AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00026
Edition Number	1
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A randomized, single-blind, placebo-controlled, phase I study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD1656 compared to placebo in T2DM patients treated with metformin and sulfonylurea

Study dates: First subject enrolled: 05 October 2009
Last subject completed: 10 February 2010

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 evaluate the safety and tolerability of AZD1656 in T2DM patients treated with metformin and glipizide.

Secondary objective

The secondary objective of the study was to evaluate pharmacokinetics and pharmacodynamics for different combinations of AZD1656, glipizide and metformin.

Exploratory objectives

Exploratory objectives of the study were:

1. To evaluate continuous glucose monitoring versus 24-hour venous glucose profiles in patients on different combinations of AZD1656, glipizide and metformin.

2. To collect and store DNA for future exploratory research into genes/ genetic variation that may influence response (ie, pharmacokinetic profile, safety, tolerability and efficacy) to AZD1656, metformin and glipizide 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 I study with parallel groups, performed in 21 (16 AZD1656 and 5 placebo) subjects (men or non-fertile women) with T2DM, treated with metformin (≥1000 mg/day) in combination with glipizide (5 mg bd). Prior to the study, eligible subjects had to be, besides metformin, on an oral anti-diabetic drug of the sulfonylurea (SU) type (ie, glyburide, glimepiride, glibenclamide, glipizide or gliclazide) at a dose of at least 25% of the maximum approved dose. They visited the study site at least 14 days before randomisation and were switched to glipizide (5 mg bd), provided by the centre. The subjects' metformin dose was kept unchanged.

From day -2 before randomisation (day 1), the subjects were hospitalised for 11 days. During this period they received the study treatment according to the following scheme: From day 1 to day 6, subjects received AZD1656 or placebo in combination with glipizide and metformin. During the first 3 days (dose titration), the AZD1656/placebo dose was increased stepwise

(12.5, 40 and 100 mg bd), based on the results of the morning fasting plasma glucose (FPG) on the actual day and the 7-point glucose profile from the day before. Once the AZD1656 / placebo dose was established, subjects continued on the achieved dose, unless reduction was needed due to hypoglycaemia, as judged by the investigator. On study days 7 to 9, glipizide was discontinued while the other treatments (AZD1656 or placebo with metformin) were maintained until day 9. On day 10, 24 hours after the last AZD1656 morning dose on day 9, the subjects were discharged from the clinic and re-started their previous anti-diabetic medication at the discretion of the investigator. In total, the study consisted of 4 visits.

Target subject population and sample size

The target population comprised of male and non-fertile female subjects with T2DM, treated with sulfonylurea and metformin. The planned 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 AZD1656 and 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 25 mg/mL, batch number: 09-003059AZ
- Placebo oral suspension, batch number: 08-002909AZ

The IP (AZD1656 or placebo) was administered orally at doses of 12.5, 40, and 100 mg bd.

Duration of treatment

The IP (AZD1656 or placebo) was administered twice daily for 9 consecutive days.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

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

PD variables: Plasma glucose (PG), plasma insulin: $AUC_{0-24h}/24$.

Criteria for evaluation - safety (main variables)

Adverse events (including hypoglycaemic events), vital signs (blood pressure, pulse), body weight, safety laboratory variables (including FPG), plasma glucose 7-point+night profile (measured at study site), physical examination, electrocardiogram (ECG).

Statistical methods

The analysis of the PK variables was based on the PK analysis set. Calculations were made using a non-compartmental model. Due to the fact that the study subjects did not all receive the same dose of AZD1656 and to enable comparison with existing data, AZD1656 and metabolite AZ12555623 plasma concentrations and the respective derived PK parameters

AUC_{0-24} and C_{max} were adjusted to a dose regimen of 100 mg AZD1656 bd. Geometric means, coefficients of variation (CV%), and 90% and 95% confidence intervals (CI) were calculated for dose-adjusted AUC_{0-24} and C_{max} of AZD1656 and AZ12555623, as well as for (unadjusted) AUC_{0-24} and C_{max} of glipizide. Statistical analyses were performed with a mixed-effect analysis of variance (ANOVA) model.

The analysis of the PD variables was based on the PD analysis set and employed the same mixed-effect ANOVA model as used for the analysis of the PK variables, except for the analysis of the interaction of glipizide with AZD1656 and placebo, where a mixed-effect ANCOVA model was used. In all PD analyses, the 24-hour AUCs were standardised to one hour (ie, AUC_{0-24} was divided by 24).

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

Safety variables were analysed only descriptively; no formal comparisons were performed.

