AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00027
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An Open-Label, Randomised, Placebo-Controlled, Two-Way Crossover, Phase I Single Centre Study in Type 2 Diabetes Mellitus Patients Treated with Metformin to Evaluate the Pharmacokinetics and Pharmacodynamics of Warfarin During Co-administration with AZD1656

Study dates: First patient enrolled: 19 April 2010
Last patient last visit: 23 August 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 study centre in the United Kingdom (Quintiles Drug Research Centre at Guy's Hospital, London).

Publications

None at the time of writing this Clinical Study Report (CSR).

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
Evaluate the single dose pharmacokinetics of warfarin (R- and S-warfarin) when administered alone or in combination with AZD1656 at steady state.	AUC and C_{max}	PK
Secondary	**Secondary**	
Evaluate the anticoagulant activity of warfarin upon co-administration with AZD1656	Prothrombin time, INR_{max}, $tINR_{max}$ and INR-$AUC_{(0-168)}$	Pharmaco-dynamics (PD)
Evaluate the safety of AZD1656 in combination with warfarin	Electrocardiogram (ECG), weight, pulse, blood pressure, laboratory variables (including 7-point glucose), physical examination and adverse events (AEs)	Safety
Describe the PK of AZD1656 and its metabolite AZD5658 during concomitant warfarin administration	$AUC_{(0-24)}$, C_{max}, C_{trough}, t_{max}, $t_{1/2}$ (AZD1656 only) and CL/F (AZD1656 only)	PK
Exploratory		
To collect and store DNA samples for potential future research into genes which may influence drug response (PK profile, drug safety, efficacy and tolerability) of AZD1656, metformin and/or warfarin	Not applicable	Pharmaco-genetics

AUC: Area under the plasma concentration-time curve from zero extrapolated to infinite time, calculated by linear up/log down trapezoidal summation
$AUC_{(0-24)}$: Area under the concentration-time curve in the plasma from zero (pre dose) until 24 hours post-dosing, calculated by linear up/log down trapezoidal summation
C_{max}: Maximum concentration in the plasma, obtained directly from the observed concentration versus time data for AZD1656 and AZD5658 based on the morning (AM) dose
CL/F: Apparent oral clearance (L/h), calculated as total daily dose/$AUC_{(0-24)}$ (ie, (AM+PM dose)/ $AUC_{(0-24)}$; for AZ1656 only)
C_{trough}: Plasma concentration immediately before the next dose on Day 1 to Day 7, Day 9 and Day 11
INR_{max}: Maximum observed international normalised ratio
INR-$AUC_{(0-168)}$: Area under the INR time-curve from zero to 168 hours post-dose
$t_{1/2}$: Apparent terminal half-life (h), determined as $\ln 2/\lambda z$ (for AZD1656 [afternoon -PM dose] only)
t_{max}: Time of maximum plasma concentration (h), obtained directly from the observed concentration versus time data
$tINR_{max}$: Time to maximum observed INR
Note: Results from any genetic research, if performed, will be reported separately from this CSR

Study design

This was an open-label, randomised, placebo-controlled, two-way crossover, single-centre, Phase I, drug-drug interaction study in patients with Type 2 diabetes mellitus (T2DM). Male or female patients of non-childbearing potential, aged ≥18 years, treated with either metformin alone or metformin and one other oral anti-diabetic (OAD) (dipeptidyl peptidase-4 inhibitor [DPP-4 inhibitor] or sulphonylurea [SU]) were enrolled in the study.

The investigational products were administered in a crossover design in either sequence AB or sequence BA. Treatment A included AZD1656 twice daily from Day 1 to Day 10 and warfarin 25 mg on Day 4, and Treatment B included placebo twice daily from Day 1 to Day 10 and warfarin 25 mg on Day 4. Eligible patients treated with a DPP-4 inhibitor or a SU, stopped taking their DPP-4 inhibitor or SU 7 to 10 days (wash-out period) before administration of AZD1656/placebo on Day 1.

On Day 1, patients received AZD1656 40 mg/placebo twice daily, on Day 2, patients received AZD1656 100 mg/placebo twice daily, and on Day 3 to Day 10, patients received AZD1656 100 mg/placebo twice daily or if this was not well tolerated on Day 2, AZD1656 40 mg/placebo twice daily. A single dose of 25 mg warfarin was administered in the morning of Day 4 during each treatment period. The treatment periods were separated by a 2 day to 5 day wash-out period.

Blood samples for the analysis of plasma concentrations of warfarin and AZD1656 and its metabolite AZD5658 were collected during the 168 hours following warfarin administration, ie, from the morning of Day 4 until the morning of Day 11. Trough PK samples were taken from Day 6 to Day 11.

Target subject population and sample size

The target population was males and females of non-childbearing potential with T2DM aged ≥18 years, with a body mass index (BMI) ≥19 and ≤42 kg/m^2, treated with either metformin alone or metformin and one other OAD (DPP-4 inhibitor or SU). Eligible patients continued their metformin treatment during the study. Sixteen (16) patients were to be randomised in order to have 12 evaluable patients.

