Clinical Study Report

Drug Substance	Esomeprazole
Study Code	D9612C00003/SH-NEG-0003*
Edition Number	1
Date	25 March 2010

An open, randomized, multicenter, phase IIIB study during 10 years to assess long-term efficacy and tolerability of esomeprazole compared to laparoscopic anti-reflux surgery in adult patients with chronic gastro-esophageal reflux disease - LOTUS.

Study dates: First patient enrolled: 16 October 2001
Last patient completed: 07 April 2009

Phase of development: Therapeutic comparative IIIB

This study was performed in compliance with Good Clinical Practice.

* Two different study codes (D9612C00003 and SH-NEG-0003) are used in parallel for the same study, with the acronym LOTUS, as a consequence of changes in AstraZeneca's internal system of study coding, during the course of the study. In this document, the study is referred to as D9612C00003 or LOTUS, as applicable.

AstraZeneca

Drug Product	Nexium	**SYNOPSIS**	
Drug Substance	Esomeprazole		
Study Code	D9612C00003		
Edition Number	Version 1		
Date	25 March 2010		

An open, randomized, multicenter, phase IIIB study during 10 years to assess long-term efficacy and tolerability of esomeprazole compared to laparoscopic anti-reflux surgery in adult patients with chronic gastro-esophageal reflux disease - LOTUS.

Study centre(s)

This was a multicentre study with 58 centres in 11 countries: Belgium (10), Denmark (8), France (5), Germany (10), Austria (2), Iceland (1), Italy (7), Norway (8), Sweden (1), UK (1), and The Netherlands (1). The Netherlands did not take part in the 5-year prolongation part of the study.

Publications

Attwood SE, Lundell L, Ell C, Galmiche J-P, Hatlebakk J, Fiocca R, et al. The LOTUS Trial Group. Standardization of Surgical Technique in Antireflux Surgery: the LOTUS Trial Experience. World J Surgery 2008;32:995-98.

Attwood SE, Lundell L, Hatlebakk JG, Eklund S, Junghard O, Galmiche J-P, et al. Medical or Surgical Management of GERD Patients with Barrett's Esophagus: the LOTUS Trial 3-year Experience. J Gastrointestinal Surgery 2008;12:1646-55.

Fiocca R, Mastracci L, Engström C, Attwood S, Ell C, Galmiche J-P, et al. Long-term outcome of microscopic esophagitis in chronic GERD patients treated with esomeprazole or laparoscopic anti-reflux surgery, in the LOTUS trial. Am J Gastroenterol. 2009;631. [published online November 2009]

Lundell LR, Hatlebakk JG, Attwood S, Ell C, Fiocca R, Galmiche J-P, et al. The LOTUS trial - Comparing Esomeprazole to Laparoscopic Anti-Reflux Surgery for the Management of Chronic Gastroesophageal Reflux Disease: a 3-year Interim Analysis. Gastroenterology 2007;132(suppl 2):A-107 abstract 753.

Lundell L, Attwood S, Ell C, Fiocca R, Galmiche J-P, Hatlebakk J, et al, and on behalf of the LOTUS trial collaborators. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut. 2008;57:1207-13.

Study dates		**Phase of development**
First patient enrolled	16 October 2001	Therapeutic comparative (IIIB)
Last patient completed	07 April 2009	

Objectives

Primary objective:

Investigate the efficacy of long-term treatment of esomeprazole compared to laparoscopic anti-reflux surgery in the control of gastroesophageal reflux disease (GERD) by the assessment of time to treatment failure

Secondary objectives:

- Histopathological changes in the squamous epithelium of the distal esophagus, the mucosa of the Z-line, and in the gastric mucosa
- Point/periodic prevalence of endoscopic and symptomatic recurrences during 0.5 to 10 years' treatment
- Gastrointestinal (GI) symptoms associated with GERD
- In cases of Barrett's esophagus, the extent of columnar lined esophagus
- Per-operative events
- Post-operative symptoms and post-fundoplication complaints
- Assessment of 24-hour pH-metry, manometry, and Symptom Association Probability (SAP)
- Changes in the laboratory screen variables
- All serious adverse events (SAEs) and those adverse events (AEs) causing premature discontinuation of study treatment and/or study (DAEs)
- Patient-reported outcomes assessed by the Gastrointestinal Symptoms Rating Scale (GSRS) and Quality of Life in Reflux and Dyspepsia (QOLRAD)

