AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00020
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A double-blind, placebo controlled, randomized, two centre phase IIA pharmacodynamic cross-over study to assess the effect of AZD3355, 65 mg bid, on transient lower esophageal sphincter relaxations (TLESRs) in GERD patients with an incomplete response to PPI treatment

Study dates: First patient enrolled: 19 February 2007
Last patient completed: 13 February 2008

Phase of development: Therapeutic exploratory (II)

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

Publications

None at the time of writing this report.

Objectives

Primary objective:

The primary objective of this study was to assess the effect of repeated oral administration of AZD3355, 65 mg twice daily (bid), measured as reduction in the number of transient lower esophageal sphincter relaxations (TLESRs), compared to placebo during 4 hours post third dose.

Secondary objectives:

- to assess the number of acid-, weakly acidic- and weakly alkaline reflux episodes and time with esophageal pH<4 by ambulatory impedance-pH measurements during 24 hours post first dose
- to assess the number of TLESRs, acid-, weakly acidic- and weakly alkaline reflux episodes and time with esophageal pH<4 by combined impedance-pH and manometric measurements during 4 hours post third dose
- to assess the number of concurrent TLESRs and acid-, weakly acidic- and weakly alkaline reflux episodes during 4 hours post third dose
- to assess the lower esophageal sphincter (LES) pressure during 4 hours post third dose
- to assess the effect of AZD3355 on the number of swallows during 4 hours post third dose

- to study the relationship between total reflux, acid- and non acid (weakly acidic- and weakly alkaline) reflux episodes and GERD symptoms during 24 hours post first dose
- to assess the pharmacokinetic profile of AZD3355 in GERD patients
- to assess the safety and tolerability of AZD3355

Study design

This was a double-blind, placebo controlled, randomised, two-centre, phase IIA pharmacodynamic cross-over study to assess the effect of repeated oral doses of AZD3355 (65 mg bid) as add-on to proton pump inhibitor (PPI) on TLESRs in GERD (gastroesophageal reflux disease) patients with an incomplete response to PPI treatment.

Target patient population and sample size

This study targeted male and female patients (not of child-bearing-potential) aged 18 to 70 years who had long-term GERD symptoms (≥6months), and an incomplete response to PPI treatment. The patients must have been on continuous PPI treatment with approved doses during the last 6 weeks prior to the enrolment visit.

Assuming that the standard deviation of the difference is 5.2, a sample size of 20 has 90% power to detect a difference in means of 4.0, using a paired t-test with a 0.05 two-sided significance level. In order to have at least 24 patients completing the study, and among them at least 20 with evaluable manometric recordings after both treatments, 30 randomised patients were initially desired.

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

AZD3355 65 mg (drug in capsule) orally bid or placebo. Batch number was SD/0317.

Duration of treatment

Each subject received three doses of AZD3355 (65 mg bid) and placebo, divided into two treatment periods separated by a wash-out period of at least five days.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Efficacy

- Number of TLESRs
- Lower esophageal sphincter pressure (LESP)
- Number of swallows

- *Reflux episodes (4 and 24 hours recording):*

  Number of acid -, weakly acidic -, and weakly alkaline reflux episodes

- *Acid exposure (4 and 24 hours recording):*

  Fraction time (percentage of registration time with esophageal pH<4)

  Mean acid clearance time

- *Reflux content (4 and 24 hours recording):*

  Number of liquid -, mixed gas/liquid -, and gas reflux episodes

- Mean proximal extent of reflux
- Mean bolus clearance time
- Number of concurrent TLESRs and reflux episodes
- Symptom analysis for reflux episodes

Pharmacokinetic

$AUC\tau$, R_{ac}, C_{max}, C_{trough} and t_{max}

Criteria for evaluation - safety (main variables)

AE recording, laboratory variables and vital signs (BP and pulse)

Statistical methods

The pharmacokinetic variables, with exception for t_{max}, were logarithmically transformed and the results are presented as geometric means. Depending on the frequency distribution of the number of TLESRs, either the difference in arithmetic means were estimated based on untransformed data or the ratio of geometric means were estimated based on logarithmically transformed data. The variables derived from safety data were analysed by descriptive statistics.

