max/glucose}$, and $t_{max/glucose}$ for plasma glucose (P-glucose).

Criteria for evaluation - safety (main variables)

Assessment of AEs during the study; BP; pulse; body weight; safety laboratory variables (including P-glucose); and ECG.

Statistical methods

All variables are presented with descriptive statistics for all patients.

Patient population

The first patient was randomised on 04 March 2009 and the last patient finished the study on 30 September 2009. In total, 65 patients were enrolled, and 10 male and 2 female patients were randomised into the study at 1 study site. Eleven (11) of the 12 randomised patients completed the study. Patients received 4 different dosing regimens: 90 mg AZD1656 tablet once in the morning without food (treatment A); 90 mg AZD1656 tablet once in the morning with food (treatment B); 90 mg AZD1656 suspension once in the morning without food (treatment C); and a control treatment in a fed state (treatment D). Patient E0001050 (treatment sequence CBAD) voluntarily withdrew consent to continue study participation after checking in for the period A visit 3. No PK samples were drawn for this patient for period A, therefore PK data was available for all 12 patients for periods B and C, but only 11 patients for period A.

Summary of pharmacokinetic results

Single dose administration of the tablet and oral suspension formulations under fasting conditions resulted in comparable overall exposure to both AZD1656 and its metabolite, AZ12555623. Under fasting conditions, the total systemic exposure to the metabolite AZ12555623 was approximately 11.3% (suspension) to 14.4 % (tablet) of the AZD1656 exposure. Further, under fasting conditions, peak concentrations of AZD1656 following intake of the tablet formulation were on average 17% lower than those observed for the suspension formulation, and t_{max} was observed later for the tablet compared to the oral suspension.

Administration of the tablet formulation under fed conditions resulted in a 24% increase in peak AZD1656 concentrations, and t_{max} was observed much earlier than under fasting conditions. However, the overall exposure of AZD1656 was not affected by administration of the tablet formulation with food. Similar results were observed for the metabolite AZ12555623.

The mean estimated elimination $t_{½}$ of the metabolite AZ12555623 (approximately 18 hours), was much longer compared to the half-life of the parent compound (3.7 hours to 4.3 hours). The estimated elimination $t_{½}$ for AZD1656 following the suspension formulation was 2.6 hours to 4.8 hours.

Summary of pharmacodynamic results

In this T1DM patient population in which insulin therapy was omitted on the morning of the study day during all 3 treatments and the exploratory period, an increase in P-glucose levels compared to baseline was observed for all 3 treatments as well as in exploratory period. Overall, the increase in P-glucose was less in patients who received AZD1656 under fasted conditions (tablet or suspension) compared to the fed conditions (with tablet or with food alone). $AUEC_{0-4}$ for P-glucose following food alone was 19% lower than that following the tablet formulation under fed conditions (estimated GMR = 80.59%, 95% CI = 66.33% to 97.90%).

Summary of safety results

There were no deaths, SAEs, discontinuations of IP due to AEs, or other significant AEs in the study. Most AEs were evaluated as mild in severity. There were no clinically relevant trends in clinical laboratory results, ECGs, or vital signs. A number of patients had glucose levels in this study that were low, and 2 patients had 5 low P-glucose levels reported as an AE.