AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00012
Edition Number	1
Date	2 July 2009

A Randomized, Open, Two-Way Cross-Over, Single-Centre, Phase I Study to Assess the Counter Regulatory Response during Hypoglycaemia in Healthy Male Volunteers after a Single Oral Dose of AZD1656 Suspension in Comparison with Insulin Infusion

Study dates: First healthy volunteer enrolled: 03 November 2008
Last healthy volunteer completed: 17 February 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 assess the counter regulatory response (glucagon, epinephrine, norepinephrine, growth hormone and cortisol) during hypoglycaemia in healthy male volunteers after a single oral dose of AZD1656 in comparison with insulin infusion.

Secondary objectives

The secondary objectives of the study were:

1. To describe safety and tolerability of AZD1656 after a single oral dose.

2. To evaluate pharmacokinetic (PK) properties of AZD1656 after a single oral dose.

3. To assess the response in C-peptide, insulin and free fatty acids (FFA) during hypoglycaemia in healthy male volunteers after a single oral dose of AZD1656 in comparison with insulin infusion.

Exploratory objectives

1. To evaluate effect of AZD1656 on incretin plasma levels in terms of glucagon-like-peptide-1 (GLP-1) and gastric inhibitory peptide (GIP).

2. To collect and store deoxyribonucleic acid (DNA) samples for potential future research into genes which may influence drug response i.e. drug disposition (PK profile), efficacy, safety and tolerability 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 designed to compare the hormonal counter regulatory response during hypoglycaemia after a single oral dose of AZD1656 suspension and insulin infusion during a hypoglycaemic clamp where the glucose levels were lowered stepwise. Glycaemic plateaus of 5 mmol/L (for 60 min), 4 mmol/L (for 30 min), and 3.2 mmol/L (for 60 min) were maintained by glucose infusion. Plasma glucose was then clamped to a nadir of 2.7 mmol/L (for 30 min) and released at 180 min, followed by

a subsequent recovery period of 1 hour, during which blood glucose was allowed to increase to the euglycaemic range.

Target healthy volunteer population and sample size

The study was to be conducted in male healthy volunteers, aged between ≥20 and ≤45 years and with a body mass index (BMI) of ≥19 and ≤30 kg/m^2 (during the study lowered to 26 kg/m^2 by Amendment 3 to the study protocol). The inclusion and exclusion criteria were defined such that healthy volunteers apparently free from any significant illness could be selected. The planned number of evaluable healthy volunteers in this study was 12, which was considered sufficient to evaluate tolerability and safety.

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

AZD1656 oral suspension 25 mg/mL, batch number: H 2001-01-01-02, and regular human insulin solution for injection, 100 IU/mL, intravenous infusion of 1 mIU/kg/min. The first 2 healthy volunteers received an AZD1656 dose of 40 mg; the remaining healthy volunteers received 80 mg. Regular human insulin was given as a fixed-rate infusion of 1 mIU/kg/min during 180 minutes. The insulin infusion rate could be increased to 1.25 mIU/kg/min if a subject reached a plateau at a plasma glucose level above the target level of 2.7 mmol/L (±10%) for ≥10 minutes. Amendment 2 added a supporting fixed rate iv insulin infusion (1.25 mIU/kg/min) starting 15 minutes before the end of the 3.2 mmol/L plateau to the AZD1656 treatment. Amendment 3 introduced a supporting iv insulin infusion, added to the AZD1656 treatment and starting when there were no further declines in glucose values for at least 10 minutes before achieving either the 3.2 mmol/L or the 2.7mmol/L plateau. For both study arms the initial insulin infusion rate should be at 1 mIU/kg/min and was to be increased as necessary to achieve the nadir of a plasma glucose level of 2.7 mmol/L.

Duration of treatment

One single oral dose of AZD1656 (plus supporting insulin infusion) and an insulin infusion over180 minutes, separated from each other by a wash-out period of at least 2 weeks.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

Primary PD variables: Glucagon, epinephrine, norepinephrine, growth hormone and cortisol concentration in plasma.

Secondary PD variables: C-peptide, insulin and FFA concentration in serum.

Exploratory PD variables: Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) concentration in plasma.

PK variables: AZD1656 and metabolite AZ12555623 concentration in plasma; derived parameters AUC, C_{max}, t_{max}, $t_{1/2}$, and CL/F.

