AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00020
Edition Number	1
Date	04 December 2009

A Randomised, Single-Blind, Placebo-Controlled, Phase IIa Study to Assess the Safety and Tolerability after Multiple Oral Doses of AZD1656 during Four Weeks in T2DM Subjects Treated with Insulin

Study dates: First subject enrolled: 27 February 2009
Last subject completed: 11 August 2009

Phase of development: Therapeutic exploratory (IIa)

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 study safety and tolerability after repeated oral doses of AZD1656 during out-patient conditions in T2DM subjects treated with basal night-time insulin.

Secondary objectives

The secondary objectives of the study were:

1. To evaluate the pharmacokinetics (PK) of AZD1656 and AZ12555623 during repeated oral dosing under out-patient conditions in T2DM subjects treated with basal night-time insulin.

2. To evaluate plasma glucose and endogenous insulin levels (insulin and C-peptide) after administration of repeated oral doses of AZD1656 during out-patient conditions in T2DM subjects treated with basal night-time insulin.

Exploratory objectives

The explorative objective of the study was to collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes that may influence drug response ie, distribution (pharmacokinetics [PK] profile), 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 randomised, single-blind, placebo-controlled, single-centre phase IIa study with parallel groups, performed in 20 (15 AZD1656 and 5 placebo) subjects with type 2 diabetes mellitus (T2DM), treated with basal night-time insulin (insulin glargine). Subjects were given repeated oral doses of AZD1656 or placebo twice daily for a total of 28 consecutive days.

About 2 weeks before randomisation, eligible subjects came to the site to be switched to basal night-time insulin (insulin glargine) as the only anti-diabetic treatment (ie, any other insulins or oral anti-diabetic drugs were stopped). During the subsequent wash-out period, the insulin dose was adjusted aiming for fasting plasma glucose (FPG) between 7.0 and 13.0 mmol/L (126 and 234 mg/dL). A few days before randomisation, the subjects returned to the clinic for

final adjustments of the insulin dose to ensure glucose levels within a safe range at start of the randomised treatment. Following randomisation, the dose of AZD1656/placebo was increased based on the individual glucose response (AZD1656 dose steps: 12.6 mg bd, 25 mg bd, 50 mg bd, and 90 mg bd) during up to 4 days of titration, as defined by the dosing guidelines in the study protocol. After at least 2 days on maintenance dose, subjects were discharged from the clinic and returned for pre-scheduled visits twice weekly, including 2 short overnight stays. After completion of the 28-day treatment with investigational product (IP), the subjects re-started their previous anti-diabetic treatment at the discretion of the investigator and attended a follow-up visit 7-10 days after day 29. In total, the study consisted of 11 visits.

Target subject population and sample size

The target population comprised of male and non-fertile female subjects with T2DM, treated with insulin alone or insulin in combination with other anti-diabetic drugs. The sample size of 15 subjects in the active and 5 subjects in the placebo treatment group was primarily based on experience from previous similar studies with other compounds, and it was determined without formal statistical considerations or formal power calculation.

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

- AZD1656 oral suspension 0.63 mg/mL, batch number: H 2085-01-01-01
- AZD1656 oral suspension 1.25 mg/mL, batch number: H 2086-01-01-01
- AZD1656 oral suspension 2.50 mg/mL, batch number: H 2087-01-01-01
- AZD1656 oral suspension 4.50 mg/mL, batch number: H 2088-01-01-01
- Placebo oral suspension, batch number: H-2053-01-03-01

Duration of treatment

The IP (AZD1656 or placebo) was administered twice daily for 28 consecutive days.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

PK variables: AZD1656 and metabolite AZ12555623 concentrations in plasma: AUC_{0-24}, C_{max}, C_{trough}, t_{max}, $t_{1/2}$ (only AZD1656), CL/F (only AZD1656), ratio AZ12555623/AZD1656 for AUC_{0-24} and C_{max}

PD variables: Plasma glucose (PG), serum C-peptide and insulin: $AUC_{0-24h}/24$, proportion of PG measurements below 5 mmol/L, within 5-8 mmol/L, and above 8 mmol/L, fasting plasma glucose (FPG), HbA1c

Criteria for evaluation - safety (main variables)

Adverse events (including hypoglycaemic events), vital signs (blood pressure, pulse), body weight, safety laboratory variables, physical examination, Electrocardiogram (ECG)

Statistical methods

The analysis of the PK variables was performed by means of descriptive methods. Variables were calculated using a non-compartmental model. Plasma concentrations of AZD1656 and AZ12555623 and derived PK parameters were adjusted to a dose regimen of 50 mg AZD1656 bd. Geometric means, coefficients of variation (CV%) and 95% confidence intervals (CI) for dose-adjusted AUC_{0-24} and C_{max} of AZD1656 and AZ12555623 were calculated.

In all PD analyses, AUCs were standardised to one hour. The analysis of the PD variables used descriptive methods as well as formal statistical comparisons. Within-treatment comparisons of AUCs between different days and baseline as well as between-treatment comparisons of AUC changes were performed using a mixed-effect ANCOVA model.

All statistical tests were two-sided with a significance level of α=0.05.