Subject population

Table S1 Patient population and disposition

Demographic or baseline characteristic		Total (n=27)	
Demographic characteristics			
Sex	Male (n [%])	16	(59)
	Female (n [%])	11	(41)
Age (years)	Mean (SD)	51.6	(10.2)
	Range	27 to 72	
BMI (kg/m2)	Mean (SD)	25.9	3.3
Baseline characteristics	**n and (% of patients)**		
History of reflux disease (years)	0.5 - <1	1	(4)
	1 - <5	9	(33)
	5 - <10	4	(15)
	≥10	13	(48)
History of erosive esophagitis	Yes	17	(63)
	No	8	(30)
	Unavailable	2	(7)
History of hiatal hernia	Yes	14	(52)
	No	8	(30)
	Unknown	5	(19)
Helicobacter pylori	Positive	3	(11.1)
Primary RDQ items at baseline[a]			
Days with symptoms/week	Daily	12	(46)
	5-6 days	5	(19)
	3-4 days	9	(35)
Max symptom intensity n and (% of patients)	Moderate-Severe	25	(96)

[a] Measured with 7 days recall at enrolment (visit 1).

Summary of efficacy results

- AZD3355 reduced the geometric mean number of TLESRs, 0-3 h after meal intake, 1 to 4 h post third dose, by 25% (geometric mean ratio 0.75 [95% CI: 0.60, 0.93]) as compared to placebo

- The geometric mean LESP was increased during AZD3355 treatment compared to placebo by 28% (geometric mean ratio 1.28 [95% CI: 1.05, 1.57]) during 3 hours post meal, post third dose as compared to placebo.

- No effect of AZD3355 was shown on the number of swallows during 3 hours post meal, post third dose, as compared to placebo.

- The mean value for the total number of reflux episodes was reduced by 39% (geometric mean ratio 0.61 [95% CI: 0.52, 0.71]) during AZD3355 treatment compared to placebo during 24 hours post first dose.

- The mean value for the total number of reflux episodes during AZD3355 treatment compared to placebo was reduced by 10 (95% CI: -15, -4.8), corresponding to a relative reduction of 47%, during 3 hours post meal, post third dose.

- The mean value for the number of acid reflux episodes during AZD3355 treatment compared to placebo was reduced by 16 (95% CI: -23, -8.3), which corresponds to a relative reduction of the mean of approximately 55%, during 24 hours post first dose, and by 7.9 (95% CI: -14, -2.1), which corresponds to a relative reduction of the mean of approximately 81%, during 3 hours post meal, post third dose.

- The number of pure liquid - and mixed gas/liquid reflux episodes were lower during AZD3355 treatment compared to placebo, during both 24 hours post first dose and 3 hours post meal, post third dose. No difference was seen in pure gas reflux episodes.

- The acid exposure in esophagus was lower during AZD3355 treatment compared to placebo, during both 24 hours post first dose and 3 hours post meal, post third dose.

- The mean number of proximal reflux events was lower during both 24 hours post first dose and 3 hours post meal, post third dose with AZD3355 treatment compared to placebo.

- No effect was seen on the total number of GERD symptom episodes.

Summary of pharmacokinetic results

AZD3355 was rapidly absorbed with median t_{max} values of 1.25 and 1.44 hours after the first and third doses, respectively. Measured trough plasma concentrations of AZD3355 indicate achievement of steady state already after the third dose of bid administration. AUC_{τ} after the third dose was 75% higher than the AUC during 0-12 h after the first dose.

Summary of pharmacokinetic/pharmacodynamic relationships

No clear relations were observed between pharmacokinetics and the reduction in the number of TLESRs.

Summary of safety results

There were no SAEs during the study, and the evaluation of AEs raised no safety concerns. There were no clinically relevant changes related to AZD3355 treatment in the clinical laboratory safety parameters. Further, no clinically relevant observations with respect to vital signs, ECG observations or physical findings were reported during the study.