Clinical Study Report Synopsis

Drug Substance	AZD2066
Study Code	D9126C00001
Edition Number	1
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A double-blind, randomized, placebo-controlled, single-centre phase I pharmacodynamic cross-over study to assess the effect of a single dose of AZD2066 oral solution in comparison with placebo on transient lower esophageal sphincter relaxations (TLESRs) in healthy subjects

Study dates: First subject enrolled: 30 December 2008
Last subject last visit: 5 November 2009

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)

The study was conducted at a single site, the Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands.

Reading of impedance recordings were performed by Daniel Sifrim, Barts and The London School of Medicine and Dentistry, London, UK.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of the study was to assess the effect, measured as number of TLESRs during 3 hours after meal, of oral administration of AZD2066 13 mg compared to placebo (Part A of the study).	Number of TLESRs during 3 hours after meal	Efficacy
Secondary	**Secondary**	
To assess the effect, measured as the number of TLESRs during 3 hours after meal, of oral administration of 2 different doses (≤10mg) of AZD2066 compared to placebo (Part B of the study)	Number of TLESRs during 3 hours after meal	Efficacy
To assess the lower esophageal sphincter pressure (LESP) during 3 hours after meal.	LESP during 3 hours after meal	Efficacy
To assess the number of acid-, weakly acidic- and weakly alkaline reflux episodes during 3 hours after meal	Number of acid-, weakly acidic- and weakly alkaline reflux episodes during 3 hours after meal	Efficacy
To assess the number of concurrent TLESRs and acid-, weakly acidic- and weakly alkaline reflux episodes during 3 hours after meal	Number of concurrent TLESRs and acid-, weakly acidic- and weakly alkaline reflux episodes during 3 hours after meal	Efficacy
To assess percentage of registration time with esophageal pH<4	Percentage of registration time with esophageal pH<4	Efficacy

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To assess the effect of AZD2066 on the number of swallows during 3 hours after meal	Number of swallows during 3 hours after meal	Efficacy
To assess the pharmacokinetic profile of AZD2066	AUC, C_{max}, t_{max}	Pharmaco kinetic
To assess the safety and tolerability of AZD2066	Adverse events, laboratory variables (haematology, clinical chemistry, urinalysis), ECG, vital signs (blood pressure, pulse)	Safety

Study design

This was a double-blind, randomized, placebo-controlled, single-centre phase I pharmacodynamic study to assess the effect of a single oral dose of AZD2066 in comparison with placebo. The study was conducted in two sessions, Part A and Part B, with an interim analysis in between.

Target subject population and sample size

This study was conducted in healthy volunteers.

The sample size calculation was based on a true effect of 50% reduction of the number of TLESRs. Based on this, the number of subjects required in Part A was 12 and in Part B at least 16, yielding a total number of 30 subjects in the entire study. However, the results of the interim analysis of Part A indicated that the true effect was in fact lower and thus the sample size needed to be increased to maintain sufficient statistical power. The re-calculated number of subjects required to be included in Part B to have a balanced design (ie,18 subjects) was at least 22, yielding a total number of 36 subjects in the entire study.

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

Oral solution of AZD2066 and matching placebo oral solution was prepared by AstraZeneca Pharmaceutical and Analytical R&D, Sweden. The investigational products were supplied in bottles and sent as bulk supply.

Table S 2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Formulation/Batch number
AZD2066	Oral solution 0.1 mg/mL	AstraZeneca	08-002090AZ
Placebo	Oral solution Placebo	AstraZeneca	08-001296AZ and 08-001830AZ

Duration of treatment

In Part A, all 13 healthy volunteers received single oral doses of 13 mg AZD2066 and placebo in a two-way cross-over study design. In Part B all 19 healthy volunteers received single oral doses of 2 mg AZD2066, 6 mg AZD2066 and placebo in a three-way cross-over design.

