AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD2516
Study Code	D3830C00001
Edition Number	1
Date	21 March 2011

A double-blind, randomized, placebo-controlled, two-centre, phase IIa pharmacodynamic cross-over study to assess the effect of AZD2516 on the total number of reflux episodes in healthy male volunteers

Study dates: First subject enrolled: 27 May 2010
Last subject last visit: 7 September 2010

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

This study was conducted at 2 centres, 1 in the Netherlands and 1 in Belgium.

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[a]	Outcome variables	Type
Primary	**Primary**	
The primary study objective was to assess the effect of AZD2516, measured as reduction in the total number of reflux episodes, during a 3-hour post meal period compared to placebo.	The total number of reflux episodes 0 to 3 hours post meal.	Efficacy
Secondary	**Secondary**	
To assess the effect of AZD2516, measured as reduction in the number of transient lower esophageal sphincter relaxations (TLESRs), during a 3-hour post meal period compared to placebo.	Number of TLESRs during 0 to 3 hours post meal.	Efficacy
To assess the number of acid-, weakly acidic- and weakly alkaline reflux episodes during a 3-hour post meal period.	-Number of acid reflux episodes (pH<4) 0 to 3 hours post meal -Number of weakly acidic reflux episodes (4≤pH<6.5) 0 to 3 hours post meal. -Number of weakly alkaline reflux episodes (pH≥6.5) 0 to 3 hours post meal. -Mean acid clearance time 0 to 3 hours post meal (derived).	Efficacy
To assess the height (mean proximal extent) and content (liquid, gas or a mixture) of the refluxate.	-Mean proximal extent (derived). -Mean bolus clearance time 0 to 3 hours post meal (derived). -Reflux content (liquid, gas or mixture) 0 to 3 hours post meal.	Efficacy
To assess the time with esophageal pH between 4 and 6.5 during a 3-hour post meal period.	Time with esophageal pH between 4 and 6.5, 0 to 3 hours after meal (derived).	Efficacy
To assess the time with esophageal pH<4 during a 3-hour post meal period.	Time with esophageal pH<4, 0 to 3 hours post meal (derived).	Efficacy
To assess the lower esophageal sphincter (LES) pressure during a 3-hour post meal period.	Mean LES pressure 0 to 3 hours post meal (derived).	Efficacy

Objectives[a]	Outcome variables	Type
To assess the number of concurrent TLESRs and acid- and weakly-or non acid reflux episodes during a 3-hour post meal period.	Number of concurrent TLESRs and acid and weakly or non-acidic reflux episodes 0 to 3 hours post meal (derived).	Efficacy
To assess the effect of AZD2516 on the number of swallows during a 3-hour post meal period.	Number of swallows 0 to 3 hours post meal.	Efficacy
To assess the pharmacokinetic profile of AZD2516.	$AUC_{(0-t)}$, $AUC_{(1-4\ h)}$, C_{max}, $C_{average\ (1-4\ h)}$, $t_{½}$, $t_{max.}$	Pharmaco-kinetic
To assess the safety and tolerability of AZD2516.	AEs, blood pressure, pulse, body temperature, ECG, laboratory variables (haematology, clinical chemistry, urinalysis), C-SSRS.	Safety
To collect and store DNA for future exploratory research into genes/genetic variation that could influence response (ie, distribution, safety, tolerability and efficacy) to AZD2516.	DNA	Exploratory Pharmaco-genetic[b]

[a] In all secondary variables, reflux episodes refer only to manually identified reflux episodes. All efficacy variables were calculated from impedance/pH and manometric recordings.
[b] Pharmacogenetic results are not presented in this CSR.

Study design

This was a double-blind, randomized, placebo-controlled, 2-centre, phase IIa pharmacodynamic cross-over study to assess the effect of oral doses of AZD2516 compared to placebo. The study was planned to include 2 parts with an interim analysis in between, but after the interim analysis of the first part it was decided to not run the second part.

Target subject population and sample size

This study was conducted in healthy volunteers.

A sample size of 16 evaluable subjects was required to have at most 10% type II risk and an type I risk of 5%. The sample size was based on a true treatment effect of 50% reduction in number of reflux episodes and a within subject standard deviation of the difference in the logarithm of number of reflux episodes of 0.88. In order to have 16 evaluable subjects, 20 subjects were to be randomized in part A and B.

