AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00019
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A Randomised, Single-Blind, Placebo-Controlled, Phase IIA Study to Assess the Safety and Tolerability after Multiple Oral Doses of AZD1656 in Patients with Type 2 Diabetes Mellitus Treated with Metformin

Study dates: First patient enrolled: 24 February 2009
Last patient completed: 20 July 2009

Phase of development: Phase 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: Healthcare Discoveries, LLC, San Antonio, Texas, USA

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the safety and tolerability after repeated oral doses of AZD1656 during outpatient conditions in patients with T2DM treated with metformin.

Secondary objectives

To evaluate the pharmacokinetics (PK) of AZD1656 during repeated oral dosing under outpatient conditions in patients with T2DM treated with metformin

To evaluate the potential of AZD1656 to affect the CYP3A4 activity by assessment of urine 6β-OH-cortisol/cortisol ratio at baseline and on Day 28 during AZD1656 treatment

To evaluate P-glucose, S-insulin and S-C-peptide levels after administration of repeated oral doses of AZD1656 during outpatient conditions in patients with T2DM treated with metformin

Exploratory objective

To collect and store deoxyribonucleic acid 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 report.

Study design

This was a randomised, single-blind, placebo-controlled, Phase IIa study in 27 (19 AZD1656 and 8 placebo) patients with T2DM treated with metformin in an outpatient setting.

A screening visit took place within 28 days before randomisation. If the patients with T2DM were eligible to enter the study they came to the clinic 8 days (Day -8) before randomisation to switch to the metformin provided by the centre.

After randomisation, patients were titrated to the maximum dose (or the individual tolerated dose if maximum not reached) of AD1656 administered as an oral suspension during 4 days of titration using 4 dose levels: 5 mg bd, 12.6 mg bd, 25 mg bd, and 50 mg bd.

Patients were confined to the clinic from study Day -2 until study Day 7, ie, during pre-assessment, dose titration and during the first 2 days on maintenance dose. The patients

left the clinic in the morning of study Day 7; thereafter, patients followed the outpatient procedures outlined in the CSP. Patients were confined again to the clinic during Day 28 (last treatment day). A follow-up visit was scheduled 7 to 10 days after last dose.

Target population and sample size

Twenty (15 AZD1656 and 5 placebo) male and female patients with T2DM treated with metformin as a single anti-diabetic treatment, 30-75 years of age and with a BMI ≥19 and ≤40 kg/m^2.

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

The details of the investigational products are given in Table S1.

Table S1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form and strength	Manufacturer	Formulation number	Batch number[a]
AZD1656	Oral suspension 0.25 mg/mL	AstraZeneca R&D	H 2084-01-01	H 2084-01-01-01
AZD1656	Oral suspension 0.63 mg/mL	AstraZeneca R&D	H 2085-01-01	H 2085-01-01-01
AZD1656	Oral suspension 1.25 mg/mL	AstraZeneca R&D	H 2086-01-01	H 2086-01-01-01
AZD1656	Oral suspension 2.50 mg/mL	AstraZeneca R&D	H 2087-01-01	H 2087-01-01-01
Placebo	Oral suspension Placebo	AstraZeneca R&D	H 2053-01-03	H 2053-01-01-01
Metformin	Oral tablets 850 mg	Teva	N/A	33500219A
		Zygenerics		MH3136
Metformin	Oral tablets500 mg	Mutual Pharmaceutical	N/A	61822 62162
		Glenmark		Q10088012

[a] Batch numbers are not required for non-investigational product/test drug.

After randomisation, patients were titrated to the maximum dose (or the individual tolerated dose if maximum not reached) of AD1656 administered as an oral suspension during 4 days of titration using 4 dose levels: 5 mg bd, 12.6 mg bd, 25 mg bd, and 50 mg bd.

Duration of treatment

After randomisation, the dose was titrated during 4 days to the maximum dose (or the individual tolerated dose if maximum not reached) and patients were thereafter treated with this dose for another 24 days, ie, in total 28 days with AZD1656 treatment and at least 25 days on target dose.

