AstraZeneca

Drug substance:	Omeprazole	**SYNOPSIS**	
Study code:	D9584C00004		
Date:	11 July 2007		

Omeprazole versus anti-reflux surgery in the long-term management of reflux esophagitis: a 10-year follow up study of patients previously studied for 5 years - a Nordic multi-center study

D9584C00004 [**S**afety of **O**meprazole in **P**eptic **R**eflux Esophagitis: **A** **N**ordic Open Study (SOPRAN)] was a multi-center, open, randomized, parallel group long-term follow-up study of patients from the previous study I-635 (omeprazole versus anti-reflux surgery in the long-term management of peptic esophagitis - a Scandinavian, comparative multi-center study). I-635, the first 5-year follow-up study subsequent to treatment of reflux esophagitis, has already been accounted for in a final clinical study report (CSR), see Appendix 12.1.13. The present CSR is mainly based on SOPRAN, but updates details from patients in both studies (I-635 and SOPRAN). The outcomes of the entire study period (from baseline in I-635 to end of SOPRAN prolongation) are presented in accordance with the objectives stated in the clinical study protocol (CSP) of SOPRAN. Therefore, "baseline" and "at entry" hereinafter refer to baseline at entry of I-635 unless otherwise stated.

An addendum to this CSR will be issued when details are available regarding deaths of patients exiting the I-635/SOPRAN up to the time of closing the study (October 30, 2005), in accordance with SOPRAN CSP Amendment 5 (10 May 2007).

Study center(s)

SOPRAN was an international, multi-center study carried out in 16 centers in Denmark (6 centers), Finland (1), Norway (5) and Sweden (4). There were 18 participating centers in the previous study I-635, but 2 centers (centers 4 and 10) did not contribute any patients to SOPRAN.

Publications based on SOPRAN

Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Thor K, Andersson A et al. Lack of effect of acid suppression therapy on gastric atrophy. Gastroenterology 1999;117:319-26.

Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Thor K, Lamm M et al. Long-term management of gastro-oesophageal reflux disease with omeprazole or open anti-reflux surgery: results of a prospective randomized trial. Eur J Gastroenterol Hepatol 2000;12:879-87.

Lundell L, Miettinen P, Myrvold HE, et al. Continued (5-year) follow-up of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001;192:172-9.

Lundell L, Havu N, Miettinen P, Myrvold HE, Wallin L, Julkunen R et al. Changes of gastric mucosal architecture during long-term omeprazole therapy: results of a randomized clinical trial. Aliment Pharmacol Ther 2006;23:639-47.

Lundell L, Miettinen P, Myrvold HE, Hatlebakk JG, Wallin L, Malm A. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis. Br J Surg 2007;94:198-203.

Myrvold HE, Lundell L, Miettinen P, et al. The cost of long term therapy for gastro-oesophageal reflux disease: a randomised trial comparing omeprazole and open anti-reflux surgery. Gut 2001;49:488-94.

Abstracts based on SOPRAN

Hatlebakk JG, Lundell LR, Wallin L, Myrvold HE, Miettinen P, Malm A. Manometry and 4-hour pH-metry during 10 years' follow-up in patients randomized to anti-reflux surgery or omeprazole. Gastroenterology 2007;132(4 Suppl 1):A-108, Abs 755.

Lundell L and the Nordic GORD Study Group. The impact of 7 years omeprazole included inhibition on the development of gastric glandular atrophy in H. pylori-infected GORD patients. Helicobacter 2003;8(4):406, Abs 07.25.

Lundell L, Myrvold HE, Miettinen P, Wallin L, Hatlebakk J, Julkunen R et al. Medical or surgical therapy for gord revisited; 7 year follow-up of a randomised, clinical trial. Gut 2003;52(Suppl 6):A134, Abs TUE-G-072.

Lundell L, Havu N, Miettinen P, Myrvold HE, Wallin L, Julkunen R et al. The impact of seven years omeprazole induced acid inhibition on the development of gastric glandular atrophy in H.pylori infected GORD patients. Gut 2003;52(Suppl 6):A135, Abs TUE-G-077.

Lundell L, Myrvold H, Miettinen P, Wallin L, Hatlebakk J, Julkunen R et al. Medical or surgical therapy for reflux esophagitis; 7 year follow-up of a randomised, clinical trial. Gastroenterology 2004;126(4 Suppl 2):A-18, Abs 129.

Lundell L, Havu N, Miettinen P, Myrvold H, Wallin L, Julkunen R et al. Influence of seven years omeprazole induced acid inhibition on the gastric morphology in patients with chronic gastro-esophageal reflux disease. Gastroenterology 2004;126(4 Suppl 2):A-533, Abs W918

Lundell LR, Miettinen P, Myrvold HE, Hatlebakk JG Wallin L, Malm A et al. Anti-reflux surgery compared with maintenance omeprazole for reflux esophagitis. Results after 12 years. Gastroenterology 2007;132(4 Suppl 1):A-107, Abs 754.