Study design

This study was designed as a 5-year, randomised, open, parallel-group, multicentre trial with a 5-year prolongation (ie, a total study time of 10 years). After having new data from other long-term trials (the SOPRAN and the ProGERD studies), it became clear that the extended part of the LOTUS study was not expected to provide further scientific information which

would be of value in terms of improved treatment practice and patient benefit. Therefore, it was decided to close the study following approval by the authorities/ethics committees of Amendment 5 of the Clinical Study Protocol (CSP) (after the last patient completed 5 years in the study).

Target patient population and sample size

The target population was male or female patients, 18 to 70 years of age, with a history of chronic (>6 months) reflux esophagitis (RE) (endoscopically verified) or a history of chronic (>6 months) symptomatic GERD with pathological 24-h pH-metry according to local standards and in need for long-term treatment with acid suppressive therapy. All patients should have been considered suitable for surgical treatment and long-term management with esomeprazole. Patients should not have had more than Los Angeles (LA) grade B endoscopic-visualised mucosal breaks or more than mild symptoms of GERD prior to randomisation and should have responded to esomeprazole treatment in the 12-week run-in period.

The true rate of treatment successes (ie, patients who had not experienced treatment failure within 5 years) was assumed to be at least 70% for both treatments. With 275 patients receiving each treatment the true difference between treatments was, with a probability of 95%, not differing by more than 8 percentage points from the observed difference.

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

The investigational product was esomeprazole (Nexium™) 20-mg gastro-resistant tablets orally once daily (formulation number H 1189-04-01 and batch number -08; formulation number H 1370-01-02 and batch numbers -06, -07, -10, -14, -15, -16, -17, -19, and -20; and formulation number H 1559-01-01 and batch numbers -01 and -02).

Comparator: Laparoscopic anti-reflux surgery

Duration of treatment

The 5-year study was prolonged with 5 additional years (ie, a total study time of 10 years). After having new data from other long-term trials (the SOPRAN and the ProGERD studies), it became clear that the extended part of the LOTUS study was not expected to provide further scientific information which would be of value in terms of improved treatment practice and patient benefit. Therefore, it was decided to close the study following approval by the authorities/ethics committees of Amendment 5 of the CSP (after the last patient had completed 5 years in the study). In reality, patients would have completed between 5 years (Visit 16) and 7 years (Visit 33) in the study.

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Criteria for evaluation (main variables)

Efficacy

- Primary variable was the number of days from randomisation to treatment failure or, in case of no treatment failure, from randomisation to last visit in the study.
- Secondary variables:
  - Histological assessments
  - Endoscopic relapse (RE LA grade C to D) between scheduled endoscopies. Symptomatic relapse between scheduled visits
  - Endoscopic relapse (RE LA grade C to D) at scheduled endoscopies. Symptomatic relapse at scheduled visits. Symptom assessments at clinical visits
  - GI symptoms associated with GERD
  - Per-operative events
  - Post-operative symptom assessments during the first 30 post-operative days
  - Percentage of time with intragastric and intraesophageal pH ≤ 4
  - Association between symptoms and reflux episodes
  - GSRS and QOLRAD questionnaires at clinical visits

Safety

- Secondary variable:
  - Safety

Safety assessments included all SAEs and DAEs. They also included clinical laboratory tests, including haematology, clinical chemistry and urinalysis. A physical examination and an assessment of vital signs, including blood pressure and pulse rate, were performed at baseline. Vital status and cardiovascular events were followed up for all randomised patients, both ongoing and discontinued, except for those patients who withdrew their consent from the study (Amendment 4 to the CSP).

Pharmacogenetics

It was optional for all patients that were included in the 5-year prolongation of the study to participate in the genetic part of the study. Patients provided a blood sample at the 5-year visit. The purpose of the genetic research was to generate data for use in future analyses.

