AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD6370
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A Dose-Ranging Study to Evaluate Fasting and Postprandial P-Glucose, Safety and Tolerability after Oral Single, B.I.D and Q.I.D Dosing of AZD6370 in Patients with Diabetes Mellitus: a Randomized, Single-Blind, Placebo-Controlled, Phase I study

Study dates: First patient enrolled: 11 February 2008
Last patient completed: 10 June 2008

Phase of development: Clinical pharmacology (I)

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

Study centres

The study was conducted at 3 centres in Sweden; Quintiles AB, Phase I Unit, Strandbodgatan 1, SE-753 23 Uppsala, Quintiles Hermelinen AB, Varvsgatan 53, SE-972 33 Luleå and Berzelius Clinical Research Center AB, Berzelius Science Park, SE-582 25 Linköping.

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to evaluate the effect of AZD6370 on plasma glucose (P-glucose) and serum insulin (S-insulin) under fed and fasting conditions after single oral dosing of AZD6370 in type 2 diabetes mellitus (T2DM) patients.

The secondary objectives of the study were:

1. To describe the safety and tolerability of AZD6370 after one day of oral dosing under fed and fasting conditions in T2DM patients.

2. To evaluate the pharmacokinetic (PK) profile of AZD6370 in T2DM patients.

3. To evaluate the 24h P-glucose profile following different dosing regimens of AZD6370 (equal daily doses administered once, twice and 4 times daily) compared with placebo treatment.

4. To evaluate the effect of AZD6370 on C-peptide under fed and fasting conditions after single oral dosing of AZD6370 in T2DM patients.

Study design

This was a randomized, placebo-controlled, single blind, phase I study in diet or metformin treated T2DM patients. The study consisted of 2 parts, A (single ascending dose) and B (4 way cross over).

Target patient population and sample size

The target population consisted of males or postmenopausal females aged ≥30 to ≤65 and with a diagnosis of T2DM within the previous 5 years. Selected patients were required to be undergoing treatment either with diet or metformin. Stable glycemic control was required to be indicated by no change in treatment within the previous 3 months. Twenty-four (24) randomized patients were recruited and divided into 3 blocks of 8 patients (2 blocks, fasting and fed, of 8 patients in part A and one block of 8 patients in part B).

Investigational product: dosage, mode of administration and batch numbers´

Table S1 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD6370	Oral suspension, 10mg/ml	AstraZeneca R&D Mölndal	H 1887-01-01	H 1887-01-01-04
AZD6370	Oral suspension, placebo	AstraZeneca R&D Mölndal	H 1888-01-01	H 1888-01-01-05

In Part A of the study, patients were treated with single oral doses of AZD6370 and placebo in 4 dose steps under fed (block 1) or fasting (block 2) conditions. During each study session, 6 patients received AZD6370 and 2 patients received placebo. The doses were separated by a washout period of at least 48h.

In Part B of the study, each of the 8 patients from block 3 participated in 4 sessions in which they were dosed with AZD6370 suspension or placebo 4 times daily. AZD6370 suspension was administered o.d. (180mg, 0000h), b.i.d (90mg, 0000h and 1200h) and q.i.d. (45mg, 0000h, 0600h, 1200h and 1800h). At time points when no active dose was given, placebo was administered. A dose was selected that had pharmacological effect in Part A. The doses were separated by a washout period of at least 30h.

Duration of treatment

Part A: Patients were treated with single doses of AZD6370 or placebo during each of 4 one day visits to the study centre.

Part B: In this crossover part of the study, each patient received all 4 treatments. At administration of each treatment, AZD6370 suspension (3 different dosing regimens) or placebo was given during one of the 4 one day visits to the study centre.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

Primary pharmacodynamic (PD) variables (to evaluate the effect of AZD6370 on P-glucose and S-insulin under fed and fasted conditions after single oral dosing of AZD6370 in T2DM patients): P-glucose and S-insulin.

Secondary PD variables (to evaluate the 24h glucose profile following different dosing regimens of AZD6370, equal daily doses administered once, twice and 4 times daily, compared with placebo treatment): P-glucose, S-insulin, C-peptide.

Secondary PD variable (to evaluate the effect of AZD6370 on C-peptide under fed and fasting conditions after single oral dosing of AZD6370 in T2DM patients): C-peptide.

Secondary PK variables (to evaluate the profile of AZD6370 in T2DM patients): AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F.