Subject population

In total 75 subjects were enrolled, 21 subjects were randomised and exposed to IP (16 to AZD1656 and 5 to placebo). The AZD1656 group consisted of 12 men and 4 women, mean (±SD) age 51.4±8.7 years and BMI 33.61±5.33 kg/m^2, the placebo group of 4 men and 1 woman, mean (±SD) age 45.0±9.9 years and BMI 33.68±5.57 kg/m^2. Of the 54 subjects who were not randomised, 50 did not fulfil eligibility criteria and 4 were screened but not further needed since the planned number of study participants was achieved. All, 21 randomised subjects completed the study. One of the completers was excluded from the PK/PD evaluation due to a positive finding for GAD antibodies (final result available after subject had completed the study). Thus, the safety analysis set consisted of all 21 randomised subjects, the PD analysis set of 20 subjects (15 AZD1656 and 5 placebo), and the PK analysis set included 15 subjects randomised to AZD1656 treatment. On treatment day 4, after dose titration was completed, 3 subjects were on a AZD dose regimen of 12.5 mg bd, 4 of 40 mg bd, and 9 on 100 mg bd. The daily metformin doses ranged from 1000 mg to 2550 mg in the AZD1656 and from 1500 mg to 2000 mg in the placebo group.

Summary of pharmacokinetic results

AZD1656 was rapidly absorbed (C_{max} reached within 1 hour for most subjects; median t_{max} 0.8 h on day 6 and 0.5 h on day 9) and rapidly eliminated with a mean terminal elimination half-life of approximately 5 hours (5.4 h on day 6 and 4.5 h on day 9). The mean apparent oral clearance (CL/F) of AZD1656 was approximately 11 L/h (11.4 L/h on day 6 and 11.2 L/h on day 9). Geometric mean dose-adjusted AUC_{0-24} (95% CI) was 39.0 µmol*h/L (33.24; 45.70) on day 6 and 39.4 µmol*h/L (33.77; 46.05) on day 9. Geometric mean dose-adjusted C_{max} was 4.7 µmol/L (3.78; 5.95) on day 6 and 4.2 µmol/L (3.23; 5.40) on day 9.

Plasma concentrations of metabolite AZ12555623 peaked at about the same time as the parent compound AZD1656 (C_{max} reached within 1 hour for most subjects; median t_{max} 0.75 h on both day 6 and day 9). Geometric mean dose-adjusted AUC_{0-24} (95% CI) was 6.66 µmol*h/L

(5.00; 8.87) on day 6 and 6.88 µmol*h/L (5.09; 9.30) on day 9. Geometric mean dose-adjusted C_{max} was 0.55 µmol/L (0.41; 0.72) on day 6 and 0.52 µmol/L (0.39; 0.69) on day 9.

The mean exposure to AZ12555623 in terms of AUC_{0-24} was 19% (day 6) and 20% (day 9) of the exposure to AZD1656. In terms of C_{max} mean exposure was 12% (day 6) and 14% (day 9) of that to AZD1656.

Due to a change in AZ substance coding, the metabolite previously named AZ12555623 now is called AZD5658.

Glipizide was less rapidly absorbed than AZD1656 (C_{max} reached within 1.5 hours for most subjects; median t_{max} 1.5 h on day -1 and 3.0 h on day 6) and eliminated with a mean terminal elimination half-life of approximately 4-5 hours (4.6 h on day -1 and 4.2 h on day 6). The mean apparent oral clearance (CL/F) of glipizide was approximately 3-4 L/h (3.3 L/h on day -1 and 3.5 L/h on day 6.

Neither for AUC_{0-24}, nor for C_{max} of both AZD1656 and metabolite AZ12555623 the comparisons revealed a statistically significant difference between day 6 and day 9, indicating that glipizide had no influence on AZD1656 and AZ12555623 pharmacokinetics.

Compared to day -1, glipzide AUC_{0-24} and C_{max} were both decreased on day 6 (-8% and -7%, respectively). Although this difference was statistically significant for AUC_{0-24} (p=0.011), the 90% CI of the geometric means ratio day 6/day -1 (0.88-0.97) was within the bioequivalence range (0.80-1.25) and thus the reduction in AUC during AZD1656 treatment is considered to be of no or negligible clinical significance.

