AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD4017
Study Code	D2060C00002
Edition Number	1
Date	13 January 2010

A randomised, single-blind, placebo-controlled, single-centre, Phase I study in healthy volunteers to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD4017 after repeated ascending oral doses

Study dates: First subject enrolled: 03 February 2009
Last subject last visit: 29 May 2009

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was performed at one study centre in Sweden.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety and tolerability of AZD4017 following administration of multiple ascending doses	Adverse events, laboratory variables, physical examination, ECG, vital signs	Safety
Secondary	**Secondary**	
To evaluate the pharmacokinetics (plasma and urine) of AZD4017 and its glucuronic acid metabolite (AZ13046363) after single and repeated ascending oral dosing	AUC, $AUC_{(0\text{-}12/24/48h)}$, AUC_{τ} C_{max}, t_{max}, $t_{½\lambda z}$, CL/F (only for AZD4017), CL_R, $Ae_{(0\text{-}48h)}$, Ae_{τ}, $C_{ss,min}$	PK
To assess the 11-βHSD1 enzyme activity in human adipose tissue by ex-vivo methods after repeated doses of AZD4017	^{3}H cortisone to ^{3}H cortisol % conversion/100 mg tissue	PD
To assess the 11-βHSD1 enzyme activity in the liver by measuring prednisolone generation after oral prednisone challenge after repeated doses of AZD4017	Prednisone and Prednisolone concentration in plasma	PD
To assess urine glucocorticoid metabolites after multiple oral doses of AZD4017	Urinary free cortisol [UFF], urinary free cortisone [UFE], and the A-ring reduced metabolites of cortisol and cortisone [5-alphatetrahydrocortisol (5αTHF), 5β-tetrahydrocortisol (5βTHF), and tetrahydrocortisone (THE)].	PD
To assess the effect on insulin and lipid variables after multiple oral doses of AZD4017	S-Insulin, FFA, HDL-C, LDL-C, total Cholesterol, TG, Glucose and Lactate	PD
Exploratory		
To collect and store blood samples for potential future exploratory genetic research aimed at identifying/exploring genetic variations that may affect PK and PD, safety and tolerability related to AZD4017[a]		
To assess weight, waist circumference and waist/hip ratio after multiple oral doses of AZD4017	Weight, waist, hip	PD

Objectives	Outcome variables	Type
To assess the effect on biomarkers of insulin sensitivity after multiple oral doses of AZD4017	Adiponectin	PD
To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and endocrine function	Renin, 4βOHCholesterol, 5β-reductase (THE/UFE)	PD
To collect and store adipose tissue samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism and endocrine function[a]		

[a] Not reported in the CSR

Study design

This was a Phase I, randomised, single-blind, placebo-controlled single centre study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD4017 following multiple ascending dose administration to male, healthy volunteers.

Target subject population and sample size

It was planned to include a total of 45 evaluable healthy male subjects in the study. Four dose escalation panels were planned (with the option of adding one extra dose panel if needed). In each dose panel, 6 subjects were to be randomised to receive AZD4017 and 3 to placebo.

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

The details of the investigational product are given in Table 1.

Table 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
AZD4017	20 mg/mL oral suspension	AstraZeneca	F13666	62314J08, 62838I08, 62839F08, 62772E08
Placebo	0 mg/mL oral suspension	AstraZeneca	F13667	62313B08, 62771H08

In each dose panel 9 healthy volunteers were randomised to active treatment (6 healthy volunteers) or placebo (3 healthy volunteers). Each randomised subject received one single dose of study drug followed by a 48 hour wash-out and 9 days of repeated dosing given once daily for dose panel A-C and twice daily for dose panel D-E. The dose panels received: A:

75 mg single dose (sd) + 75 mg od; B: 300 mg sd + 300 mg od; C: 1200 mg sd +1200 mg od; D: 600 mg sd + 600 mg bd; E: 1500 mg sd + 900 mg bd.

Duration of treatment

The single dose was followed by a 48-hour washout before the 9 days repeated dosing was carried out.

Statistical methods

Dose proportionality, time dependency, and the extent of accumulation was analysed using an ANCOVA model, presenting point estimate and 2-sided 90% confidence interval. Other data were summarised using descriptive statistics. AUC for ACTH were analysed using an ANCOVA model, presenting point estimate and 2-sided 90% confidence interval.

Subject population

In total, 107 Caucasian healthy male volunteers were enrolled into the study at 1 study site. 45 subjects were randomised to treatment, whereof 30 received AZD4017 and 15 received placebo. Three subjects discontinued investigational product due to adverse event, whereof 1 on AZD4017 600 mg bd, 1 on AZD4017 300 mg od and 1 on AZD4017 1200 mg od, respectively. All other subjects randomised to treatment completed the study. Overall, the treatment groups were well balanced with regards to demographic characteristics apart from the subjects on AZD4017 1200 mg sd + 1200 mg od being slightly overweight (mean BMI=25,8 kg/m^2) in comparison with the other active treatment groups and placebo where mean BMI was <25 kg/m^2.

Summary of pharmacokinetic results

The plasma concentration versus time profile of AZD4017 seems to be bi-phasic with a similar profile over the dose range studied, with secondary plasma concentration peaks occasionally present. Maximum plasma concentration was generally observed within a few hours and steady state conditions of AZD4017 had been reached after 9 days of repeated dosing. The maximal individual apparent terminal half-life of AZD4017 in plasma following repeated dosing was 48 hours, however the low degree of accumulation indicates an effective half-life that is shorter, approximately 10 hours. The systemic exposure of AZD4017 increased slightly less than in proportion to dose in the dose range studied following both single and repeated once daily dosing, but there was no major influence of time on the pharmacokinetics of AZD4017. The plasma concentration versus time profile of the glucuronic acid metabolite, AZ13046363, follows the shape of the AZD4017 profile. After repeated dosing for 9 days, the geometric mean systemic exposure (C_{max} and AUC_{τ}) of AZ13046363 was approximately 20 to 50% of parent exposure over the dose range. Exploratory analysis of AZD4017 and AZ13046363 in urine showed that the renal clearance of AZD4017 is low with less than 0.25% of the given dose excreted unchanged in urine. Up to 15% of the dose was excreted as AZ13046363 in urine.