Study dates		**Phase of development**
(First patient enrolled I-635	28 February 1991)	Long-term upper gastrointestinal safety/ therapeutic comparative
First patient enrolled	6 January 1998	(Phase IIIb)
Last patient completed	30 October 2005	

Objectives

The primary objective of SOPRAN was to study the development of gastritis, with particular emphasis on glandular atrophy, during long-term omeprazole therapy, and the relation to concomitant *Helicobacter pylori* (*H. pylori)* infection.

Secondary objectives were:

- To investigate the long-term control of reflux symptoms, healing of esophagitis and persistence of post-fundoplication[2] symptoms.
- To investigate the influence of therapy on Quality of Life[3] (QoL).
- To further assess the safety profile by the use of laboratory screen variables and the frequency of serious adverse events (SAEs).

Study design

SOPRAN was a multi-center, open, randomized, parallel group, long-term, follow-up study of patients who participated in the previous study I-635.

In study I-635, patients with recurrent erosive and/or ulcerative esophagitis were treated with omeprazole, 20 or 40 mg once daily (od), to heal their esophagitis, at which point they were

[2] Anti-reflux surgery in general will be referenced to as 'fundoplication' since this was the most commonly used technique but Hill's posterior gastropexy was also allowed

[3] Patient-reported gastrointestinal symptoms and well-being. Due to change in terminology QoL will also be referenced to as Patient-reported outcomes (PRO)

randomized to either maintenance therapy with omeprazole, 20 mg or 40 mg od, or surgical treatment; all patients were then followed-up for 5 years. SOPRAN was planned to extend patient follow-up and study duration by another 5 years; this was further extended to 10 years by protocol amendment 3 (30 May 2002) and included 2 clinic visits and 3 telephone contacts with patients to assess clinical responses. However, after a total median time of 12 and 10 years in the omeprazole group and surgery group, respectively, and up to 14 years and 7 months of patient follow-up, the SOPRAN was stopped (protocol amendment 4; 9 February 2005), because the number of patients remaining in each treatment group was considered too low for meaningful conclusions to be drawn from any further data collected, as the number of participating patients was expected to continue decreasing during the following years. Updated details for patients in I-635, SOPRAN and SOPRAN prolongation are presented in this CSR.

Target patient population and sample size

Patients of the SOPRAN study consisted of those who had completed and consented to the previous study I-635. Patients were characterized by having had previous erosive and/or ulcerative esophagitis initially healed with omeprazole, 20 mg or 40 mg od, who then received either maintenance omeprazole, 20 mg or 40 mg od, for 5 years, or anti-reflux surgery.

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

Omeprazole 20 mg or 40 mg was given orally od; patients continued to take the same dose they had received in I-635. Patients requiring the higher 40 mg dose of omeprazole took 2 x 20 mg capsules od in the morning or divided into a morning and an evening dose. Initially, omeprazole capsules were given with the following batch numbers:
H 0431-14-03-13; H 0431-14-03-17; H 0431-14-03-19; H 0431-14-03-20.

Following protocol amendment 3 (30 May 2002), omeprazole 20 mg tablets (LOSEC® MUPS®) were supplied once pre-packed supplies of omeprazole capsules ran out. These had the following batch numbers: H 1066-05-07-18; H 1066-05-07-19; H 1066-05-07-20.

The comparator to omeprazole 20 mg or 40 mg was anti-reflux surgery (either fundoplication or Hill's posterior gastropexy).

Duration of treatment

Study treatment with omeprazole was planned to continue for an additional 10 years after completion of study I-635. However, SOPRAN was stopped prematurely because the number of patients remaining, in particular with regard to concomitant *H. pylori* infection, was too low for meaningful conclusions to be drawn from any further data collected; all patients completed

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their last assessment by October 2005. Patients (74 in omeprazole group and 53 in surgery group) remaining at termination of study had been treated for a total median time of 12 and 10 years in the omeprazole group and surgery group, respectively, and up to 14 years and 7 months.

Criteria for evaluation (main variables)

Efficacy:

- Primary variable: histopathological assessment of the corpus mucosa related to the development of gastritis, in terms of activity, inflammation, atrophy, *H. pylori* and intestinal metaplasia (classified according to the Sydney system).
- Secondary variables: endoscopic assessments with grade of esophagitis and severity of reflux symptoms (time to treatment failure); intra-esophageal pH; manometry; bilirubin reflux (only at centers where Bilitec® technology was available)

Safety:

- Secondary variables: degree of argyrophil cell hyperplasia; serious adverse events (SAEs); discontinuation of study treatment due to AEs; and clinical laboratory variables.

Patient-reported outcomes[4]:

Secondary variables: Gastrointestinal Symptom Rating Scale (GSRS), Ulcer Esophagitis Subjective Symptom Scale (UESS), Psychological General Well-Being (PGWB).