Summary of geometric means ratios (point estimate and 90% CI) of AUC_{0-24} and C_{max} of AZD1656, AZ12555623 and glipizide

Comparison	Parameter	Estimate	90% Confidence limits	
			Lower	Upper
Combination/AZD1656	AUC_{0-24} of AZD1656	0.99	0.94	1.04
	C_{max} of AZD1656	1.14	0.99	1.30
Combination/AZD1656	AUC_{0-24} of AZ12555623	0.97	0.91	1.03
	C_{max} of AZ12555623	1.05	0.97	1.14
Combination/glipizide	AUC_{0-24} of glipizide	0.92	0.88	0.97
	C_{max} of glipizide	0.93	0.81	1.06

Summary of pharmacodynamic results

In both treatment groups, a statistically significant decrease in P-glucose $AUC_{0-24}/24$ could be observed from day -1 to day 6 (AZD1656 -33%, placebo -12%; p<0.001 and p=0.042), followed by a significant increase from day 6 to day 9 (AZD1656 16%, placebo 11%; p<0.001

and p=0.045). Overall, there was a statistically significant decrease (-20%; p<0.001) in P-glucose AUC_{0-24}/24 from day -1 to day 9 in the AZD1656 group while in the placebo group the overall change was zero. The between-treatment comparison of day 6 revealed a statistically significantly smaller P-glucose AUC_{0-24}/24 (-24%; p=0.001) in the AZD1656 group, compared to placebo. The corresponding comparison of day 9 showed no significant difference in P-glucose AUC_{0-24}/24 between the 2 groups.

Thus, administration of AZD1656 on top of metformin and glipizide resulted in a 24% reduction of plasma glucose levels, compared to treatment with metformin and glipizide alone. Withdrawal of glipizide while continuing with AZD1656+metformin caused an increase in plasma glucose levels, although a 20% decrease compared to baseline remained in AZD1656 subjects.

In the AZD1656 group, a statistically significant increase (10%; p=0.015) in P-insulin AUC_{0-24}/24 could be observed from day -1 to day 6 while no significant change occurred in the placebo group. From day 6 to day 9 a significant decrease was seen in both treatment groups (AZD1656 25%, placebo 21%; p<0.001 and p=0.010). Overall, there was a statistically significant decrease in P-insulin AUC_{0-24}/24 from day -1 to day 9 in both groups (AZD1656 -12%, placebo -16%; p=0.003 and p=0.019). The between-treatment comparison of day 6 revealed no statistically significant difference in AUC_{0-24}/24 between the 2 groups, as well as the corresponding comparison of day 9.

Thus, administration of AZD1656 on top of metformin and glipizide did not change insulin plasma concentrations, compared to treatment with metformin and glipizide alone.

Summary of safety results

Fourteen (14) subjects (87.5%) experienced AEs during AZD1656 treatment and 2 subjects (12.5%) during AZD1656 follow-up. One (1) subject (20.0%) experienced 1 AE during placebo treatment and no subject during placebo follow-up. There were no deaths, other serious adverse events (SAEs), premature discontinuations due to adverse events (DAEs), or other significant adverse events (OAEs). The total number of AEs was 83. Seventy-nine (79) AEs were reported during AZD1656 treatment and 3 during AZD1656 follow-up; 1 AE occurred during placebo treatment and no AE during placebo follow-up. The vast majority of AEs were of mild intensity; none of the AEs was rated as severe. Three (3) AEs in 3 subjects had the outcome “still present” at the end of the study (visit 4) and were followed-up until resolution. The most frequent AEs were decreased blood glucose and/or hypoglycaemia, experienced by 11 subjects, and the majority of the other reported AEs were symptoms of hypoglycaemia. All AEs in conjunction with low blood glucose/hypoglycaemia occurred in the AZD1656 treatment group, with the vast majority occurring during triple therapy (AZD1656+metformin+glipizide.

Plasma glucose values <70 mg/dL (<3.9 mmo/L) were registered on 51 occasions (in 11 subjects), with 12 cases of associated symptoms suggestive of hypoglycaemia (ie, starting ±30 minutes around the respective measurement). PG values <54 mg/dL (<3.0 mmol/L) were registered on 4 occasions (in 3 subjects), in 1 case associated with hypoglycaemic symptoms.

The vast majority of low blood glucose measurements were observed during triple therapy with AZD1656+glipizide+metformin, and associated hypoglycaemic symptoms occurred exclusively in that period. During the AZD1656+metformin dual therapy, only 5 plasma glucose values <70 mg/dL (<3.9 mmol/L), but all above 54 mg/dL (3.0 mmol/L), were recorded (in 4 subjects), with no associated hypoglycaemic symptoms. Episodes of low blood glucose occurred at all administered AZD1656 dose levels and there was no indication of a dose-dependency of their incidence rates. None of the hypoglycaemic episodes in this study fulfilled the criteria of a major hypoglycaemic event.

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