AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD8329
Study Code	D2350C00010
Edition Number	1
Date	17 August 2011

A Phase I, Single Centre, Single-Blind, Randomised, Placebo-Controlled, Parallel-Group Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Oral AZD8329 after Administration of Multiple Ascending Doses in Abdominally Obese but otherwise Healthy Male Subjects

Study dates: First subject enrolled: 22 September 2010
Last subject last visit: 17 December 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

One study centre in the United Kingdom

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 AZD8329 following administration of multiple doses	Adverse events, laboratory variables, physical examination, vital signs, ECG	Safety
Secondary	**Secondary**	
To evaluate the PK (plasma and urine) of AZD8329 after single and multiple doses	C_{max}, t_{max}, $t_{1/2\lambda z}$, AUC_{τ}, AUC, AUC_{0-t}, CL/F, V_z/F, CL_R, and Ae; % dose and Ae_{τ}; % dose for multiple dosing	PK
To assess the 11-βHSD1 enzyme activity in human adipose tissue by ex-vivo methods after single and/or multiple doses of AZD8329	Adipose tissue biopsy: % conversion of ^{3}H cortisone to ^{3}H cortisol and, in addition, analysis of endogenous cortisone and cortisol levels in tissue with mass-spectrometry detection	PD
To assess the 11-βHSD1 enzyme activity in the liver by measuring prednisolone generation after oral prednisone challenge after multiple doses of AZD8329	Prednisone challenge: plasma concentration of prednisolone and prednisone and ratio of prednisolone/prednisone	PD
To assess urine glucocorticoid metabolites after multiple doses of AZD8329	UFF, UFE, UFF/UFE, 5αTHF, 5βTHF, THE, 5αTHF+ 5βTHF/THE, and total corticosteroids (5αTHF, 5βTHF, THE, UFF and UFE)	PD
To assess the effect on insulin, glucose, and lipid variables after multiple doses of AZD8329	P-glucose, S-insulin, and FFA, HDL-C, LDL-C, total cholesterol, triglyceride	PD
Exploratory	**Exploratory**	
To investigate the presence and/or identity of drug metabolites of AZD8329 after multiple doses of AZD8329 and, if appropriate, characterise their PK	C_{max}, AUC and other PK parameters as appropriate (not reported in the CSR)	PK
To assess weight, waist circumference, and waist/hip ratio after multiple doses of AZD8329	Weight and waist to hip ratio	PD
To assess the effect on biomarkers of insulin sensitivity after multiple oral doses of AZD8329	Leptin, adiponectin, and HOMA-IR index	PD

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism, endocrine function, or the PK of AZD8329	NA	Pharmaco-genetic
To collect and store adipose tissue samples for potential future exploratory research aimed at exploring gene expression, enzymes, and biomarkers involved in nutrient metabolism and endocrine function and/or concentrations of investigational product in adipose tissue	NA	Pharmaco-genetic
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 AZD8329	NA	Pharmaco-genetic
To collect blood samples for exploratory genetic research aimed at identifying/exploring genetic variations in CYP3A5 that may affect the PK of AZD8329	Alleles of CYP3A5 and CL/F of AZD8329	Pharmaco-genetic

5αTHF: 5α-tetrahydrocortisol; 5βTHF: 5β-tetrahydrocortisol; 11-βHSD1: 11-β hydroxysteroid dehydrogenase type 1; Ae: amount of drug excreted unchanged in urine; Ae_{τ}: amount of drug excreted unchanged in urine during a dosing interval; AUC: area under the plasma concentration-time curve; AUC_{0-t}: area under the plasma concentration-time curve from zero to time t; AUC_{τ}: area under the plasma concentration-time curve during a dosing interval; CL/F: oral plasma clearance; CL_R: renal clearance; C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; CSP: Clinical Study Protocol; CYP: cytochrome P450; dECG: digital electrocardiogram; ECG: electrocardiogram; FFA: free fatty acids; HDL-C: high density lipoprotein-cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; LDL-C: low density lipoprotein-cholesterol; NA: not applicable; PD: pharmacodynamic(s); PK: pharmacokinetic(s); $t_{1/2\lambda z}$: half-life; THE: tetrahydrocortisone; t_{max}: time to maximum plasma concentration; UFE: urinary free cortisone; UFF: urine free cortisol; V_z/F: oral volume of distribution during terminal phase.

