AstraZeneca

Drug product	Esomeprazole	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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Control of histomorphological changes associated with gastro-oesophageal reflux disease: esomeprazole versus ranitidine - CHEER

Study centre(s)

This study was conducted in Canada (4 centres), Sweden (4 centres), United Kingdom (2 centres), Belgium (2 centres) and the Netherlands (1 centre).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	16 Jan 2001	Therapeutic confirmatory (III)
Last subject completed	24 Apr 2002	

Objectives

Primary:

To examine the change in histological and other morphological features of gastro-oesophageal reflux disease (GORD) in the oesophageal squamous epithelium which occur following acid suppressive therapy.

Secondary:

To examine the relationship between oesophageal acid exposure, symptoms and histological and other morphological findings at visit 2, before acid suppressive therapy.

To examine the relationship between symptoms and histological and other morphological findings after treatment with acid suppressive therapy.

To compare esomeprazole 40 mg once daily (o.m.) and ranitidine 150 twice daily (b.i.d.) with respect to efficacy in the restoration of the oesophageal histomorphology.

To compare endoscopy negative reflux disease (ENRD) subjects with reflux oesophagitis (RO) subjects with regard to histomorphological findings at visit 2, before acid suppressive therapy.

Study design

This was a randomised, double-blind, double-dummy, parallel-group multi-centre study comparing histomorphological changes in the oesophagus and stomach of subjects given esomeprazole (40 mg o.m.) and ranitidine (150 mg b.i.d.) for a period of 4 weeks in the treatment of GORD. During a 2-week run-in period, GORD symptoms were registered in diary cards. The subject was required to be endoscopy negative and to fulfil all the other entry criteria at the randomisation visit.

Target subject population and sample size

Male and female subjects aged 18 years or older, with a history of GORD longer than 6 months and with heartburn as the predominant symptom, with at least one episode of moderate severity during the week before visit 1, as assessed by the investigator.

This was an exploratory study and the sample size was not primarily based on statistical considerations. A group of 50 randomised subjects in each treatment arm was considered sufficient to explore the response to the treatments in the most important histological and morphological variables: dilation of intercellular spaces, basal cell hyperplasia and length of papillae.

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

Esomeprazole (Nexium, H199/18) 40 mg capsule orally once daily or ranitidine 150 mg tablet orally twice daily or placebo. Doses were given in double-dummy fashion owing to the difference in dosage form. The doses and number of administrations per day were in accordance with the recommended doses. Batch numbers were esomeprazole H 1222-04-01-09, H 1222-04-01-10 and matching placebo H 0459-06-03-07, H 0459-06-03-09, ranitidine H 0538-05-01-24, H 0538-05-01-25, H 0538-05-01-27, and matching placebo H 0539-05-01-01.

Duration of treatment

4 weeks

Criteria for evaluation (main variables)

Efficacy: The primary variables were chosen as potential markers of GORD in subjects with macroscopically normal oesophageal mucosa.

- Primary variables: Dilatation of intercellular spaces in the oesophageal squamous epithelium. Histological markers of oesophageal damage, inflammatory cell infiltration and regeneration in the biopsy specimens.

- Secondary variables: Variables based on GORD symptoms assessed at clinical visits. Variables based on the baseline pH monitoring, i.e. percentage of time with pH<4 and Symptom Association Probability (SAP). Macroscopic features at the endoscopic assessment at baseline.

Safety

Safety assessments included adverse event reports, clinical laboratory data (haemoglobin, leukocytes, platelets, uric acids, creatinine, alkaline phosphatase, ASAT, ALAT and total bilirubin). Measurement of vital signs and physical examination were done at baseline. Adverse events (AEs) were recorded during the treatment period and serious adverse events (SAEs) were recorded during the whole study.

Statistical methods

The Intention To Treat (ITT) and the two Per Protocol (PP) populations were used in the statistical analysis of efficacy.

All histological and morphological variables are presented descriptively.

The difference between treatment groups in the change of length of papillae and basal cell hyperplasia was estimated using an ANOVA with the baseline value as the covariate.

All safety variables are presented descriptively.