Statistical methods

Both Intention to Treat (ITT) and Per Protocol (PP) analyses were made for the primary variable. Secondary variables were analysed for the ITT population only. In the ITT analyses all randomised patients were included. The PP population included patients with no major protocol violations, including the violation of entry criteria (the nature and reasons for these protocol violations were defined and documented before database lock). Patients eligible for safety evaluation were those who took at least 1 dose of the investigational product and for whom post-dose information was available.

The 2 treatment groups were compared regarding the primary endpoint using Life Table methods for graphic presentation and a log rank test for statistical inference.

Patient population

As shown in Table S 1, 626 patients were enrolled, 554 were randomised, and 372 completed the 5-year study visit (Visit 16).

Table S 1 Patient disposition

	Number (%) of patients		
	Surgical arm	**Medical arm**	**Total**
Patients enrolled			626
Patients not randomised			72
Patients randomised	288	266	554
Patients randomised to surgery but not operated	40[a]		40
Patients completed visit 16/5-yrs	180 (62.5)	192 (72.2)	372 (67.1)
Patients discontinued before visit 16/5-yrs	108 (37.5)	74 (27.8)	182 (32.9)
Reason for discontinuation before visit 16/5-yrs			
Eligibility Criteria not Fulfilled	1	2	3
Adverse Event	3	15	18
Lack of Therapeutic Response	20	16	36
Development of Study-Specific Discontinuation Criteria	13	2	15
Subject Lost to Follow-up	22	8	30
Other	49	31	80
Patients completed visit 39/last visit	136	158	294
Patients discontinued after visit 16/5-yrs	44	34	78
Reason for discontinuation after visit 16/5-yrs			
No consent to continue after 5 years	34	26	60
Adverse Event	1	2	3
Lack of Therapeutic Response	4	2	6
Subject Lost to Follow-up		1	1

	Number (%) of patients		
	Surgical arm	**Medical arm**	**Total**
Other	5	3	8

[a] Forty patients, being randomised to the surgical arm, chose to withdraw from the study before the operation.

Crit Criteria
LOTUS CSR C30_1

Baseline values were recorded at Visit 1 or Visit 3, or in some case for *Helicobacter pylori* (*H. pylori)*, at Visit 4 (Table S 2). The patients were predominantly Caucasian males with a mean age of 45.1 years.

Table S 2 Demographics and key baseline characteristics, ITT population

Demographic and baseline characteristic	**Treatment group**		
	Surgical arm (N=288)	**Medical arm (N=266)**	**Total (N=554)**
Sex, n (%)			
Male	199 (69.1)	199 (74.8)	398 (71.8)
Female	89 (30.9)	67 (25.2)	156 (28.2)
Age (years)			
Mean (SD)	44.8 (10.9)	45.3 (11.5)	45.1 (11.2)
Median (range)	44 (18- 72)	46 (22- 69)	45 (18- 72)
Race, n (%)			
Caucasian	287 (99.7)	265 (99.6)	552 (99.6)
Black	1 (0.3)	0	1 (0.2)
Oriental	0	1 (0.4)	1 (0.2)
Current smoker, n (%)			
No	207 (71.9)	208 (78.2)	415 (74.9)
Yes	81 (28.1)	58 (21.8)	139 (25.1)
Alcohol use, n (%)			
No	120 (41.7)	90 (33.8)	210 (37.9)
Yes	168 (58.3)	176 (66.2)	344 (62.1)
Previous upper GI surgery n (%)	5 (1.7)	6 (2.3)	11 (2.0)
***H. pylori*, n (%)**			
Absent	258 (89.6)	227 (85.3)	485 (87.5)
Present	30 (10.4)	38 (14.3)	68 (12.3)
Unknown	0	1 (0.4)	1 (0.2)
History of reflux symptoms, n (%)			
< 1 yr	7 (2.4)	3 (1.1)	10 (1.8)
1-5 yrs	97 (33.7)	91 (34.2)	188 (33.9)
>5 yrs	184 (63.9)	172 (64.7)	356 (64.3)
History of verified reflux disease, n (%)			
< 1 yr	84 (29.2)	80 (30.1)	164 (29.6)
1-5 yrs	146 (50.7)	135 (50.8)	281 (50.7)
>5 yrs	56 (19.4)	50 (18.8)	106 (19.1)
Unknown	2 (0.7)	1 (0.4)	3 (0.5)
Heartburn, n (%)			
None	102 (35.4)	92 (34.6)	194 (35.0)
Mild	72 (25.0)	61 (22.9)	133 (24.0)

