AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00004
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A Randomized, Single-blind, Placebo-Controlled, Multi-Centre, Phase I Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics after Multiple Ascending Oral Doses of AZD1656 in Japanese T2DM Patients

Study dates: First patient enrolled: 25 May 2009
Last patient last visit: 2 October 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(s)

The study was conducted at 2 centres in Japan

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective was:

To investigate the safety and tolerability of AZD1656 after repeated oral doses of AZD1656 in Japanese T2DM patients by assessment of adverse events (AEs) occurring during the study, blood pressure (BP), pulse rate, safety laboratory variables and electrocardiography (ECG).

The secondary objectives were:

- To evaluate pharmacokinetic (PK) of AZD1656 and its metabolite AZ12555623 after repeated oral doses in Japanese T2DM patients by calculation of area under the plasma-concentration versus time curve (AUC), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F) (only for AZD1656), amount of drug excreted in urine (Ae) and renal clearance (CL_R).

- To evaluate plasma glucose, S-insulin and C-peptide levels after administration of repeated oral doses of AZD1656 in Japanese T2DM patients.

Exploratory objective was:

To collect and store DNA samples for future exploratory research into genes that may influence drug response (disposition, safety, tolerability and efficacy) of AZD1656.

Study design

In this randomized, single-blind, placebo-controlled, multi-centre phase I study, the safety, tolerability, PKs and pharmacodynamic (PD) were assessed after repeated ascending oral doses of AZD1656/placebo in 24 Japanese T2DM patients. This study included 8 days randomized treatment with escalating doses (includes a short titration procedure) in 3 groups of Japanese T2DM patients with 8 patients in each group (6 patients for AZD1656 and 2 patients for placebo). Patients were not allowed to participate in several dose steps. Before proceeding to next dose step, the dose given was evaluated by the Safety Review Committee (SRC).

Target subject population and sample size

24 Japanese T2DM patients (men and surgically sterile or postmenopausal women, treated with diet and exercise or with up to two oral anti-diabetic drugs except for glitazones).

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

The details of the investigational products (IP) are given in Table S 1.

Table S 1 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
AZD1656	Oral suspension 25 mg/mL	AstraZeneca R&D Sweden	D0800106	09-000985AZ, 09-003059AZ
AZD1656	Oral suspension 2 mg/mL	AstraZeneca R&D Sweden	D0800105	09-000989AZ
Placebo suspension	Oral suspension	AstraZeneca R&D Sweden	D0800042	09-002909AZ

Duration of treatment

During the first two days, the dose was titrated up to the target dose and the target dose then continued for 6 days, ie 7 days on target dose in total. The dose titration started with patients given half the target dose (10, 20 and 40 mg twice daily) on Day 1 and the target dose on Day 2 (20, 40 or 80 mg twice daily) and the rest of study (if tolerated). Those who did not tolerate the target dose were to remain on half the target dose.

The doses (20, 40 and 80 mg twice daily) were escalated stepwise provided that the previous dose was tolerated and safety had been evaluated by SRC and Principal Investigator. PK results for Day 2 to 8 for the 20 mg group were evaluated before start of 80 mg group. Patients were hospitalized during the treatment period. A follow-up visit was performed within 7 to 10 days after last dosing of IP.

Statistical methods

The study data will be evaluated mainly using descriptive statistics and analysis of (co)variance.

Subject population

The first patient entered the study on 25 May 2009 and the last patient finished the study on 2 October 2009. In total, 24 patients were randomized into the study at 2 study sites, where of 18 patients were exposed to AZD1656 and 6 to placebo during the planned treatment visit. No randomized patient discontinued the treatment. All patients in all cohorts reached the target dose, except for 1 patient in the 20 mg bd cohort continuing on 10 mg bd dose.

All patients were treatment naive and it should be noted that only one woman was enrolled in the study. Fasting P-glucose (FPG) levels at baseline was higher in the 40 mg bd cohort than

the 20 mg bd and the 80 mg bd cohorts (mean FPG 9.5 mmol/L compared to 8.6 mmol/L and 8.6 mmol/L). Otherwise, dose groups were comparable with regards to baseline characteristics.

Summary of pharmacokinetic results

AZD1656 was rapidly absorbed in all dose groups. The formed metabolite, AZ12555623 peaked approximately at the same time as AZD1656 both at Day 2 and Day 8. Pharmacokinetic steady state of AZD1656 and AZ12555623 was reached for all patients during the study. For the investigated dose range, there was no or a small accumulation of AZD1656 and approximately 50% accumulation of AZ12555623 at steady state, which is in agreement with the short half-life (ca. 3.8 hours) of AZD1656 and the half-life determined (ca. 9.7 hours) of AZ12555623. Small amounts of AZD1656 and AZ12555623 were found in urine. These data indicate that renal function is not likely to influence the PK of AZD1656 and AZ12555623.

Summary of pharmacodynamic results

AZD1656 had a significant P-glucose lowering effect in Japan T2DM patients. There were trends to initial increases in C-peptide and S-insulin, but no changes after 8 days administration of AZD1656.

Summary of safety results

This first study including patients from the target population, Japanese T2DM patients, did not identify any tolerability or safety concerns during repeated dosing of AZD1656 up to the highest dose of 80 mg bd. Five AEs were reported in 5 patients in AZD 1656 dose group and no AE was reported in the placebo group. The most commonly reported AEs during the study were blood glucose decreased (reported by 3 patients) with the lowest observed P-glucose being 3.27 mmol/L. All of them were asymptomatic and observed at the scheduled measurements.

There were no clinically relevant treatment-related changes or trends in any safety laboratory variable, vital signs or ECG observations.