Summary of pharmacodynamic results

For those dose groups for which mean % conversion of ^{3}H cortisone to ^{3}H cortisol / 100 mg adipose tissue was determined after single dose (AZD4017 600 mg and AZD4017 1500 mg), a decrease from predose[1] was observed. The data do not suggest a sustained effect after repeated dosing for 9 days. However, ex vivo investigations suggest the possibility to obtain an inhibition also after repeated dosing at high AZD4017 concentrations.

The mean plasma concentrations of prednisolone and the mean ratios of C_{max} and $AUC_{(0-4h)}$ for prednisolone/prednisone decreased both from predose to 9 days repeated dosing (studied in AZD4017 75 mg od to 600 mg bd) as well as after single dose (studied in AZD4017 1500 mg). The mean C_{max} and $AUC_{(0-4h)}$ of prednisone also tended to decrease from predose to 9 days repeated dosing in treatment groups AZD4017 75 mg od to 600 mg bd and from predose to after single dose (studied in AZD4017 1500 mg only).

The urine glucocorticoid metabolites 5α-tetrahydrocortisol (5αTHF) and 5β-tetrahydrocortisol (5βTHF) are converted to tetrahydrocortisone (THE) by 11-βHSD1. The change in ratio of 5αTHF+5βTHF to THE was investigated to give an indication of the effect of AZD4017 on 11-βHSD1. Urinary free cortisol (UFF) and urinary free cortisone (UFE) were measured to investigate the effect of AZD4017 on 11-βHSD2. The total urinary corticosteroids (5αTHF, 5βTHF, THE, UFF and UFE) were measured to identify signs of activation of the hypothalamic-pituitary-adrenal (HPA) axis, following administration of AZD4017. There was a decrease from predose in the mean ratio of 5αTHF and 5βTHF to THE to 6 and 9 days repeated dosing in all active treatment groups. There was no consistent effect on the mean ratio of UFF/UFE after repeated dosing. The mean of total urinary corticosteroids (5αTHF, 5βTHF, THE, UFF and UFE) increased from predose in all active treatment groups to 6 and 9 days repeated dosing.

No clinically relevant effects on S-Insulin, lipids, glucose or lactate were observed from predose to 9 days repeated dosing.

The data do not suggest an effect on weight, waist or waist/hip ratio from predose to 9 days repeated dosing.

No consistent effects on 4βOH-cholesterol or renin were observed after treatment of AZD4017 for 9 days compared to before treatment. The mean ratio of THE/UFE increased from predose in all active treatment groups to 6 and 9 days repeated dosing.

The data do not suggest a consistent effect in adiponectin from predose to 9 days repeated dosing.

[1] Predose is defined as the last assessment before the single dose

Summary of pharmacokinetic/pharmacodynamic relationships

No clear correlation between exposure of AZD4017 and % change in conversion of ^{3}H cortisone to ^{3}H cortisol in adipose tissue was observed after 9 days repeated dosing. In samples taken 6 hours after the single dose (AZD4017 600 mg and AZD4017 1500 mg), there was a decrease in % conversion of ^{3}H cortisone to ^{3}H cortisol in adipose tissue without obvious dose relation.

Summary of safety results

There was 1 serious adverse event in the study: Acute appendicitis was reported in the AZD4017 600 mg bd dose group after 5 days of repeated treatment; this subject discontinued IP. The SAE was not considered to be causally related to IP by the investigator.

There were three discontinuation of IP due to AEs (DAEs)[2] in the study, whereof one was in the subject with an SAE of acute appendicitis described above. Another subject discontinued due to a non-sustained ventricular tachycardia of mild intensity after 6 days of repeated treatment with AZD4017 300 mg od and one subject discontinued due to increased transaminases (ALT >3 x ULN and AST >2 x ULN) after 8 days of repeated treatment with AZD4017 1200 mg od. There were no concurrent increases in bilirubin or ALP and a complete normalisation of ALT and AST was seen at an additional follow up of this subject after the study. Elevated ALT above ULN was observed in a few (4 of 30) subjects treated with AZD4017 (including one subject who discontinued due to increased transaminases – see DAE description above).

There were no deaths or any other significant adverse event (OAEs) in the study. Most of the AEs were of mild/moderate intensity. The type of AEs in the active treatment groups and the placebo group were similar. The most commonly reported AEs were headache, and post procedural complication.

An activation of the HPA-axis was demonstrated by an increase in ACTH and DHEA-s levels and by an increase of total urinary glucocorticoid metabolites. However, s-cortisol and testosterone levels were not changed.

An increase in mean TSH values was seen in the AZD4017 600 mg sd+ 600 mg bd and in the AZD4017 1200 mg sd + 1200 mg od treatment groups (maximal individual value of TSH>1.5 x ULN). Notably, TSH values above ULN were also seen in the placebo group. There were no consistent effects on T3 and T4 and the levels of TSH returned towards normal levels at the follow up visit.

There were no clinically relevant changes in any other safety laboratory analyses, vital signs or in ECG in the healthy volunteers exposed to AZD4017 during the study.

[2] Note, these AEs were reported as discontinuations from the study as the CRF did not contain an option to record “discontinuation of IP due to AE”.