Demographic and baseline characteristic	Treatment group		
	Surgical arm (N=288)	Medical arm (N=266)	Total (N=554)
Moderate	70 (24.3)	65 (24.4)	135 (24.4)
Severe	44 (15.3)	48 (18.0)	92 (16.6)
Acid regurgitation, n (%)			
None	132 (45.8)	125 (47.0)	257 (46.4)
Mild	62 (21.5)	52 (19.5)	114 (20.6)
Moderate	70 (24.3)	66 (24.8)	136 (24.5)
Severe	24 (8.3)	23 (8.6)	47 (8.5)
LA grade, n (%)			
A	79 (27.4)	56 (21.1)	135 (24.4)
B	64 (22.2)	71 (26.7)	135 (24.4)
C	10 (3.5)	10 (3.8)	20 (3.6)
D	1 (0.3)	0	1 (0.2)
Missing	134 (46.5)	129 (48.5)	263 (47.5)
Hiatal hernia n (%)	204 (70.8)	188 (70.7)	392 (70.8)
Barretts esophagus (ESEM) n (%)	32 (11.1)	28 (10.5)	60 (10.8)

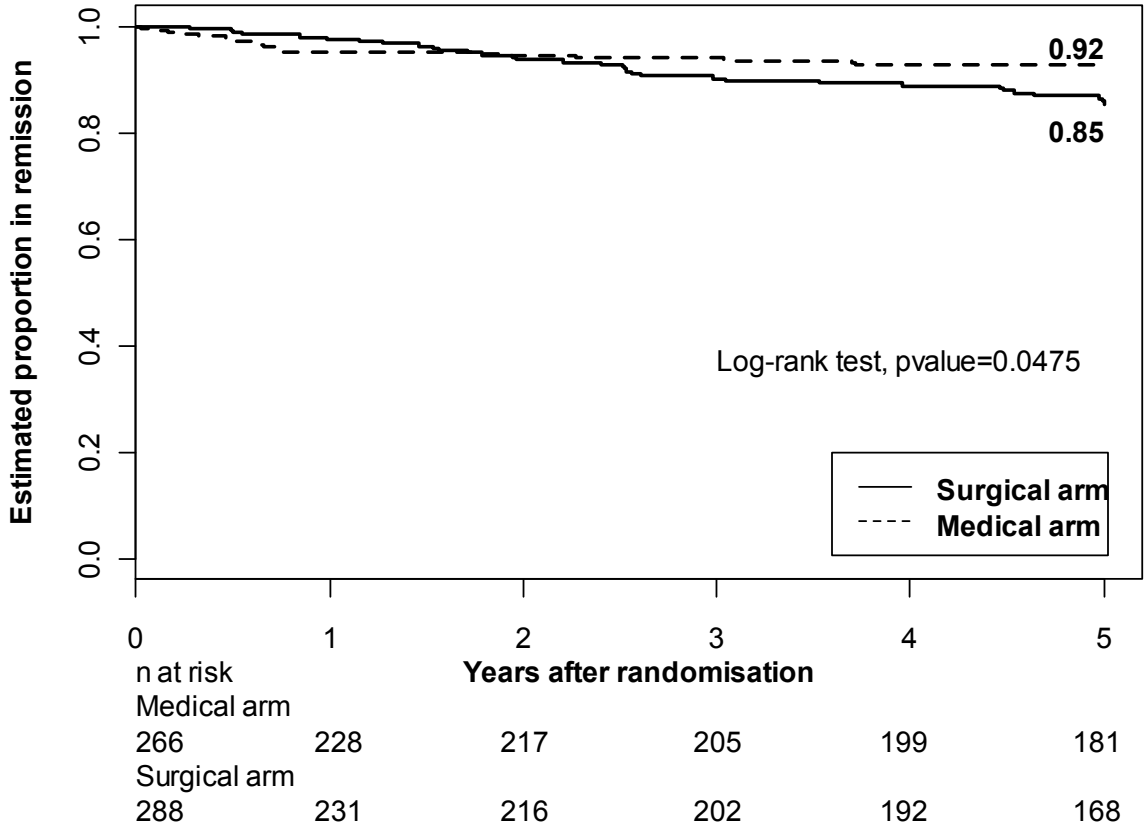
GI Gastrointestinal; *H. pylori Helicobacter pylori*; ITT Intention to treat; LA Los Angeles classification; n Number of patients meeting a criteria; N=Number of patients in the arm; SD Standard deviation.
LOTUS CSR C01_1

