AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00014
Edition Number	1
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A randomized, single-blind, placebo-controlled, phase I study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics after multiple ascending oral doses of AZD1656 in T2DM subjects treated with insulin

Study dates: First subject enrolled: 29 September 2008
Last subject completed: 13 March 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 one 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 study safety and tolerability after repeated oral doses of AZD1656 in type 2 diabetes mellitus (T2DM) subjects treated with basal night-time insulin.

Secondary objectives

The secondary objectives of the study were:

1. To evaluate the pharmacokinetics of AZD1656 after repeated oral doses in T2DM subjects treated with basal night-time insulin.

2. To evaluate glucose and endogenous insulin levels and insulin secretion after administration of repeated oral doses of AZD1656 in T2DM subjects treated with basal night-time insulin.

Exploratory objectives

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

Results from any genetic research, if performed, will be reported separately from this clinical study report.

Study design

This was a single-centre, randomized, single-blind, placebo-controlled multiple ascending dose (MAD) phase I study in T2DM subjects treated with basal night-time insulin (insulin glargine). After randomisation, a dose titration started with subjects given half the AZD1656 target dose on study day 1. If the initial dose was well tolerated, the dose was increased to the target dose on day 2, otherwise the subject was withdrawn. On study day 3 subjects continued on target dose if well tolerated, otherwise the dose was reduced to half the target dose. Subjects were then given the achieved dose or placebo for 5 more days. All subjects were hospitalised during the randomized treatment period. The target dose levels applied in this study were 10 mg bid, 30 mg bid, 90 mg bid and 150 mg bid AZD1656.

Target population and sample size

Males and non-fertile females with T2DM treated with insulin, either as single therapy or in combination with other anti-diabetic drugs. The planned number of evaluable subjects was 8 (2 on placebo and 6 on AZD1656) for each dose level.

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

- AZD1656 oral suspension 2 mg/mL, batch number H 2000-01-01-02.
- AZD1656 oral suspension 25 mg/mL, batch number H 2001-01-01-02.
- Placebo oral suspension, batch number H 2002-01-01-02.

Duration of treatment

Each subject was assigned to one dose level and received randomized treatment with AZD1656 or placebo twice daily for 8 days.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

PD variables: 24-hour P-glucose, S-insulin, S-C-peptide.

PK variables: AZD1656 and metabolite AZ12555623 concentration in plasma; derived parameters AUC, AUC_{0-24}, C_{max}, C_{trough}, t_{max}, $t_{1/2}$, and CL/F.

Criteria for evaluation - safety (main variables)

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

Statistical methods

The study data were evaluated using descriptive statistics and a mixed-effect analysis of variance / covariance (ANOVA / ANCOVA).

Subject population

In total, 81 male and female subjects with T2DM were enrolled and 30 subjects were randomized to the treatments as follows: 8 placebo, 6 AZD1656 10 mg bid, 5 AZD1656 30 mg bid, 5 AZD1656 90 mg bid, and 6 AZD1656 150 mg bid. Two (2) randomized subjects prematurely discontinued the study so that 28 subjects were completers (8 on placebo and 5 on AZD1656 at each dose level). The safety analysis set as well as the PD analysis set consisted of all 30 randomized subjects and the PK analysis set included all 22 subjects randomized to AZD1656 treatment. Two (2) subjects received 75 mg AZD1656 bid from day 3 onwards (instead of the target dose 150 mg bid), according to a pre-defined titration algorithm based on glucose response.

Overall, the treatment groups were well balanced with regard to demographic characteristics except for the gender distribution, which was different in the AZD1656 and the placebo subjects.

Summary of pharmacokinetic results

During the multiple dose regimen administered in this study, AZD1656 was rapidly absorbed (C_{max} reached within 1 hour for most subjects) and rapidly eliminated with a geometric mean terminal elimination half-life of approximately 4.5 hours. The geometric mean apparent oral clerance (CL/F) of AZD1656 on day 8 was 10.4 L/h.

