Drug Substance	AZD2207	**SYNOPSIS**	(For national authority use only)
Study Code	D3180C00001		
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A Single-Blind, Randomized, Placebo Controlled Phase I Study to Investigate the Effect of Single Oral Doses of AZD2207 with and without Food on Safety, Tolerability and Pharmacokinetics

Study dates		**Phase of development**
First subject enrolled	22 September 2006	Clinical pharmacology (I)
Last subject completed	02 March 2007	

Objectives

The primary objective of the study is to investigate the safety and tolerability of single oral doses of AZD2207 by assessment of adverse events (AEs), blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory variables

Secondary objectives

1. to investigate the pharmacokinetics of AZD2207 after administration of single oral doses of AZD2207 by assessment of AUC, C_{max}, $t_{1/2}$, CL/F, t_{max}
2. to investigate the effect of food on AUC, C_{max}, $t_{1/2}$, CL/F, t_{max} after administration of single oral doses of AZD2207
3. to investigate the effect of AZD2207 on respiration rate
4. to collect DNA samples from healthy volunteers who consent to participate in optional genetics research

Study design

This was a single-blind, randomized, placebo controlled phase I study conducted at 1 centre. The study included an 8-step dose-escalation part, in which 2 of the doses also were studied together with food, and a crossover part where ECG was investigated after the highest tolerated dose of AZD2207 (400 mg) and placebo.

Target healthy volunteer population and sample size

The study was to be conducted in healthy male volunteers aged between 20 and 40 years. The inclusion and exclusion criteria were defined such that healthy volunteers who are known to be free from any significant illness was to be selected. The study was restricted to male healthy volunteers, since reproduction toxicology data in animals were not yet available. The planned number of healthy male volunteers randomized in this study was 52, 8 on each dose in the dose-escalation part and 12 in the ECG crossover part, which was considered sufficient to evaluate tolerability and safety.

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

Single oral doses of AZD2207 ranging from 0.5 to 400 mg, or placebo, were given as capsules. AZD2207 was given as the heminapadisylate salt in capsules corresponding to 0.5, 5 and 50 mg of the base. The different capsules were combined to obtain the correct dose and had the following batch numbers:

AZD2207 0.5 mg:	H 1845-01-01-01	AZD2207 0.5 mg PLACEBO:	H 1848- 01-01-02
AZD2207 5 mg:	H 1846-01-01-01	AZD2207 5 mg PLACEBO:	H 1849-01-01-02
AZD2207 50 mg:	H 1847-01-01-01, H 1847-01-01-02	AZD2207 50 mg PLACEBO:	H 1850-01-01-02, H 1850-01-01-03

Duration of treatment

Each subject received 2 single doses of AZD2207 or placebo with a washout period of at least 3 weeks.

Variables

- **Pharmacokinetic**

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

- **Safety**

  AEs, BP, pulse, ECG and laboratory variables

Statistical methods

The full analysis set included all healthy volunteers who received study treatment and had data collected post-dose. Descriptive statistics are provided for all safety variables, and the

analyses were performed according to actual exposure, regardless of randomization. No formal comparison was performed. Geometric means together with confidence intervals were calculated for AUC, C_{max} and $t_{1/2}$. The influence of food on AZD2207 single-dose pharmacokinetics and dose proportionality were analysed with mixed-effect analysis of variance (ANOVA) models. A population specific correction of QT interval was done and a mixed-effect ANOVA model was used for analysis.

Subject population

In total, 53 male healthy volunteers (52 Caucasian and 1 Oriental) were randomised at 1 study site into the study, 8 on each dose (6 on AZD2207 and 2 on placebo) in the dose-escalation part and 12 in the ECG crossover part. Forty-nine (49) healthy volunteers randomised to treatment completed the study. Overall, the treatment groups were well balanced with regards to demographic characteristics.

Summary of pharmacokinetic results

AZD2207 was generally rapidly absorbed in all dose groups (median t_{max} = 2.5 hours). One subject on had extended absorption of AZD2207 (t_{max} was 12 and 17.9 hours for 30 and 400 mg, respectively). The mean terminal $t_{1/2}$ was 22.1 hours. There was a less than dose proportional increase in AUC and C_{max}. However, at the lower doses the increase in exposure was approximately dose proportional. AZD2207 pharmacokinetics after standardized high fat, high calorie breakfast was characterised by a later (median t_{max} = 3.3 hours) and higher peak level compared to when given during fasting conditions. Exposure was 1.5 to 2 times higher when given together with food at the higher dose level (100 mg) than when AZD2207 was given without food.

Summary of pharmacogenetics

Results from any genetic research performed are not reported in this clinical study report.

Summary of safety results

No safety or tolerability concerns were identified in this study after single doses up to 400 mg of AZD2207. Overall, there was no apparent difference between AZD2207 treated and placebo treated subjects regarding adverse events (AEs), except for Nausea that was seen in AZD2207 dose groups of 8 mg and above. In most reports the events were of very short duration (≤1 minute), and with a sudden onset and disappearance. No nausea events were reported on lower doses of AZD2207 (below 8 mg), however one subject on placebo reported nausea. The most commonly collected adverse events (AEs) were nasopharyngitis, nausea and headache. There were no clinically relevant treatment-related changes or trends in any laboratory variable or vital sign measured during the study in healthy volunteers exposed to AZD2207.

All digital ECGs were evaluated as within physiologic range for the studied population. No clinically relevant trends over time or between dose groups were observed. No clinically significant individual interval data were observed, nor judged as any clinically relevant substance effect.

No clinically relevant difference between the estimated true means with corresponding 95% CI of AZD2207 vs. placebo, regarding QT_{cX} and QT_{cF}, was observed in the crossover part included to specifically evaluate ECG. However, for the primary lead V_2, there was a less than 5 ms difference between the estimated true means for QT_{cX}, including <10 ms upper CI observed up to 4 hours post dose. At 6, 8 and 12 hours post dose 10.2 ms (upper CI 13.4), 8.0 ms (upper CI 11.9) and 6.7 ms (upper CI 10.5) respectively of estimated true means differences were observed. To some extent these relative differences are judged as associated to a decrease in QT_{cX} in the placebo group at these time points. These observations are judged as not clinically relevant since all subjects except 1 had their t_{max} at 1 to 5 hours after dose.