Subject population

Table S1 Subject population and disposition

		Not randomised		E40		R150	
Population							
N randomised (N planned)		142	-	51	(50)	52	(50)
Demographic characteristics							
Sex (n and % of subjects)	Male	77	(54.2%)	21	(41.2%)	25	(48.1%)
	Female	65	(45.8%)	30	(58.8%)	27	(51.9%)
Age (years)	Mean (SD)	46.8	(13.7)	44.2	(12.9)	48.3	(13.1)
	Range	19-83		19 to 73		19 to 72	
Race (n and % of subjects)	Caucasian	142	(100.0%)	51	(100.0%)	51	(98.1%)
	Black	0	(0.0%)	0	(0.0%)	1	(1.9%)
Baseline characteristics							
History of reflux symptoms	<6 months	1	(0.7%)	0	(0.0%)	0	(0.0%)
	6-<12 months	14	(9.9%)	7	(13.7%)	4	(7.7%)
	1-5 years	65	(45.8%)	29	(56.9%)	20	(38.5%)
	>5 years	62	(43.7%)	15	(29.4%)	28	(53.8%)
Days with heartburn before visit 1	None	3	(2.1%)	0	(0.0%)	0	(0.0%)
	1 day	7	(4.9%)	0	(0.0%)	0	(0.0%)
	2 days	4	(2.8%)	1	(2.0%)	3	(5.8%)
	3 days	6	(4.2%)	3	(5.9%)	4	(7.7%)
	4 days	12	(8.5%)	1	(2.0%)	2	(3.8%)
	5 days	6	(4.2%)	6	(11.8%)	7	(13.5%)
	6 days	15	(10.6%)	7	(13.7%)	6	(11.5%)
	7 days	76	(53.5%)	33	(64.7%)	30	(57.7%)
	Missing	13	(9.2%)	0	(0.0%)	0	(0.0%)
Severity of heartburn before visit 1	None	3	(2.1%)	0	(0.0%)	0	(0.0%)
	Mild	44	(31.0%)	16	(31.4%)	18	(34.6%)
	Moderate	71	(50.0%)	32	(62.7%)	32	(61.5%)
	Severe	11	(7.7%)	3	(5.9%)	2	(3.8%)
	Missing	13	(9.2%)	0	(0.0%)	0	(0.0%)
Disposition							
N of subjects who	completed	0		46		49	
	discontinued	142		5		3	

	Not randomised	E40	R150
N analyzed for safety	-	51	52
N analyzed for efficacy (ITT)	142	51	52
N analyzed for efficacy (PP1)	107	49	49
N analyzed for efficacy (PP2)	-	44	45

The two treatment groups were in demographic characteristics and baseline values.

Efficacy results

Baseline values for basal cell hyperplasia, length of papillae, MIB-1 and intercellular space dilatation are above the values seen in non-GORD control subjects in previous studies (Zentilin *et al* 2002). In a comparison of subjects with and without erosive oesophagitis, these histomorphological changes seem somewhat more pronounced in subjects with erosive oesophagitis. At baseline, subjects with non-erosive GORD and a pathological acid exposure in the lower oesophagus (pH<4 for more than 4% of the time) showed higher values in all studied histomorphological parameters in the oesophagus (except for intraepithelial neutrophils), both at the Z-line and 2 cm proximal to the Z-line. Dilatation of intercellular spaces was seen in half of the subjects at the oesophagus 2 cm level and in about 80% of the subjects at the Z-line. No evident association was found between the severity of heartburn and the studied histological markers at baseline.

On giving acid suppressive therapy, the recorded values for basal cell hyperplasia, length of papillae, MIB-1 labelling and intraepithelial eosinophils and lymphocytes decreased at both the Z-line and 2 cm proximal to the Z-line. The decrease was more marked in the esomeprazole group, except for intraepithelial eosinophils and lymphocytes at the Z-line. At the Z-line, but not 2 cm above the line, intercellular space dilatation also decreased after acid suppressive therapy. Changes were generally smaller than the standard deviation (SD). There was a greater reduction in length of papillae at oesophagus 2 cm in the esomeprazole than in the ranitidine group. This difference is statistically significant. The same tendency was seen for basal cell hyperplasia at this level and for both of these parameters at the Z-line. This difference was not statistically significant. After acid suppressive therapy, basal cell hyperplasia, intraepithelial lymphocytes, and dilatation of intercellular spaces, showed somewhat higher values with increasing severity of heartburn at the Z-line but not at the oesophagus 2-cm level.

Safety results

Overall both study drugs were well tolerated. No SAEs or other significant adverse events (OAEs) were registered. Two subjects in the esomeprazole group and one in the ranitidine group stopped the study drug due to AEs. In total, more AEs were reported in the ranitidine group. The laboratory values showed no trends or other changes in the parameters that were assessed related to the study treatment.

Table S2 Number of subjects who had an adverse event in any category, and total numbers of adverse events (safety population)

Treatment group:	**E40**	**R150**
No. of subjects:	**n=51**	**n=52**
No. of subjects with[a]:		
any AE	17	19
serious AE	0	0
drug stopped due to AE	2	1
temporarily stopped due to AE	1	1
AE with severe intensity	0	1
Total no. of AEs recorded[b]	*27*	*38*

a) Subjects with multiple events in the same category are counted only once in that category.
b) Events are counted by included term.

Table S3 Number of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in the whole treatment group (safety population)

Treatment group:	**E40**	**R150**	**Total**
No. of subjects:	**n=51**	**n=52**	**n=103**
Abdominal pain	3	2	5
Gastritis	1	3	4
Nausea	2	2	4
Respiratory infection	0	4	4
Chest pain	2	1	3
Diarrhoea	1	2	3
Oesophageal disorder	0	3	3
Back pain	0	2	2
Constipation	1	1	2
Dyspepsia	1	1	2
Headache	1	1	2
Melaena	1	1	2
Mouth dry	2	0	2
Pain	0	2	2
Skin dry	1	1	2

a) AEs experienced by at least 2 subjects in the safety population.

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