Clinical Study Report Synopsis

Drug Substance	AZD2820
Study Code	D3870C00002
Edition Number	1
Date	
EudraCT Number	2011-003242-41

A Phase I, Single Centre, Single-blind, Randomised, Placebo-controlled, Parallel-group Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AZD2820 after Administration of Multiple Ascending Doses

Study dates: First subject enrolled: 14 March 2012
Last subject last visit: 27 July 2012

Phase of development: Clinical Pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective Outc			ome Variable
Priority Type		**Description**	**Description**
Primary	Safety	To investigate the safety and tolerability of AZD2820 following administration of multiple ascending doses	AEs, vital signs (blood pressure, pulse rate, body temperature), 24-hour ambulatory blood pressure measurement, ECG, dECG, 24-hour telemetry, laboratory variables, physical examination, penile erection, skin pigmentation, immunogenicity, EEG, hair growth, histamine release, injection site tolerability
Secondary	PK	To evaluate the PK of AZD2820 and assess the time dependency in the PK following multiple ascending doses of AZD2820	C_{max}, $C_{ss,max}$, t_{max}, $t_{ss,max}$, λ_z, $\lambda_{ss,z}$, $t_{1/2\lambda z}$, $t_{1/2\lambda z,ss}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}tau)}$, $AUC_{ss,(0\text{-}tau)}$, AUC, CL/F, CL_{ss}/F, V_z/F, $V_{z,ss}/F$, Rac_{AUC}, Rac_{Cmax}, time dependency, $Ae_{(0\text{-}tau)}$, $Ae_{ss,(0\text{-}tau)}$, f_e, $f_{e,ss}$, and CL_R, $CL_{R,ss}$
	PD	To evaluate the impact on caloric intake of multiple ascending doses of AZD2820	Daily caloric intake
Exploratory	PD	To evaluate the impact on body weight after multiple ascending doses of AZD2820	Body weight
	Safety	To evaluate safety regarding mental state after multiple ascending doses of AZD2820	C-SSRS, HADS, POMS, MINI
	PD[a]	To evaluate the effect of AZD2820 on histamine, tryptase, and histamine urine metabolites	-
	PK/PD[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/PD of AZD2820	-

Objective Outcome		Variable
Priority Type	**Description**	**Description**
Pharmaco-genetic[a]	To collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to AZD2820	-
PK[a]	To investigate the presence and/or identity of drug metabolites of AZD2820 and, if appropriate, characterise their PK	-
Biomarker[a]	To collect blood samples for possible biomarker research	-

[a] If performed, these results will be reported separately from this Clinical Study Report.

λ_z: terminal rate constant; $\lambda_{ss,z}$: terminal rate constant at steady state; AE: adverse event; $Ae_{(0\text{-}tau)}$: cumulative amount of drug excreted unchanged into urine from zero to the end of the dosing interval; $Ae_{ss,(0\text{-}tau)}$: cumulative amount of drug excreted unchanged into urine from zero to the end of the dosing interval at steady state; AUC: area under the plasma concentration-time curve from zero to infinity; $AUC_{(0\text{-}tau)}$: area under the plasma concentration-time curve from zero to the end of the dosing interval; $AUC_{(0\text{-}t)}$: area under the plasma concentration-time curve from zero to the time of the last quantifiable measureable concentration; $AUC_{ss,(0\text{-}tau)}$: area under the plasma concentration-time curve from zero to the end of the dosing interval at steady state; C-SSRS: Columbia-Suicide Severity Rating Scale; CL/F: apparent subcutaneous plasma clearance; CL_R: renal clearance; $CL_{R,ss}$: renal clearance at steady state; CL_{ss}/F: apparent subcutaneous plasma clearance at steady state; C_{max}: maximum plasma concentration; $C_{ss,max}$: maximum plasma concentration at steady state; dECG: digital electrocardiogram; ECG: electrocardiogram; EEG: electroencephalogram; fe: fraction of dose excreted unchanged into urine; fe_{ss}: fraction of dose excreted unchanged into urine at steady state; HADS: Hospital Anxiety and Depression Scale; MINI: Mini International Psychiatric Interview; PD: pharmacodynamics; PK: pharmacokinetic(s); POMS: Profile of Mood States; R_{ac}: accumulation ratio; $t_{1/2\lambda z}$: terminal half-life; $t_{1/2\lambda z,ss}$: terminal half-life at steady state; t_{max}: time to maximum plasma concentration; $t_{ss,max}$: time to steady state maximum plasma concentration; V_z/F: apparent volume of distribution; $V_{z,ss}/F$: apparent volume of distribution at steady state.