Subject population

In total 50 subjects were enrolled, 20 subjects were randomised and exposed to IP (15 to AZD1656 and 5 to placebo). The AZD1656 group consisted of 6 men and 9 women, mean (±SD) age 52.6±7.4 years and BMI 31.95±4.85 kg/m^2, the placebo group of 2 men and 3 women, mean (±SD) age 57.2±11.4 years and BMI 32.64±4.98 kg/m^2. Of the 30 subjects who were not randomised, 23 were screening failures and 7 discontinued between enrolment and randomisation. One subject of the AZD1656 group was withdrawn from the study on day 7 of treatment and lost to follow-up. Thus, 19 subjects (14 on AZD1656 and 5 on placebo) completed the study. The safety as well as the PD analysis set consisted of all 20 randomised subjects and the PK analysis set included 14 subjects randomised to AZD1656 treatment. Four (4) subjects received 12.6 mg, 2 subjects 50 mg and 9 subjects 90 mg AZD1656 twice daily as maintenance dose. The daily insulin glargine doses ranged from 10 IU to 70 IU in the AZD1656 and from 14 IU to 65 IU in the placebo group. Between day -4 and day 28, the insulin dose was reduced in 6 subjects of the active group and in 4 subjects of the placebo group whereas the dose was increased in 8 subjects of the active group and in 1 subject of the placebo group.

Summary of pharmacokinetic results

AZD1656 was rapidly absorbed (C_{max} reached within 1 hour for most subjects, median t_{max}=0.5 h) and rapidly eliminated with a mean terminal elimination half-life of approximately 5 hours. The mean apparent oral clearance (CL/F) of AZD1656 was approximately 9 L/h. Geometric mean AUC_{0-24} (95% CI) was 23.49 µmol*h/L (18.73 ; 29.45) and geometric mean C_{max} 2.415 µmol/L (1.992 ; 2.928).

Plasma concentrations of metabolite AZ12555623 peaked slightly later than the parent compound AZD1656 (C_{max} reached within 1.5 hours for most subjects, median t_{max}=1.0 h).

Geometric mean AUC_{0-24} (95% CI) was 3.975 µmol*h/L (3.170 ; 4.983) and geometric mean C_{max} 0.327 µmol/L (0.270 ; 0.396).

The mean exposure to AZ12555623 in terms of AUC_{0-24} and C_{max} was 18% and 14% of the exposure to AZD1656.

Summary of pharmacodynamic results

The study was not primarily designed to evaluate PD effects and there was an imbalance between treatment groups at baseline (eg, regarding glucose control). Thus, the PD results must be interpreted with caution and no definitive conclusions can be made regarding PD results.

P-glucose $AUC_{0-24}/24$ showed in the AZD1656 group a significant decrease from baseline (day -1) on day 6 (estimated geometric mean: -10%, 95% CI: -17% ; -3.4%)) and day 16 (-11%, CI: -19% ; -0.8%), but not on day 28 (-7%, 95% CI: -19% ; 6.2%). No significant changes were observed for the placebo group. Between treatment group comparisons did not reveal any significant differences in changes from baseline between AZD1656 and placebo.

S-C-peptide $AUC_{0-24}/24$ displayed no significant changes from baseline, neither in the within treatment group nor in the between treatment group comparisons.

S-insulin $AUC_{0-24}/24$ showed in the placebo group a significant decrease from baseline on day 6 (estimated geometric mean: -29%, 95% CI: -44% ; -12%), day 16 (-25%, CI: -38% ; -8.3%), and day 28 (-29%, CI: -45% ; -9.3%). No significant changes were observed for the AZD1656 group. Between treatment group comparisons of AZD1656 vs placebo revealed a significant difference in change from baseline on day 16 (41%, CI: 11% ; 79%, p=0.007) and on day 28 (38%, CI: 2.5% ; 85%, p=0.035). The difference on day 6 (30%, CI: -0.2% ; 69%, p=0.051) was not significant.

Summary of safety results

Adverse events (AEs) were collected from the first IP administration until the follow-up visit, serious adverse events (SAEs) from enrolment until follow-up. Thirteen (13) subjects (86.7%) experienced at least one AE during AZD1656 treatment and 1 subject (7.1%) during

AZD1656 follow-up. Three (3) subjects (60.0%) experienced at least one AE during placebo treatment and 1 subject (20.0%) during placebo follow-up. There were no deaths, premature discontinuations due to adverse events (DAEs) or other significant adverse events (OAEs). One (1) serious adverse event (SAE) was reported, occurring prior to any IP administration on the day of enrolment. The total number of AEs was 63. Forty-seven (47) AEs occurred during AZD1656 treatment and 2 during AZD1656 follow-up; 13 AEs occurred during placebo treatment and 1 during placebo follow-up. The majority of AEs were of mild intensity. The most frequent AE was headache, reported by 10 subjects (66.7%) during AZD1656 treatment and by 1 subject (20%) during placebo treatment. Four (4) of the 47 AEs were episodes of PG measurements below 3.9 mmol/L (70 mg/dL) as all PG values $\leq$ 3.9 mmol/L (70 mg/dL) were to be reported as AEs according to the study protocol. There were no plasma glucose values below 3.0 mmol/L (54 mg/dL) or any episodes of symptomatic hypoglycaemia in this study.

There were no clinically relevant changes or trends observed in laboratory variables, vital signs, weight, 7-point+night PG profiles, ECGs or physical examination findings.