Clinical Study Report Synopsis

Drug Substance AZD5213

Study Code D3030C00003

Edition Number 1

An Open-label Positron Emission Tomography Study to Evaluate Use of Histamine H_3 Receptor Radioligand [^{11}C]AZ12807110 and to Determine Histamine H_3 Receptor Occupancy of AZD5213 after Oral Administration to Healthy Volunteers

Study dates: First subject enrolled: 2 November 2010
Last subject last visit: 8 June 2011

Phase of development: Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at a single centre: Quintiles AB, Global Phase I Services, Uppsala, 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 Pilot Panel	**Primary**	
To characterise the distribution and kinetics of [^{11}C]AZ12807110 in human brain measured with PET	PD: %SUV, %ID, V_T	PD
Primary Main Panel	**Primary**	
To describe the relationship between plasma concentrations of AZD5213 and receptor occupancy at the histamine H_3 receptor in the brain in healthy volunteers	PK: C_{max}, t_{max}, $t_{½\lambda z}$, λ_z, AUC, AUC_{PET}, $C_{av,PET}$ PD: V_T, V_{ND}, RO PK/PD relationship: RO versus $C_{av,PET}$, $K_{i,pl}$	PK, PD, PK/PD
Secondary Main Panel	**Secondary**	
To evaluate the safety and tolerability of AZD5213	Adverse events, laboratory assessments (clinical chemistry, haematology and urinalysis), physical examination, Electrocardiogram (resting 12-lead electrocardiogram and telemetry), vital signs (body temperature, blood pressure and pulse), Columbia Suicide Severity Rating Scale, sleep quality	Safety
Exploratory Main Panel	**Exploratory**	
To quantify any significant delay between plasma concentration of AZD5213 and receptor occupancy if present	PK: C_{max}, t_{max}, $t_{½\lambda z}$, λ_z, AUC, AUC_{PET}, $C_{av,PET}$ PD: V_T, V_{ND}, RO PK/PD relationship: RO versus $C_{av,PET}$, $K_{i,pl}$	PK, PD, PK/PD
To collect and store DNA for future exploratory research into genes/genetic variation that may influence the response (ie, distribution, safety, tolerability and efficacy) to AZD5213[a]	genotype	PGX

AUC area under the plasma concentration-time curve from zero to infinity; AUC_{PET} area under the plasma concentration-time curve during the PET measurement; $C_{av,PET}$ average plasma concentration during the PET measurement; C_{max} maximum plasma concentration; %ID percentage of injected dose; $K_{i,pl}$ the plasma concentration resulting in 50% RO; PD pharmacodynamic(s); PGX Pharmacogenetic(s); PK pharmacokinetic(s); t_{max} time to C_{max}; %SUV standardized uptake value; $t_{½\lambda z}$ terminal plasma half-life; V_{ND} distribution volume of non-displaceable compartment; V_T total distribution volume; λ_z elimination rate constant

[a] reported separately from this Clinical Study Report.

Study design

This was an open-label, non-randomised, single-centre, exploratory PET study in healthy male volunteers in whom histamine H_3 receptor occupancy induced by AZD5213 was studied by PET examinations with the radioligand [^{11}C]AZ12807110. The study consisted of 2 panels, a pilot panel which was designed to provide information on the radioligand distribution and kinetics in the brain, and a main panel in which histamine H_3 receptor occupancy of AZD5213 was examined.

Target subject population and sample size

The main inclusion criteria were healthy male and non-fertile female volunteers aged ≥20 to ≤45 years with a body mass index between 18 and 30 kg/m^2 (extremes included) and with a normal magnetic resonance image scan. Females had to be of non-childbearing potential.

Up to 13 healthy volunteers could be included, 4 in the pilot panel and 6 in the main panel with an option to include 3 additional healthy volunteers in the main panel.