Criteria for evaluation (main variables)

AZD1656 and AZD12555623: AUC_{0-24}, C_{max}, and C_{trough}, and t_{max}
AZD1656: $t_{1/2}$, CL/F, and λ_z

6β-OH-cortisol in urine and cortisol in urine

P-glucose: fasting P-glucose values and change from baseline in fasting P-glucose. For 24-hour measurements (Days 1, 6, and 28): AUC_{0-24}, $AUC_{0-24/24}$, proportion of measurements <5 mmol/L, proportion of measurements within 5 to 8 mmol/L, proportion of measurements above 8 mmol/L

S-insulin and S-C-peptide: for 24-hour measurements (Days -1, 6, and 28): AUC

Assessment of AEs during the study; BP; pulse; body weight; safety laboratory variables (including P-glucose); physical examination; and ECG.

Statistical methods

Descriptive statistics included n, mean, standard deviation (SD), min, median, and max, and for variables log-transformed in the analysis, also geometric mean and coefficient of variation.

Patient population

In total, 27 patients were randomised (16 white males and 11 white female patients at 1 study site). Twenty-one (21) of the 27 randomised patients completed the study. Of the randomised patients, the following discontinued prematurely: 3 patients from the active treatment group (1 voluntarily, 1 due to an AE, and 1 for other reason); 3 patients from the placebo group (1 voluntarily, 1 due to development of study specific discontinuation criteria, and 1 for severe non-compliance to protocol).

Following a starting dose of 5 mg bd, the majority of patients were successfully titrated to the maximum dose of 50 mg bd. Of those treated with AZD1656, 2 patients who had been titrated to 50 mg bd by Day 4 were down-titrated to 25 mg on Day 5 and remained at this dose level throughout the study. One (1) patient remained at the starting dose throughout the study.

Twenty-two (22) patients provided informed consent for participation in the genetic part of the study and blood samples were collected from all of them.

Summary of pharmacokinetic results

In this study, the PK properties of AZD1656 and its active metabolite AZ12555623 were evaluated following a repeated dose regimen over a longer treatment period than investigated in previous studies. At the end of the 28-day period, AZD1656 was generally rapidly absorbed and eliminated, and the active metabolite, AZ12555623, peaked slightly later than the parent compound. Overall exposure to the metabolite was much lower than the exposure to AZD1656. Trough plasma concentrations of the 2 analytes, measured regularly from Day 7 to Day 29, revealed no further accumulation. Overall, PK findings in this study were consistent with the information already gathered on AZD1656 PK properties and indicate a predictive PK behavior of the drug and its metabolite, rapid absorption and elimination, and time-invariant PK.

Based on urine 6ß-OH-cortisol and cortisol levels measured at baseline and on Day 28, treatment with AZD1656 for 28 days did not result in induction of CYP3A4 activity. This is consistent with pre-clinical studies that observed no induction of CYP following oral administration of AZD1656 in rats for 28 days.

Summary of pharmacodynamic results

P-glucose was reduced by approximately 24% by Day 6 of AZD1656 treatment and remained at this level throughout the period of AZD1656 treatment. Neither S-insulin nor S-C-peptide was affected by 28 days of AZD1656 treatment. This reduction in P-glucose following AZD1656 administration is consistent with its glucose kinase activator activity.

Summary of safety results

No safety and tolerability concerns were identified in this Phase IIa study in patients with T2DM treated with AZD1656 and metformin during out-patient conditions for a period of 28 days.

There was 1 SAE (rapid atrial fibrillation) reported during the study; this event also led to the patient's discontinuation from the study. No deaths were reported. No clinically relevant trends were observed in clinical laboratory results (other than blood glucose decrease), ECGs, or vital signs.

Following a starting dose of 5 mg bd, the majority of patients were successfully titrated to the maximum dose of 50 mg bd. Of those treated with AZD1656, 2 patients who had been titrated to 50 mg bd by Day 4 were down-titrated to 25 mg on Day 5 and remained at this dose level throughout the study. One (1) patient remained at the starting dose throughout the study. All other patients tolerated the 50 mg bd dose for 28 days in combination with metformin dosing.