Pharmacogenetics (exploratory): DNA samples to for potential future research on pharmacogenetic biomarkers.

Criteria for evaluation - safety (main variables)

Adverse events (AEs), safety laboratory tests, physical examination, electrocardiogram (EGG), vital signs, weight, hypoglycaemic symptoms.

Statistical methods

For the primary PD variables, the comparison AZD1656 vs insulin infusion was done by fitting a mixed analysis of covariance (ANCOVA) model to data. Secondary PD variables were analysed in the same manner, except for FFA, where baseline FFA was not included as a covariate in the mixed model. Safety variables were summarised by means of descriptive statistics. Geometric means together with confidence intervals were calculated for the derived PK parameters.

Subject population

In total 28 healthy volunteers were enrolled, 19 were randomised and received at least one of the study treatments, thus constituting the safety analysis set. Within this analysis set, 16 subjects received AZ1656 and 17 the insulin infusion. Apart from the 2 subjects dosed with 40 mg ADZ1656 and 2 of the subjects dosed with 80 mg (both discontinued), all AZD1656-treated subjects received a supporting insulin infusion. Five (5) of the 19 randomised healthy volunteers prematurely discontinued the study on sponsor's decision (because of inability to reach hypoglycaemic targets) so that 14 were study completers. Two (2) of these completers (the 2 subjects dosed with 40 mg AZD1656) were considered as protocol violators since they did not reach the predefined target plasma glucose level of 2.7 mmol/L, and were therefore excluded from the PD/PK analyses. Thus, the PD and PK analysis set consisted of 12 subjects. Overall, the treatment sequence groups were well balanced with regards to demography and baseline characteristics.

Summary of pharmacokinetic results

AZD1656 was generally rapidly absorbed and eliminated. Median t_{max} was 0.88 hours (range: 0.5 to 5.0 hours) and mean oral plasma clearance (CL/F) (±SD) was 9.4±3.3 L/h. Mean terminal half-life ($t_{1/2}$) was 3.00±0.60 hours. Mean C_{max} was 3.87±0.75 µmol/L, mean total AUC was 19.6±5.69 µmol*h/L.

The active metabolite AZ12555623 reached C_{max} at approximately the same time as AZD1656. The initial decline in AZ12555623 was virtually parallel to the decline in AZD1656, but AZ12555623 had a slower terminal elimination phase. Median t_{max} was 0.88 hours (range: 0.5 to 5.0 hours) and mean terminal $t_{1/2}$ 7.33±1.59 hours. Mean C_{max} of AZ12555623 (0.34±0.11 µmol/L) was about 1/10 that of AZD1656 and mean overall exposure to the metabolite (AUC: 2.50±1.38 µmol*h/L) was markedly lower (about 1/8) than the exposure to AZD1656.

Summary of pharmacodynamic results

The counter regulatory response as measured by epinephrine, norepinephrine, growth hormone and cortisol was independent of the origin of the hypoglycaemia (ie, there were no statistically significant differences between the respective AUCs of the AZD1656 and the insulin treatment). However, glucagon was significantly lower for AZD1656 than for insulin (estimate -31%, left-sided 95% CI [-infinity to -20%], one-sided p=0.001).

C-peptide was significantly greater with AZD1656 than with insulin infusion (estimate 461%, 95% CI [349% to 600%], p<0.001). Insulin levels were increased by the insulin infusion during the hypoglycaemic clamp. Insulin was significantly lower for AZD1656 than for insulin infusion (estimate -39%, 95% CI [-50% to -26%], p<0.001). Free fatty acids were significantly greater for AZD1656 than for insulin (estimate 109%, 95% CI [57% to 179%], p<0.001).

Summary of safety results

No safety or tolerability signals were observed in this study. Fifteen subjects (94%) experienced at least 1 adverse event (AE) during study sessions with oral AZD1656 suspension and 12 (71%) during study sessions with insulin infusion. There were no deaths, other serious adverse events (SAEs), premature discontinuations due to adverse events (DAEs), or other significant adverse events (OAEs). The majority of AEs were of mild intensity. Hypoglycaemic symptoms, which were collected with specific questions using a pre-specified list of common symptoms of low blood glucose, occurred with a similar pattern, frequency and intensity during hypoglycaemic episodes induced with both AZD1656 and insulin.