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

- AZD1656, 40 mg ([as 2 x 20 mg oral tablets] twice daily or 100 mg [as 2 x 50 mg oral tablets] twice daily, manufactured by AstraZeneca, Batch number 10-001788AZ and 10-001789AZ, respectively)
- AZD1656 placebo, matching oral tablets twice daily, manufactured by AstraZeneca, Batch number 10-001790AZ and 10-004268AZ
- Warfarin, 25 mg oral tablet on Day 4 of each treatment period, manufactured by Goldshield plc, Batch number DT9003

Duration of treatment

There were 2 treatment periods of 10 days each with a 2 day to 5 day wash-out between the treatment periods.

Statistical methods

Plasma concentrations of AZD1656, its metabolite AZD5658 and warfarin, and the derived PK parameters were summarised by treatment using descriptive statistics.

To assess the effect of AZD1656 on warfarin PK, the PK parameters of warfarin were analysed using analysis of variance (ANOVA) model on the log-transformed warfarin AUC and C_{max} with fixed effects for sequence, period and treatment, and patient nested within sequence as a random effect. Ratios of geometric means (test/reference) and the associated 90% confidence intervals (CIs) were presented.

To assess the effect of AZD1656 on the PD of warfarin, the PD parameters (INR-$AUC_{(0\text{-}168h)}$ and INR_{max}) of INR were analysed using analysis of covariance (ANCOVA) model on the log-transformed INR-$AUC_{(0\text{-}168h)}$ and INR_{max} with fixed effects for sequence, period and treatment, and patient nested within sequence as a random effect. Period specific, log-transformed INR baseline (pre-dose, hour 0) was included in the model as a covariate. Ratios of geometric means (test/reference) and the associated 90% CIs were presented.

The inferential analyses for both PK and PD were carried out on combined data from all patients including patient(s) receiving 40 mg AZD1656 in Treatment A. A confirmatory analysis was also performed excluding patient(s) that received 40 mg AZD1656.

Adverse events were summarised by frequency within treatment. Laboratory safety tests, ECGs and vital signs were summarised by treatment group and time points within treatment groups.

Patient population

A total of 15 patients with T2DM were randomised in this study. The first patient was enrolled on 19 April 2010 and the last patient completed the study on 23 August 2010. All randomised patients completed the study.

Summary of pharmacokinetic results

R-warfarin and S-warfarin mean concentration-time profiles were comparable following treatment with warfarin + placebo and warfarin + AZD1656.

The geometric least squares mean ratio (AZD1656/placebo) for key PK parameters (AUC and C_{max}) were 103.89 (90% CI: 101.50, 106.33) and 95.48 (90% CI: 89.92, 101.39), respectively for R-warfarin, and 100.81 (90% CI: 97.52, 104.22) and 92.18 (90% CI: 85.58, 99.30), respectively for S-warfarin.

From the statistical analyses results, it can be concluded that repeated administration of 100 mg AZD1656 twice daily did not affect the PK of R-warfarin and S-warfarin following a single dose of 25 mg warfarin.

The geometric mean (median for t_{max}) key PK parameters $AUC_{(0-24)}$, C_{max}, t_{max}, $t_{1/2}$ and CL/F for AZD1656 were 51.8 µmol*h/L, 4.79 µmol/L 0.78 hours, 4.33 hours, and 8.07 L/h respectively whereas the key PK parameters for AZD5658 ($AUC_{(0-24)}$, C_{max}, t_{max}) were 6.57 µmol*h/L, 0.544 µmol/L and 1.5 hours respectively.

Summary of pharmacodynamic results

The geometric least squares mean ratio (AZD1656/placebo) for key INR PD parameters ($INRAUC_{(0-168)}$ and INR_{max}) were 98.08 (90% CI: 94.66, 101.63) and 99.59 (90% CI: 91.53, 108.37), respectively.

The 90% CIs for the geometric mean ratios of $INRAUC_{(0-168)}$ and INR_{max} after a single administration of warfarin in combination with AZD1656 at steady state versus warfarin alone were contained within the interval 80.00% to 125.00%. Thus, AZD1656 when administered with warfarin did not change the INR value.

Summary of safety results

No SAEs, other significant AEs or discontinuation of investigational product due to AEs (DAEs) were reported during the study conduct.

Hypoglycaemia was the most commonly reported AE and was only reported when administered AZD1656 with warfarin. Other AEs were abdominal discomfort, diarrhoea, a procedural site reaction, arthralgia, dizziness, headache, somnolence and oropharyngeal pain reported by no more than 2 patients. In the placebo and warfarin treatment group, 1 patient reported increased blood glucose.

There were no clinically relevant changes in clinical laboratory, vital signs, ECG, physical examination findings, or weight.