The metabolite AZ12555623 generally reached C_{max} at approximately the same time as AZD1656 but had a slower terminal elimination phase. The exposure to the metabolite was markedly lower than the exposure to AZD1656, with mean exposure being approximately 12% of the parent drug with reference to AUC_{0-24h} and 10% with reference to C_{max}.

The estimated ratio of AZD1656 exposure at day 8 (AUC0-24) vs day 2 (AUC) for all dose levels combined was 1.10 (0.98; 1.22). The estimated ratio AUC_{0-24} day 8 vs day 2 (accumulation ratio) for AZD1656 was 1.09 (95% CI: 1.01; 1.17) and the respective C_{max} ratio 1.07 (95% CI: 0.91; 1.25), for all dose levels combined. The corresponding accumulation ratio for AZ12555623 was 1.63 (95% CI: 1.48; 1.80) with reference to AUC_{0-24} and 1.51 (95% CI: 1.29; 1.76) with reference to C_{max}. Taken together, these data suggest that the PK of AZD1656 is time-independent with no or negligible accumulation while AZ12555623 has an accumulation of approximately 50% which is in agreement with an "effective" half-life of approximately 8-12 hours.

Dose-proportionality of the AZD1656 AUC_{0-24} was proven statistically for day 2 as well as for day 8 (estimated β 0.99 [0.88; 1.10] and 1.05 [0.91; 1.20], respectively). C_{max} also showed a dose-proportional increase on day 2 (estimated β 0.88 [0.72; 1.04]) as well as on day 8 (estimated β 0.88 [0.74; 1.02]).

For AZ12555623 dose-proportionality of C_{max} was proven for both days (estimated β 1.09 [0.85; 1.33] for day 2 and 1.15 [0.93; 1.37] for day 8). AUC_{0-24} showed a more than dose-proportional increase (estimated β 1.32 [1.06; 1.58] for day 2 and 1.31 [1.06; 1.55] for day 8).

The full human dose range was investigated in the study since two subjects in the highest dose group exceeded the predefined maximum exposure limit for AZD1656 (ie, 71 μmol*h/L for AUC and 43 μmol/L for C_{max}).

Summary of pharmacodynamic results

In comparison to placebo, there was a statistically significant reduction in plasma glucose, as characterised by the AUC over 24 hours. For day 8, at the 30 mg bid dose level, the estimated quotient AZD1656/placebo was 0.79 [0.62; 0.99]. For day 2 and day 8, at the 150 mg bid dose level, the estimated quotient AZD1656/placebo was 0.78 [0.68; 0.90] and 0.69 [0.55; 0.87], respectively. No significant changes were observed in the 10 mg bid and the 90 mg bid dose group.

Descriptive statistics of fasting plasma glucose (FPG) showed for the 150 mg bid dose level a reduction during treatment with AZD1656 by approximately 30%-40%.

In comparison to placebo, there were no statistically significant changes in S-insulin or S-C-peptide, as characterised by the respective AUCs over 21 hours on either day and at each dose level.

Summary of safety results

No safety or tolerability concerns were raised in this study. The numbers of subjects reporting at least 1 AE were as follows: 6 (75.0%) during placebo, 4 (66.7%) during the 10 mg bid, 4 (80.0%)during the 30 mg bid, 3 (60.0%) during the 90 mg bid, and 4 (66.7%) during the 150 mg bid AZD1656 regimen. The most common AE was headache (reported by 3 placebo and 3 AZD1656 treated subjects). One (1) subject (AZD1656 10 mg bid) experienced mild/moderate hypoglycaemic symptoms without verified hypoglycaemia. Another (1) subject (AZD1656 150 mg bid) had two mild hypoglycaemic episodes, one asymptomatic and the other symptomatic. There were no deaths, other serious adverse events (SAEs) or other significant adverse events (OAEs). There were 2 drop-outs: One (1) subject treated with AZD1656 10 mg bid met study specific discontinuation criteria for hyperglycaemia on day 6, and 1 subject treated with AZD1656 150 mg bid withdrew consent on day 5 due to person al concerns regarding post-prandial hyperglycaemia. The majority of AEs were of mild intensity.