Study design

This was a multiple ascending dose study in obese, but otherwise healthy male volunteers with a starting dose of 1 mg per day for 14 days (Cohort 1). The dose was increased to 3 mg in Cohort 2 and to 6 mg in Cohort 3. After a single administration of 6 mg AZD2820, 1 volunteer had a severe serious adverse event (SAE) of hypersensitivity and was hospitalised. Due to this SAE, one of the stopping criteria was fulfilled and the study was prematurely terminated.

Each volunteer participated in 1 cohort only. The study consisted of 4 visits: screening, residential period (Day -2 to Day 15), follow-up (Day 25 to Day 29) and an immunogenicity assessment on Day 44.

Target subject population and sample size

Healthy male volunteers aged 18 to 45 years with a body mass index of 27 to 40 kg/m^2 who provided written informed consent.

Planned: Up to 72 volunteers in 8 cohorts

Screened: 132 volunteers

Randomised: 18 volunteers in 3 cohorts

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

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD2820	Solution for injection, 5 mg/mL	AstraZeneca	11-002825AZ
AZD2820	Solution for injection, 50 mg/mL	AstraZeneca	11-002823AZ
Placebo	Solution for injection	AstraZeneca	11-002457AZ

Duration of treatment

14 days

Statistical methods

The analyses of safety and tolerability were summarised descriptively including tables, graphs and listings. Pharmacodynamic and pharmacokinetic data were summarised descriptively including tables, listings and graphs, as appropriate. Statistical assessments for dose proportionality, time-independence, and accumulation were performed.

Subject population

In total, 18 male volunteers were randomised into the study at 1 study centre. Sixteen volunteers each received 1 administration per day for 14 days of the investigational product (AZD2820 or placebo) during the planned treatment visits. One volunteer (6 mg AZD2820) was withdrawn due to a severe SAE, considered related to the investigational product by the Investigator, and 1 volunteer (placebo) was withdrawn due to the study being terminated.

Summary of pharmacokinetic results

Following single and repeated subcutaneous administration of AZD2820, the maximum concentration (C_{max}) of AZD2820 was reached after approximately 1 hour. The exposure (both C_{max} and AUC) seemed to increase in proportion to the administered dose.

The geometric mean $t_{1/2,\lambda z}$ was estimated to be approximately 4 hours after both single and repeated dosing.

The renal clearance as well as fraction of administered drug excreted unchanged in urine (f_e) were similar between doses and on both Day 1 and 7, with approximately 60% of the administered dose excreted unchanged in urine.

The accumulation of AZD2820 in plasma was low as reflected by the geometric LS mean ratios Day 7/Day 1 for $AUC_{(0-24)}$, (101 to 102%; 1.01 to 1.02-folds) and C_{max} (106 to 110%; 1.06- to 1.10-folds). The ratio $AUC_{ss(0-tau)}/AUC_{Day1}$ was close to 1 and did not indicate any time dependency in the pharmacokinetics.

Summary of pharmacodynamic results

Overall, mean change from baseline caloric intake and body weight in the AZD2820 treatment group were comparable to that observed in placebo over the course of the study. Change from baseline body weight and change from baseline total caloric intake showed a similar pattern, with no obvious differences between the placebo and AZD2820 treatment groups.

Summary of safety results

No deaths were reported. At least 1 AE was reported for all 18 volunteers. One volunteer, with no known history of allergy or asthma, developed severe hypersensitivity and was subsequently hospitalised. This was reported as a severe, life-threatening suspected unexpected serious adverse reaction. At least 1 AE in the SOC General disorders and administration site conditions were reported on both AZD2820 and placebo. At least 1 AE considered to be related to the investigational product was reported for all volunteers on AZD2820. The SAE of hypersensitivity was considered severe in intensity, 3 moderate AEs were reported and all other AEs were considered to be mild in intensity.

The number of volunteers with mild clinical events during the assessment of injection site tolerability was similar between AZD2820 and placebo, while moderate clinical events were reported for 6 volunteers on AZD2820 and no volunteers on placebo.

No relevant trends over time and between treatments were noted in laboratory measurements. Decreases from baseline in mean systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, and mean arterial blood pressure were noted on placebo during the ambulatory blood pressure measurement (ABPM), with a greater decrease on Day 12 than on Day 1. There was not as clear a trend of blood pressure decrease on the active treatment but there was no relationship to dose and no clear difference from placebo.

All electrocardiogram (ECG) intervals and morphologies were within the expected physiological range for the studied population for placebo and 1 mg and 3 mg AZD2820.

Variation, but no trends, over time and between treatments were noted in mean and median values for base mean rigidity, base mean tumescence, base total time with rigidity >60%, tip mean rigidity, tip mean tumescence, and tip total time with rigidity >60% for penile erection assessments.