Overall the groups were well balanced with regards to baseline characteristics. GI symptoms and RE were affected by proton pump inhibitors taken at baseline for some of the patients. Approximately 10% of the patients had Barrett's esophagus at baseline.

Efficacy results

Both treatment arms resulted in a high proportion of patients in remission and there was a statistically significant difference in remission rate over 5 years in the favour of esomeprazole (Figure S 1). This was shown in both the ITT and PP analysis.

Figure S 1 Time to treatment failure, ITT population



ITT Intention to treat; n Number of patients in a category.

In the ITT analysis, the difference between the remission curves was statistically significant, according to the log-rank test, p=0.0475. The estimated percent in remission at 5 years was 85% for the surgical arm and 92% for the medical arm. There were 19 treatment failures in the medical arm and 33 in the surgical arm.

Heartburn (Table S 3) and acid regurgitation were somewhat more frequent in the medical arm than in the surgical arm. On the contrary, symptoms like bloating and flatulence were more common in the surgical group.

Table S 3 Heartburn by treatment and visit, ITT population

		Number of patients											
Treatment	**Severity**	**Baseline**	**Random-isation**	**0.5 year**	**1 year**	**1.5 year**	**2 year**	**2.5 year**	**3 year**	**3.5 year**	**4 year**	**4.5 year**	**5 year**
Surgical arm	Missing	0	0	0	0	0	1	0	0	0	2	1	3
	None	102	205	221	201	196	193	189	187	180	170	160	163
	Mild	72	79	14	20	13	12	13	10	17	16	21	11
	Moderate	70	4	1	1	2	1	1	1	0	1	5	3
	Severe	44	0	0	0	0	0	0	0	0	2	0	0
	Total	288	288	236	222	211	207	203	198	197	191	187	180
Medical arm	Missing	0	0	0	0	0	0	0	1	0	1	0	0
	None	92	193	175	176	166	163	167	163	166	161	165	161
	Mild	61	67	41	40	43	43	31	37	31	27	24	25
	Moderate	65	4	22	9	10	6	9	6	2	9	4	3
	Severe	48	2	2	1	0	3	2	1	1	2	1	2
	Total	266	266	240	226	219	215	209	208	200	200	194	191

ITT Intent-to-treat
LOTUS CSR C04_2

At both the Z-line and 2 cm above the Z-line, there was a substantial improvement in labelling for an antibody against Ki-67, a protein expressed in proliferating cells (MIB 1) and total score for microscopic reflux-related changes in the distal esophagus in both groups as compared to baseline, showing that the pathological mucosa seen at baseline markedly improved over 5 years in both treatment arms (Table S 4 and Table S 5).

Table S 4 Histological assessments in the surgical arm, esophagus at Z-line, ITT population

Surgical arm	**Number (%) of patients**			
	Baseline (N=288)	**1 year (N=214)**	**3 year (N=190)**	**5 year (N=158)**
Basal cell hyperplasia				
Absent	27 (9.4)	40 (18.7)	48 (25.3)	74 (46.8)
Mild/Dubious	117 (40.6)	115 (53.7)	107 (56.3)	62 (39.2)
Marked	117 (40.6)	37 (17.3)	16 (8.4)	4 (2.5)
Missing	27 (9.4)	22 (10.3)	19 (10.0)	18 (11.4)
Dilatation of intercellular spaces				
Absent	49 (17.0)	54 (25.2)	31 (16.3)	51 (32.3)
Mild/Dubious	102 (35.4)	83 (38.8)	94 (49.5)	72 (45.6)
Marked	111 (38.5)	57 (26.6)	49 (25.8)	17 (10.8)
Missing	26 (9.0)	20 (9.3)	16 (8.4)	18 (11.4)
Columnar epithelium				
Missing	288 (100.0)	214 (100.0)	190 (100.0)	158 (100.0)
Granulationtissue and/or necrosis				
No	243 (84.4)	194 (90.7)	171 (90.0)	135 (85.4)
Yes	21 (7.3)	4 (1.9)	4 (2.1)	6 (3.8)
Missing	24 (8.3)	16 (7.5)	15 (7.9)	17 (10.8)