Statistical methods

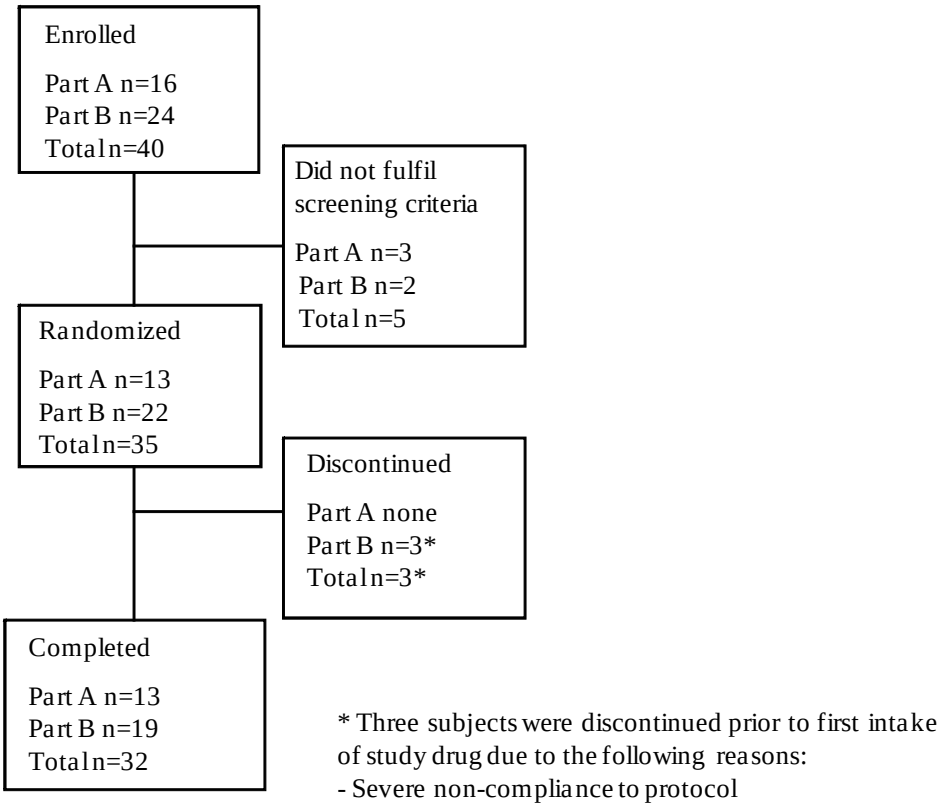
Separate analyses were performed for part A and B.

Treatment effect differences between AZD2066 and placebo were estimated as arithmetic mean differences or geometric mean ratios depending on whether the response variable was log-transformed prior to analysis or not. Analysis was done using an analysis of variance (ANOVA) with treatment, period, and sequence as fixed effects and patient id as a random effect. The estimated difference of AZD2066 – Placebo together with a 95% confidence interval was calculated. When a log transformation has been used, estimates and confidence intervals have been anti-log transformed in order to give results for geometric means and ratios thereof. All confidence intervals are presented unadjusted for multiple comparisons.

If not otherwise stated a logarithm transformation has been used when ever possible, ie, if all values of the analysis variable are strictly positive (>0).

Subject population

Figure S 1 Subject disposition



Summary of efficacy results

A 27% reduction in number of TLESRs 0-3 hours post meal was observed for AZD2066 13 mg compared to placebo, no reduction in TLESRs was observed for AZD2066 2 mg or 6 mg.

No significant effect on LES pressure was observed with AZD2066.

AZD2066 13 mg reduced the total number of reflux episodes 0-3 hours post meal by 51%. AZD2066 6 mg reduced the total number of reflux episodes 0-3 hours post meal by 39%, however, this reduction was largely driven by 2 individuals. No reduction in reflux episodes was observed for AZD2066 2 mg. Inspection of the residuals from the model used in the analysis reflux episodes revealed at least two subjects with large absolute residuals in part B. To investigate the effect off possible outliers, two additional analyses were performed (signed rank test and ANOVA after removal of 2 subjects with large residuals). These analyses showed that the significant reduction in total number of reflux episodes observed for the 6 mg dose was largely driven by 2 individuals (outliers/high responders).

The number of acid reflux episodes was decreased with AZD2066 13 mg, and a borderline significant decrease was observed for the 6 mg dose. No decrease was observed for the 2 mg dose.

A trend towards a decreased time with esophageal pH <4 was observed with AZD2066 13 mg, but no significant changes were observed with 6 mg or 2 mg doses.

No significant effect on swallows was observed with AZD2066.

Summary of pharmacokinetic results

The absorption of AZD2066 was considered to be fast and t_{max} was in general reached within 1 hour post dose. For the 2 and 6 mg doses median t_{max} was reached within 0.5 hour and for the 13 mg dose median t_{max} was reached at 0.75 hour.

Geometric mean C_{max} after single oral administration of AZD2066 was 258.6 nmol/L at 2 mg, 711.8 nmol/L at 6 mg and 1214 nmol/L at a 13 mg dose. The geometric mean $AUC_{(0\text{-}12h)}$ was 1604, 4483 and 9150 h*nmol/L for 2, 6 and 13 mg doses, respectively. The geometric mean $AUC_{(0.5\text{-}3.5h)}$ (i.e. 3 hours after meal) was 516.5, 1482 and 2953 h*nmol/L for 2, 6 and 13 mg doses, respectively. Both C_{max}, $AUC_{(0\text{-}12h)}$ and $AUC_{(0.5\text{-}3.5h)}$ were considered to increase in proportion to the increase in dose.

Summary of safety results

The AE profile in this study was similar to what has been seen in previous studies using single oral dose administration of AZD2066. All AEs were mild and the most commonly reported AEs during treatment periods were related to nervous system disorders (headache, dizziness, disturbances in attention, and somnolence). No deaths, SAEs, DAEs or OAEs were seen in this study.

No clinically relevant changes were observed in laboratory, vital signs or ECG parameters.