Study design

In this multiple ascending dose study, the starting dose of AZD8329 was 25 mg. In each cohort, 9 subjects were to be randomised to receive AZD8329 or placebo. Ultimately, 3 cohorts were administered 25 mg, 100 mg, or 300 mg AZD8329 or placebo. All subjects were to receive 10 mg prednisone on Day -2 (Visit 2) and Day 13 (Visit 3). Subjects were to receive a single dose of AZD8329 or placebo on Day 1 (Visit 3) and twice daily doses of AZD8329 or placebo from Day 4 to Day 12 (Visit 3).

Target subject population and sample size

A planned 45 abdominally obese, but otherwise healthy male subjects, aged 20 to 50 years.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number	Expiry date
AZD8329	Solution, 20 mg/mL, oral	AstraZeneca	10-005190AZ	31 August 2011
			10-004724AZ	30 April 2011
			10-004450AZ	31 March 2011
			10-004240AZ	31 March 2011
			10-225192AZ	31 July 2011
Placebo	Solution, 0 mg/mL, oral	AstraZeneca	10-005192AZ	31 July 2011
			10-004726AZ	31 July 2011
			10-004453AZ	31 March 2011
			10-004249AZ	31 March 2011

Duration of treatment

The study consisted of 4 visits. Screening (Visit 1) from Day -34 to Day -4. Subjects were to be admitted to the study centre for pre-dose procedures at Visit 2 on Day -4. AZD8329 or placebo was administered during Visit 3, Day -1 to Day 14. Follow-up assessments were performed at Visit 4, 14 to 17 days after the last dose.

Statistical methods

No formal statistical hypothesis testing was performed. The analyses of safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) were summarised descriptively in tables, listings, and graphs, as appropriate.

Subject population

Planned: 45 subjects

Enrolled: 27 subjects

Randomised: 26 subjects

Completed: 26 subjects

All subjects were eligible for enrolment in this study. Overall, the dose groups were well balanced with regards to the demographic characteristics.

Summary of pharmacokinetic results

The absorption of AZD8329 was fast with a median time to C_{max} (t_{max}) of around 1 hour within the dose range studied and after both single and repeated dosing. The inter-individual variability (CV%) in the C_{max} and different area under the plasma concentration-time curve (AUC) estimates was low to moderate (<50%).

The volume of distribution (V_z/F) estimated Day 1 was low and consistent within the dose range studied (geometric mean V_z/F ranging between 41 and 49 L). The oral plasma clearance (CL/F) of AZD8329 was low and similar for all 3 doses studied at both Day 1 and Day 12 (geometric mean CL/F of 1.5 to 2.1 L/h). The geometric mean terminal half-life ranged between 13 to 20 hours at Day 1 and between 9.3 and 11 hours after the evening dose Day 12.

The renal clearance was low both in value (around 0.01 L/h) and in comparison to the oral plasma clearance. Less than 1% of the administered dose was excreted as unchanged drug in urine after both single and repeated dosing.

Table S3 Summary of pharmacokinetic parameters of AZD8329 Day 1 presented as geometric mean and CV% (PK analysis set)

Parameter	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)
C_{max} (µmol/L)	4.92 (14.3)	23.3 (18.4)	67.2 (18.1)
t_{max} (h)[a]	0.67 (0.67-0.67)	0.68 (0.67-1.00)	0.67 (0.67-1.50)
AUC (h*µmol/L)	34.9 (44.8)	112 (24.9)	333 (27.7)
AUC_{τ} (h*µmol/L)	22.9 (28.4)	86.0 (17.4)	258 (22.8)
CL/F (L/h)	1.69 (44.7)	2.11 (25.0)	2.14 (27.6)
$t_{½\lambda z}$ (h)	20.0 (10.2)	13.8 (19.6)	13.4 (25.8)

[a] Median and range (minimum-maximum).
[b] n=4.