Surgical arm	Number (%) of patients			
	Baseline (N=288)	1 year (N=214)	3 year (N=190)	5 year (N=158)
Papillae enlogation				
Absent	50 (17.4)	102 (47.7)	88 (46.3)	87 (55.1)
Mild/Dubious	71 (24.7)	50 (23.4)	58 (30.5)	44 (27.8)
Marked	100 (34.7)	14 (6.5)	20 (10.5)	8 (5.1)
Missing	67 (23.3)	48 (22.4)	24 (12.6)	19 (12.0)
Intraepithelial eosinophils				
0	168 (58.3)	145 (67.8)	116 (61.1)	98 (62.0)
1-2	67 (23.3)	41 (19.2)	40 (21.1)	35 (22.2)
3-9	22 (7.6)	10 (4.7)	14 (7.4)	4 (2.5)
10-14	2 (0.7)	1 (0.5)	1 (0.5)	1 (0.6)
15 or more	4 (1.4)	1 (0.5)	4 (2.1)	2 (1.3)
Missing	25 (8.7)	16 (7.5)	15 (7.9)	18 (11.4)

ITT Intent-to-treat; N=Number of patients in the arm.
LOTUS CSR C15_1

Table S 5 Histological assessments in the medical arm, esophagus at Z-line, ITT population

Medical arm	Number (%) of patients			
	Baseline (N=266)	1 year (N=221)	3 year (N=200)	5 year (N=180)
Basal cell hyperplasia				
Absent	25 (9.4)	37 (16.7)	68 (34.0)	103 (57.2)
Mild/Dubious	101 (38.0)	138 (62.4)	104 (52.0)	57 (31.7)
Marked	122 (45.9)	22 (10.0)	8 (4.0)	2 (1.1)
Missing	18 (6.8)	24 (10.9)	20 (10.0)	18 (10.0)
Dilatation of intercellular spaces				
Absent	51 (19.2)	60 (27.1)	41 (20.5)	79 (43.9)
Mild/Dubious	88 (33.1)	82 (37.1)	110 (55.0)	68 (37.8)
Marked	109 (41.0)	55 (24.9)	32 (16.0)	16 (8.9)
Missing	18 (6.8)	24 (10.9)	17 (8.5)	17 (9.4)
Columnar epithelium				
Missing	266 (100.0)	221 (100.0)	200 (100.0)	180 (100.0)
Granulationtissue and/or necrosis				
No	230 (86.5)	199 (90.0)	180 (90.0)	163 (90.6)
Yes	22 (8.3)	1 (0.5)	3 (1.5)	1 (0.6)
Missing	14 (5.3)	21 (9.5)	17 (8.5)	16 (8.9)
Papillae enlogation				
Absent	38 (14.3)	113 (51.1)	117 (58.5)	122 (67.8)
Mild/Dubious	64 (24.1)	49 (22.2)	48 (24.0)	33 (18.3)
Marked	106 (39.8)	11 (5.0)	5 (2.5)	6 (3.3)
Missing	58 (21.8)	48 (21.7)	30 (15.0)	19 (10.6)
Intraepithelial eosinophils				
0	159 (59.8)	138 (62.4)	139 (69.5)	127 (70.6)
1-2	69 (25.9)	44 (19.9)	32 (16.0)	26 (14.4)
3-9	13 (4.9)	13 (5.9)	7 (3.5)	6 (3.3)
10-14	2 (0.8)	1 (0.5)	0	2 (1.1)
15 or more	9 (3.4)	4 (1.8)	5 (2.5)	2 (1.1)

Medical arm	Number (%) of patients			
	Baseline (N=266)	1 year (N=221)	3 year (N=200)	5 year (N=180)
Missing	14 (5.3)	21 (9.5)	17 (8.5)	17 (9.4)

ITT Intent-to-treat; N=Number of patients in the arm.
LOTUS CSR C15_2

The pH results showed small changes from 6 months to the final observation at 5 years. Both treatments effectively reduced acid reflux into the esophagus, but more profoundly, so did surgery. Intragastric pH was unaltered by surgery but reached stable values of time with pH >4 after 6 months which remained so after 5 years of esomeprazole therapy.