Criteria for evaluation - safety (main variables)

Secondary safety variables (to describe the safety and tolerability of AZD6370 after one day of oral dosing under fed and fasted conditions in T2DM patients): Laboratory variables, ECG, vital signs, adverse events

Statistical methods

The hypothesis was that AZD6370 decreased P-glucose levels and increased insulin secretion.

All variables were presented with descriptive statistics within each treatment group and within each dose. This was done separately for fed and fasting patients.

PK: The influence of food was analyzed with a mixed-effect analysis of variance (ANOVA) model using the logarithm of AUC (and C_{max}) as the response variable and dose and food condition (fed or fasting) as fixed factors. In addition, ratios of true geometric means together with confidence intervals (2-sided 95%) for $AUC_{fed}/AUC_{fasting}$ and C_{max} fed/C_{max} fasting were estimated for each dose separately and for all doses combined. Dose proportionality was analyzed with a mixed-effect ANOVA model using the logarithm of AUC (and C_{max}) as the response variable and the logarithm of the dose as an independent variable (covariate) and subject as random factor.

PD: PD variables were log-transformed before they were assessed in the model, and were analysed with a mixed-effect ANOVA model using change in PD variables (log-transformed values - log-transformed baseline values) as the response variable.

Safety: Descriptive statistics were provided for all safety variables, and the analyses were performed according to actual exposure, regardless of randomization. No formal comparison was performed.

Subject population

Thirty-nine (39) patients enrolled in the study of whom 24 (16 males and 8 females) aged 39 to 65 years were randomized. With the exception of one Asian participant, all randomized patients in the study were white. Two (2) randomized patients did not complete the study.

Subjects participating in the study were all T2DM patients and complied with specifications in the CSP. The treatment groups were well-balanced and adequately represented the target population for AZD6370.

Summary of pharmacokinetic results

AZD6370 was generally rapidly absorbed, with the median time to maximum plasma concentration (t_{max}) between 0.3 and 0.7h in all dose groups tested. The decline in plasma concentrations was rapid, with mean oral plasma clearance between 54.6 and 65.9 L/h in the

different dose groups. The mean terminal half-life varied between 8.9 and 10.9h in the dose groups receiving 60mg and 180mg AZD6370 while the mean half-life in the 20mg dose groups was lower (between 5.1 and 5.8h). Terminal $t_{½}$ is probably underestimated at the lowest dose level since the terminal phase is below LLOQ and can therefore not be captured.

Food seemed to have no effect on the PK of AZD6370 when the dose was administered within 5 minutes before intake of a standardised high-fat breakfast.

A linear relationship between C_{max} and dose was found in T2DM patients receiving 20-180mg of AZD6370. Although the increase in AUC was slightly greater than expected from the increase in dose, the deviation from dose-linearity was not considered to be clinically significant.

Summary of pharmacodynamic results

The effect of AZD6370 on P-glucose, S-insulin and C-peptide levels after administration to fasting and fed patients when measured up to 4h (AUC 0-4h) after single oral dosing in T2DM patients (Part A) is summarized in Table S2.

Table S2 The effect of AZD6370 on P-glucose, S-insulin and C-peptide levels after administration to fasting and fed patients

AZD6370	P-glucose[1]	S-insulin	C-peptide
Fasting	Statistically significant reduction at 60mg AZD6370	Statistically significant increase at 180mg AZD6370	Statistically significant increase at 60mg AZD6370
Fed	Statistically significant reduction at 60mg AZD6370	Statistically significant increase at 60mg AZD6370	Statistically significant increase at 20mg AZD6370

[1] Although, as expected, the fed group of patients had higher base levels of P-glucose than the fasting group, the effect of AZD6370 was similar

Changes in the profiles of P-glucose following different dosing regimens of AZD6370 (administered as a single daily dose of 180mg, 2 daily doses of 90mg or 4 daily doses of 45mg) (Part B), compared with placebo treatment, is presented in Table S3.

Table S3 Change in profiles of P-glucose levels over the 24h period (AUC 0-24h) following different dosing regimens of AZD6370: comparison with placebo treatment

AZD6370 treatment regimen	P-glucose
o.d.	-12%
b.i.d.	-17%
q.i.d.	-14%

Summary of pharmacokinetic/pharmacodynamic relationships

The PK/PD relationship for P-glucose showed a dose-dependent glucose lowering effect of AZD6370.

Summary of safety results

There were no deaths, other SAEs, premature discontinuation of treatment with investigational product due to an AE or OAEs in the study. Overall, there was no apparent difference in the frequency of occurrence of AEs between AZD6370 treated and placebo treated patients

The most commonly collected AEs were headaches. The majority of AEs were of mild or moderate intensity.