AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2820
Study Code	D3870C00001
Edition Number	1
Date	10 April 2012
EudraCT Number	2010-024470-19

A randomised, single-blind, placebo-controlled, single centre phase I study in healthy male volunteers to assess the safety, tolerability, and pharmacokinetics of AZD2820 after single ascending doses

Study dates: First subject enrolled: 4 May 2011
Last subject last visit: 15 November 2011

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.

Study centre(s)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To assess the safety and tolerability of AZD2820 following administration of single ascending doses	Adverse events, laboratory variables, physical examination, ECG, vital signs, penile erection, EEG, immunogenicity, C-SSRS, SSAI, histamine release, and injection site tolerability
Secondary	PK	To evaluate the PK of AZD2820 and assess the dose proportionality of the PK following single ascending doses of AZD2820	C_{max}, $t_{max,}$ $AUC_{(0-6)}$, $AUC_{(0-t)}$, AUC, λ_z, $t_{1/2\lambda z}$, CL/F, A_e, CL_R
Exploratory	PK	To explore the effect of the location of administration (thigh and abdomen) on the PK of AZD2820	Dose normalized AZD2820 mean plasma concentration-time profiles
	Pharmaco-genetic[a]	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 AZD2820 treatment	Not applicable
	PK[a]	To collect and store blood samples for potential future exploratory research aimed at exploring biomarkers involved in nutrient metabolism, metabolic diseases, or the PK of AZD2820	Not applicable
	PK[a]	To investigate the presence and/or identity of drug metabolites of AZD2820 and, if appropriate, characterise their PK	Not applicable

[a] Reported separate from the clinical study report.
λ_z: terminal rate constant; A_e: amount of drug excreted unchanged or as metabolites in urine; AUC: area under the plasma concentration-time curve; $AUC_{(0-6)}$: area under the plasma concentration-time curve from zero to 6 hours; $AUC_{(0-t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; CL/F:apparent oral clearance; CL_R: renal clearance; C_{max}: maximum plasma (peak) drug concentration after single dose administration; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; EEG: electroencephalography; PD: pharmacodynamics; PK: pharmacokinetics;

SSAI: Spielberger State Anxiety Inventory; $t_{1/2\lambda z}$: terminal plasma half-life; t_{max}: time to reach peak or maximum concentration.

Study design

This was a first time in human, randomised, single-blind, placebo-controlled, single centre, single ascending dose study in healthy male volunteers.

The study was to consist of 10 cohorts. Each cohort was to receive an escalating dose of AZD2820. Nine healthy volunteers participated in each cohort, randomised to receive AZD2820 or placebo (administered in the abdomen or thigh) in a 6:3 ratio. The randomisation scheme was produced using the global randomisation system (GRand).

The starting dose was 0.03 mg. After each cohort the Safety Review Committee (SRC) reviewed and assessed the available safety and PK data (up to 24 hours postdose) from at least 4 healthy volunteers who received AZD2820, and decided on the next dose level to be administered.

The dose levels administered were 0.03 mg, 0.15 mg, 0.75 mg, 2.25 mg, 6 mg, 9 mg, and 12 mg. The 12 mg dose level was not well tolerated by the healthy volunteers and the SRC made the decision to investigate a dose level between 6 mg and 12 mg (ie, 9 mg). The SRC also decided that there would be no further administration of the investigational product after the 9 mg dose level.

The study consisted of 3 periods. Visit 1 (Days -21 to -2) was the screening period. Visit 2 was the treatment period and healthy volunteers were resident in the study centre from Days -1 to 3. The investigational product was injected subcutaneously (all dose levels were administered as 1 injection) in the abdomen or thigh on Day 1. The follow-up assessments were conducted at Visit 3 (Day 8), Visit 4 (14 to 18 days after Day 1), and Visit 5 (Day 29).

Target subject population and sample size

Nine healthy male volunteers participated in each cohort, randomised to receive AZD2820 or placebo (administered in the abdomen or thigh) in a 6:3 ratio

Due to the exploratory nature of the study the sample size was not based on formal statistical considerations. The sample size was based on experience from previous similar phase I studies with other compounds.

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

Each subject received AZD2820 or placebo injected subcutaneously in the abdomen or thigh on Day 1.

The dose levels administered were 0.03 mg, 0.15 mg, 0.75 mg, 2.25 mg, 6 mg, 9 mg, and 12 mg.

AZD2820 batch numbers: 1 mg/mL: 11-000765AZ; 50 mg/mL: 11-000771AZ.

Placebo batch number: 11-000726AZ.

Duration of treatment

Single dose.

Statistical methods

The analyses of the data were based on different analysis sets according to the purpose of the analysis, ie, for safety and PK, respectively.