Safety results

Safety results are reported in the CSR body for the entire study period, including run-in and the total randomised study period (including time after the 5-year visit); for some patients this extended up to 7 years. However, the randomised period 5-year results are presented here for the number of patients with SAEs and/or DAEs and the number of SAEs and/or DAEs in Table S 6 and Table S 7, respectively.

Table S 6 Number (%) of patients who had an SAE and/or DAE in the study, including AEs within 5 years, safety population

Category of adverse event[a]	Surgery arm Not operated	Surgery arm Operated	Medical arm
	n=40	n=248	n=266
SAE	3 (7.5)	71 (28.6)	64 (24.1)
SAE leading to death	0	1 (0.4) [b]	4 (1.5) [b]
Discontinuation of study treatment due to AE	1 (2.5)	0	9 (3.4)
Discontinuation of study due to AE	2 (5.0)	2 (0.8)	15 (5.6)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] One patient in each treatment arm died after the study stopped. SAEs started during the study.
AE Adverse event; DAE Discontinuation due to AE; n Number of patients in a category; SAE Serious adverse event.
LOTUS CSR C12_1

Table S 7 Number of SAEs and DAEs in the study, including AEs within 5 years, safety population

Category of adverse event [a]	Surgery arm Not operated	Surgery arm Operated	Medical arm
	n=40	n=248	n=266
SAE	4	114	113
SAE leading to death	0	1 [b]	8 [b]

Category of adverse event [a]	Surgery arm Not operated	Surgery arm Operated	Medical arm
	n=40	n=248	n=266
Discontinuation of study treatment due to AE	1	0	19
Discontinuation of study due to AE	3	3	25

[a] Number of SAE-episodes are counted, eg 'keratitis' occurring twice for a patient are counted as 2 SAEs
[b] One patient in each treatment arm died after the study stopped. SAEs started during the study.
AE Adverse event; DAE AE leading to discontinuation of a patient from study treatment; SAE Serious adverse event.
LOTUS CSR C12_2

There were 3 patients with SAEs leading to death (0 in the surgical arm and 3 in the medical arm). Two additional SAEs were reported during the study and led to death that occurred after study termination (1 in each treatment arm). The total number of fatal SAEs was too low to allow any inferences regarding any discrepancy between the 2 treatment arms.

The total frequency of reported SAEs up to 5 years was similar between the treatment groups.

The 2 most commonly reported SAEs by system organ class (SOC) up to 5 years were from Injury, Poisoning and Procedural Complications and Gastrointestinal Disorders.

Numerical differences by SOC in SAE reporting frequency between the medical and the surgical arms represented post-operative complications as well as a huge variety of different symptoms and conditions without any consistent pattern.

Malignant tumours were extensively reviewed and evaluated; the numerical difference seen for the SOC Neoplasms Benign, Malignant and Unspecified did not raise any safety concerns.

DAEs were reported in a higher frequency in the medical arm.

SAE and DAE data for the entire study period, including run-in and total randomised study period (including time after the 5-year visit), showed similar results with regard to reporting frequency as the 5-year period.

No signal indicating an increased risk of cardiac death, myocardial infarction, myocardial interventions, or stroke in patients treated with esomeprazole was detected.

There was an increase in mean values over time for serum (S-) gastrin and S-chromogranin A in the medical arm, while no changes were seen in the surgical arm. These findings were expected and a well known effect of acid-suppressive therapy and seemed to stabilise at 5 years. There were no clinically relevant changes over time in mean haematology and clinical chemistry values, including S-cobalamine, S-iron, S-homocystein, S-calcium, S-ALP, or S-25-Hydroxy-D-vitamin; and there were no differences between treatment groups.

Date of the report

25 March 2010