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

The investigational product (3 different doses of AZD2516 or placebo) was administered as 1 loading dose and 2 maintenance doses over a period of 1.5 hours. The AZD2516 doses given were 5 mg (3+1+1 mg), 16 mg (10+3+3 mg), 40 mg (20+10+10 mg). Placebo was given to all healthy volunteers together with all AZD2516 treatments as part of the double-dummy principle.

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
AZD2516	Oral capsule 1 mg	AstraZeneca	10-000702AZ
AZD2516	Oral capsule, 5 mg	AstraZeneca	08-003387AZ
AZD2516	Oral capsule, 10 mg	AstraZeneca	08-003388AZ
Placebo for AZD2516	Oral capsule	AstraZeneca	10-000900AZ

Duration of treatment

The investigational product was administered on 4 separate 1-day treatment periods in a 4-way cross-over design, with a 5 to 28 day wash-out period in between each treatment period.

Statistical methods

Treatment effect differences between AZD2516 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, study period, centre and treatment sequence as fixed effects and patient id as a random effect. The estimated difference of AZD2516 and placebo together with a 95% confidence interval were calculated. When a log transformation was used, estimates and confidence intervals were anti-log transformed in order to give results for geometric means and ratios thereof. All confidence intervals are presented unadjusted for multiple comparisons.

Generally, a logarithm transformation were used where ever possible, ie, if all values of the analysis variable were strictly positive (>0).

Subject population

Table S 3 Disposition of study subjects

	Centre 1, Belgium	Centre 2, the Netherlands	Total
Enrolled	14	11	25
Screening failures	4	1	5
Randomized (received investigational product)	10	10	20
Completed	10	10	20

Summary of efficacy results

There was no effect on the total number of reflux episodes 0 to 3 hours after meal (primary efficacy variable) of any of the AZD2516 doses compared with placebo. AZD2516 40 mg gave a significant reduction of 38% in the number of TLESRs 0 to 3 hours after meal compared with placebo. The greatest number of reflux episodes and TLESRs were observed during the first hour after a provocative meal, and the number of reflux episodes and TLESRs had almost returned to baseline within the 3 hour measurement period.

The number of weakly acidic reflux episodes 0 to 3 hours after meal was reduced with 31% with the AZD2516 40 mg dose compared with placebo, but there was no effect of any of the AZD2516 doses on the number of acid reflux episodes (the number of weakly alkaline reflux episodes were too few to be analysed).

No effect was observed on any of the AZD2516 doses on mean LES pressure, number of swallows, fraction of time with esophageal pH below 4 or between 4 and 6.5, or mean acid clearance time 0 to 3 hours after meal.

There was a significant reduction of 20% in the mean bolus clearance time 0 to 3 hours after meal for the AZD2516 40 mg dose compared with placebo.

The number of mixed gas/liquid reflux episodes 0 to 3 hours after meal was reduced with 29% with the AZD2516 40 mg dose compared with placebo. There was no effect of any of the AZD2516 doses on the pure liquid reflux episodes.

AZD2516 5 mg reduced the proximal extent with 11% compared with placebo.

Summary of pharmacokinetic results

The results from the pharmacokinetic evaluation were as predicted. The absorption of AZD2516 was considered to be fast and t_{max} was in general reached within 1 hour after dose. The pharmacokinetics for AZD2516 was found to be dose proportional within the studied dose range. The half-life ($t_{1/2}$) of AZD2516 was found to be between 1.2 and 1.6 hours.

The average plasma concentrations ($C_{average\ (1\text{-}4h)}$) were approximately 45 nmol/L, 180 nmol/L and 510 nmol/L for the AZD2516 dose levels 5 mg, 16 mg and 40 mg, respectively.

Summary of safety results

AZD2516 dose-dependently induced a higher number of adverse events (AEs) compared with placebo, with placebo having the lowest incidence of AEs. All AEs were of mild intensity except for 1 case which was of moderate intensity. The most commonly reported AEs during the AZD2516 treatment were related to nervous system disorders (disturbance of attention, dizziness and headache), and the number of this category of AEs increased with the AZD2516 dose. No deaths, serious AEs, discontinuations of the investigational product due to AEs or any other significant AEs were seen.

There were no clinically significant changes observed in laboratory variables, vital signs, ECG variables, physical examination or other observations related to safety (including Columbia Suicidality Severity Rating Scale).