Table S4 Summary of pharmacokinetic parameters of AZD8329 Day 12 morning presented as geometric mean and CV% (PK analysis set)

Parameter	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)
C_{max} (µmol/L)	7.35 (30.2)	26.0 (19.4)	77.7 (15.7)
t_{max} (h)[a]	0.67 (0.67-1.02)	0.67 (0.67-1.00)	0.84 (0.67-1.50)
AUC_{τ} (h*µmol/L)	40.2 (46.1)	117 (18.6)	425 (31.2)
AUC_{0-24} (h*µmol/L)	78.2 (45.2)	243 (15.0)	856 (29.9)
CL/F (L/h)	1.47 (46.1)	2.03 (18.6)	1.67 (31.2)

[a] Median and range (minimum-maximum).

Table S5 Summary of pharmacokinetic parameters of AZD8329 Day 12 evening presented as geometric mean and CV% (PK analysis set)

Parameter	25 mg (n=6)	100 mg (n=6)	300 mg (n=6)
C_{max} (µmol/L)	4.96 (35.1)	19.3 (16.6)	65.7 (23.2)
t_{max} (h)[a]	1.45 (0.97-1.50)	1.25 (0.67-2.50)	0.75 (0.62-1.43)
AUCτ (h*µmol/L)	38.0 (44.4)	126 (12.5)	430 (28.8)
CL/F (L/h)	1.56 (44.3)	1.87 (12.6)	1.65 (28.7)
$t_{½\lambda z}$ (h)	11.3 (36.0)	9.32 (33.8)	9.45 (8.8)

[a] Median and range (minimum-maximum).

Summary of pharmacodynamic results

At Day 1 of treatment with AZD8329 a dose dependent reduction in the mean percent conversion of ^{3}H cortisone to ^{3}H cortisol in comparison to baseline was seen. This effect was less pronounced at Day 12.

There was a placebo corrected decrease in the cortisol/cortisone ratio assessed by mass spectrometry of adipose tissue both after single and repeated doses of AZD8329 at the highest dose of 300 mg twice daily.

After the prednisone challenge, both prednisolone and prednisone decreased after repeated administration of AZD8329. The decrease in prednisolone generation can be explained as an effect of inhibition of 11-βHSD1 in liver, while, the decrease in prednisone was an unexpected effect.

There were no significant changes or trends observed for glucose and insulin after repeated dosing of AZD8329 in healthy human. Similarly there were no trends observed for lipid variables.

No change in waist to hip ratio was observed after repeated dosing with AZD8329 in this study. This is not unexpected, as in most instances to observe any substantial change in this variable, the dosing would have to be for longer periods of time than was in this study.

An activation of the HPA-axis was indicated by an increase in ACTH and DHEAS-levels after treatment with AZD8329. However, s-cortisol and testosterone levels were not consistently changed.

Summary of pharmacokinetic/pharmacodynamic relationships

There was a relationship between change from baseline in percent conversion of ^{3}H cortisone to ^{3}H cortisol in adipose tissue versus plasma concentrations of AZD8329 after single dosing with AZD8329 but this relationship was not as obvious after repeated dosing.

Summary of safety results

There were no deaths, discontinuation due to adverse events (DAEs), or any other significant adverse events (OAEs) in the study. One serious adverse event (SAE), not considered to be causally related to the investigational product, diffuse large B-cell lymphoma, was reported after completion of the study. No safety concerns, based on the adverse events (AEs) reported, laboratory measurements, vital signs, electrocardiogram (ECG), and physical examination, were reported.