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

Table S1 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation number	Batch number
AZD5213 (main panel only)	Oral solution, 0.1 mg/mL	AstraZeneca	D1000031	10-000896AZ
AZD5213 (main panel only)	Oral solution, 2 mg/mL	AstraZeneca	D1000033	10-000897AZ
Radioligand [^{11}C]AZ12807110 (both panels)	Solution for intravenous injection	PET Centre, Karolinska University Hospital, Solna	Not applicable	Not applicable

Duration of treatment

Each healthy volunteer in the main panel was administered up to 2 single doses of AZD5213 (0.05 mg to 30 mg) on an individual basis. Each dose was separated by at least 1 week. Healthy volunteers in the pilot panel got 1 intravenous injection of the [^{11}C]AZ12807110 radioligand whereas healthy volunteers in the main panel got up to 3 intravenous injections of the [^{11}C]AZ12807110 radioligand, 1 at baseline PET and 2 post-dose of AZD5213 administration (2 to 4 h after dose in the main part of the main panel and 24 to 26 h after dose in the optional part of the main panel).

Statistical methods

The data were summarised using descriptive statistics.

Subject population

A total of 13 healthy volunteers were included in the study. Four healthy volunteers were included in the pilot panel and all 4 completed the study. Nine healthy volunteers were included in the main panel, 4 in the main part and 5 in the optional part (of which 2 were replacement subjects). In the main panel, there were 2 discontinuations of investigational product due to adverse events. Both events were assessed as unrelated to treatment with investigational product by the Investigator. One healthy volunteer was withdrawn from the study due to a positive cotinine test after receiving 1 injection of the [^{11}C]AZ12807110 radioligand. Twelve of the healthy volunteers were included in the safety analysis set, 11 were included in the PD analysis set and 7 were included in the PK analysis set.

Summary of pharmacokinetic results

The plasma concentrations of AZD5213 during the 2 h PET measurements were close to C_{max} and at trough plasma concentrations (C_{trough}), as measured at 2 to 4 hours and 24 to 26 hours after drug administration, respectively. The decline in plasma concentration during the PET measurements was minor (generally less than 30%). Overall, the plasma PK parameters of AZD5213 were in agreement with the results in the AZD5213 single ascending dose and multiple ascending dose studies. The healthy volunteers in this PET study were therefore regarded as representative for a larger population with respect to the current knowledge of the PK of AZD5213.

Summary of pharmacodynamic results (PET)

Pilot panel

[^{11}C]AZ12807110 distribution was non-homogenous with highest radioactivity in the dorsal striatum, followed by cortex, thalamus, cerebellum and pons. This pattern corresponds to the known pattern of histamine H_3 receptor density. The radioligand reached stable distribution volume in all brain regions, as assessed by different analysis methods, at about 120 minutes after intravenous injection.

Main panel

A dose-dependent decrease in the uptake of the radioligand was observed after single dose administration of AZD5213 (0.05 mg to 30 mg).

Summary of pharmacokinetic/pharmacodynamic relationships

This study was conducted to determine the relationship between AZD5213 plasma concentrations and histamine H_3 RO in healthy volunteers. The results showed saturable, concentration-dependent AZD5213 binding to histamine H_3 receptors. Quantitative analysis of PET data demonstrated that AZD5213 reached 50% H_3 RO at a plasma concentration of 1.14 nmol/L.

Summary of safety results

There were no deaths, other serious adverse events, or any other significant adverse events in the study. Two healthy volunteers were discontinued from investigational product due to adverse events: pyrexia pre-dose at Visit 5, PET 3 and anxiety in the PET camera before the first injection of the radioligand at Visit 3. None of the events were assessed as causally related to treatment with the investigational product by the Investigator. In the main panel, 8 healthy volunteers reported 21 AEs after the first injection of the radioligand. Fifteen of these adverse events were of mild and 6 were of moderate intensity. The most common adverse event was headache which occurred in 3 healthy volunteers. All other AEs were reported by a maximum of 2 healthy volunteers. Twelve AEs were judged by the Investigator to be provoked by study procedures and included orthostatic hypotension, injection site haematoma, haematoma, back pain,peripheral oedema, catheter site pain, headache and musculoskeletal stiffness. There were no clinically relevant treatment-related changes or trends in any laboratory variables, vital signs, electrocardiograms or physical examinations as assessed by the Investigator. There were no findings based on Columbia Suicide Severity Rating Scale or self-reported duration and quality of sleep.