Drug Substance	AZD2207	**SYNOPSIS**	(For national authority use only)
Study Code	D3180C00007		
Edition Number	1		
Date	28 March 2008		

A Randomized, open, single-dose, single centre, Phase I study to compare the relative bioavailability of two IR tablet formulations to a capsule formulation of AZD2207 after administration to healthy male and female subjects

Study centre

This study was conducted in Sweden (Quintiles AB, Phase I Services, Strandbodgatan 1,

SE-753 23 Uppsala

Study dates		**Phase of development**
First subject enrolled	28 August 2007	Clinical pharmacology (I)
Last subject completed	18 October 2007	

Objectives

The primary objective of the study was to compare the relative bioavailability of two immediate release (IR) tablet formulations of AZD2207 (hydrochloric salt) to a capsule formulation of AZD2207 (heminapadisylate salt) after administration to healthy male and postmenopausal female subjects. The relative bioavailability was assessed by means of the

ratios of the area under the plasma-concentration time curve (AUC) and the maximum concentration (C_{max}).

The secondary objectives of the study were:

1. To assess the safety and tolerability of AZD2207 in two different IR tablet formulations and oral capsule by assessment of AE, blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory variables.

2. To study the pharmacokinetic (PK) properties of AZD2207, when given as a capsule and as IR tablets, by assessment of the area under the plasma concentration versus time curve from time zero to the last quantifiable concentration (AUC_t), C_{max}, time to C_{max} (t_{max}), half life ($t_{1/2}$) and apparent oral clearance.

3. To investigate the effect of food on the PK after administration of single oral doses of the two IR formulations of AZD2207 by assessment of AUC, AUC_t, C_{max}, t_{max}, $t_{1/2}$ and CL/F.

4. To collect and store DNA samples for potential future research into genes which may influence drug response (PK profile, drug safety and tolerability).

Study design

This was a randomized, open, single-centre, 4 periods crossover study to compare the relative bioavailability of two IR tablet formulations of AZD2207 (hydrochloric salt) to a capsule formulation (heminapadisylate salt). The first 3 periods were followed by a parallel group design where the two IR tablet formulations were administered together with food to see if this had an effect on bioavailability.

Target subject population and sample size

Twelve healthy volunteers, male or female, aged 20 to 64 years. Female volunteers had to be post-menopausal and/or bilateral oophrectomised or hysterectomised.

Investigational product and comparators: dosage, mode of administration and batch numbers

Single oral doses of AZD2207 hydrochloride, 40 mg (single 9 mm IR tablet, batch H 1938-01-01-01), AZD2207 hydrochloride, 40 mg (single 12 mm IR tablet, batch H 1938-02-01-01) and AZD2207 heminapadisylate (8 x 5 mg capsules, batch H 1846-01-01-03).

Duration of treatment

Four 5-day treatment periods (from administration of AZD2207 to collection of final PK blood sample)

Variables

- **Pharmacokinetic**

- AUC_t, AUC, C_{max}, t_{max}, $t_{1/2}$ and CL/F

The primary PK variable (relative bioavaiability) was defined as the AUC and C_{max} ratio and was estimated for each subject

- **Safety**

- AEs, BP, pulse, ECG and laboratory variables

Statistical methods

All variables were analysed using descriptive statistics within the treatment group. Geometric means together with confidence intervals were calculated for all applicable PK parameters. Relative bioavailability was analyzed using a mixed-effect analysis of variance (ANOVA) model. The influence of food was analyzed with a mixed-effect ANOVA model.

Treatment	N	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)
AZD2207	12	48.3 (21 - 62)	79.1 (56.5 - 96.1)	173.6 (156 - 190)	26.2 (22.6 - 29.8)
AZD2207 Males	6	38.0 (21 - 62)	86.8 (79.1 - 96.1)	182.5 (177 - 190)	26.1 (23.1 - 29.8)
AZD2207 Females	6	58.5 (54 - 62)	71.5 (56.5 - 86.5)	164.7 (156 - 177)	26.3 (22.6 - 28.9)

Summary of pharmacokinetic results

The relative bioavailability of AZD2207 after administration of both tablet formulations was lower in comparison to administration of the capsule formulation. Further, bioavailability was higher and absorption slightly delayed in the fed state compared to the fasting state for both tablet formulations.

While no difference in bioavailability between the two tablet formulations was reported in the fasting state, IR tablet 2 led to slightly higher bioavailability than IR tablet 1 in the fed state.

Inter-subject variation for AUC and C_{max} of AZD2207 were similar for the tablet formulations and the capsule formulation.

The $t_{1/2}$ of AZD2207 was similar for the different formulations and was not affected by food intake.

CL/F was higher for both IR tablet formulations compared to the capsule during the fasting state. CL/F was decreased when AZD2207 was administered together with food.

Summary of safety results

All subjects who entered the study were evaluated for safety. Nausea and headaches were the most commonly reported AEs and no serious AEs were reported. No significant differences in any safety variables were reported between any of the treatment groups.

AZD2207 was well tolerated and no safety concerns were raised.