The Safety analysis set included all healthy volunteers who received at least 1 dose of randomised investigational product, AZD2820 or placebo, and for whom any postdose data were available.

The PK analysis set included all evaluable PK data appropriate for the evaluation of interest (with no important protocol deviations or violations thought to significantly affect the PK of the investigational product) from all healthy volunteers who received AZD2820. Healthy volunteers who received placebo were not included in the PK analysis set.

Data were presented by actual dose level (not by cohort), and healthy volunteers who received placebo were pooled across cohorts for the purposes of summarising the safety results.

Subject population

Sixty three (63) healthy volunteers were randomised in the study and received AZD2820 or placebo.

Summary of pharmacokinetic results

The absorption of AZD2820 after subcutaneous administration was fast with median time for reaching C_{max} ranging between 0.75-1.14 hours. The decline in plasma concentrations was also fast with the geometric mean terminal half-life ranging between 2.47-4.38 hours.

AZD2820 was to a large part excreted as unchanged drug in urine, (with a geometric mean ranging from 36.5-64.7% for different doses). The CL_R and fraction of dose excreted unchanged in urine was similar among the dose groups except for at the 0.15 and 0.75 mg doses, with lower and more variable estimations of CL_R and A_e (%) than for the other dose groups.

The site of injection did not have any appreciable effects on the concentration-time profiles of AZD2820. AZD2820 had a similar shape of the plasma concentration versus time profile when administered in the thigh and abdomen, respectively. However the peak concentration seemed to be slightly higher following administration in the abdomen.

A summary of key plasma PK parameters for AZD2820 is presented in Table S1.

Table S1 Geometric mean (CV%) of key AZD2820 plasma PK parameters by dose group

AZD2820 dose group	C_{max} (nmol/L)	t_{max} (h)[a]	$AUC_{(0-t)}$ (nmol·h/L)	AUC (nmol·h/L)	$t_{½}$ (h)	CL/F (L/h)	$AUC_{(0-6)}$ (nmol*h/L)
0.15 mg (N=6)	4.56 (14.9)	1.02 (0.52 – 1.25)	14.0 (12.9)	ND	2.47 (18.3)	ND	14.8 (6.7)
0.75 mg (N=6)	23.4 (25.5)	1.14 (0.75 – 1.75)	102 (13.7)	110 (11.4)	3.39 (14.0)	6.52 (11.5)	80.7 (13.8)
2.25 mg (N=6)	69.5 (17.1)	0.75 (0.50 – 1.50)	312 (18.0)	322 (17.2)	4.05 (11.6)	6.69 (17.2)	231 (16.5)
6.0 mg (N=6)	180 (14.5)	1.02 (0.77 – 1.23)	1000 (8.7)	1020 (8.8)	4.38 (12.7)	5.60 (8.7)	675 (9.6)
9.0 mg (N=6)	261 (20.5)	0.77 (0.52 – 1.02)	1430 (9.8)	1460 (9.7)	4.36 (4.9)	5.89 (9.7)	960 (13.0)
12.0 mg (N=6)	424 (15.2)	0.885 (0.27 – 1.03)	2040 (15.6)	2070 (15.7)	4.17 (7.8)	5.53 (15.7)	1420 (15.3)

[a] Data presented as median (range); ND not determined.

Based on a statistical assessment of dose proportionality, C_{max} was shown to increase proportionally with dose (90% confidence interval for the slope 0.98-1.04) whereas a slightly more than proportional increase in dose was indicated for AUC (90% confidence interval for the slope 1.03-1.10).

Summary of safety results

There were no deaths, serious adverse events, discontinuations of the investigational product due to an adverse event (AE), or any other significant AEs in the study. Adverse events were reported at all dose levels as well as placebo. All AEs reported at 0.03 mg, 0.15 mg, 0.75 mg, 2.25 mg, and 6 mg were mild in intensity.

The most frequently reported AE was injection site reaction (reported at all dose levels except 0.03 mg and placebo) and more healthy volunteers reported injection site reaction with the abdomen as the administration site than the thigh. Nausea, vomiting, increased erection, and decreased appetite were reported at 9 mg and 12 mg. Moderate (increased erection, headache, concussion, nausea, and vomiting) and severe (nausea and vomiting) AEs were reported at 9 mg and 12 mg.

Overall, the most frequently reported AEs considered to be related to the investigational product by the investigator, were injection site reaction, nausea, and vomiting.

No clinically relevant findings were observed for any safety laboratory variables, immunogenicity, histamine release, vital signs, ECG, physical examinations, EEG, SSAI, or C-SSRS.

Penile rigidity and tumescence increased with dose level and prolonged erections were observed at the 9 mg and 12 mg dose levels.