Statistical methods

Degree of gastritis (in terms of activity, inflammation, atrophy and intestinal metaplasia) and degree of argyrophil cell hyperplasia was summarized with descriptive statistics by treatment group and *H. pylori* status. Change from baseline to last visit (last value carried forward) was summarized in shift tables.

A logrank test was used to compare the randomized treatment groups with regard to time to treatment failure. Treatment failure was defined as symptomatic and endoscopic relapse of esophagitis, need for additional therapy [ie, proton-pump inhibitor (PPI) for at least 8 weeks for the surgery group or surgery for the omeprazole group] or unacceptable adverse event (intolerance to the medical treatment).

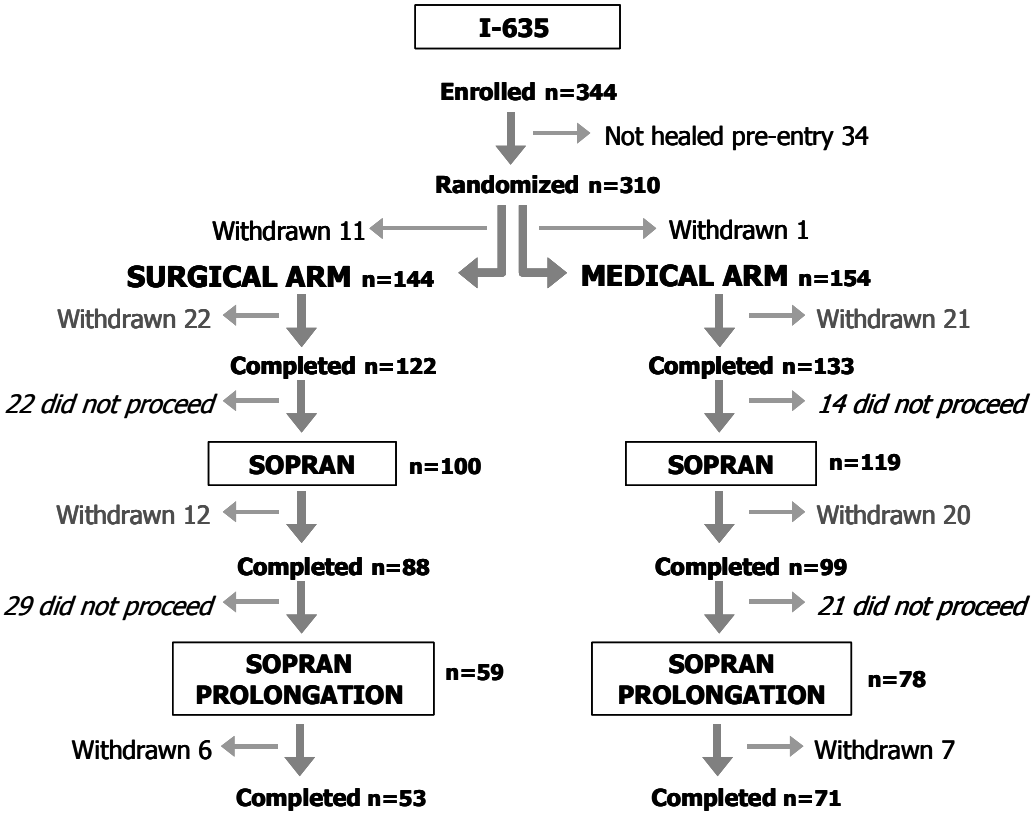
All other variables were summarized using descriptive statistics or listings as relevant.

[4] Previously referenced to as Quality of Life (QoL)

Patient population

Figure S 1 shows the flow of patients from enrolment into I-635, further to SOPRAN and the SOPRAN prolongation.

Figure S 1 Patient disposition (completion or withdrawal)



Of the 310 patients healed during run-in and randomized to maintenance treatment (either omeprazole or surgery) in I-635, 255 patients completed the study and were thus eligible for participation in SOPRAN. Of these, 219 patients continued into SOPRAN on the same treatment as in I-635 (119 in omeprazole group, 100 in the surgery group). When SOPRAN prolongation was terminated prematurely only 124 patients remained in the study, 71 in the omeprazole group (46% of 155 entering the I-635 omeprazole group), and 53 in the surgery group (34% of the 155 entering the I-635 surgery group). There were a total of 21 patients (15%) in the omeprazole group that changed therapy so that they had fundoplication performed. In the surgical group there were a total of 45 patients (31%) who were treated with omeprazole for at least 8 weeks. The majority of these patients were given omeprazole as maintenance therapy [ie >1 year as continuous treatment (25%)]. Table S 1 shows key patient demographics and disposition.

Patients whose esophagitis did not heal during the run-in omeprazole course of study I-635 were not randomized but were offered and underwent anti-reflux surgical treatment. Progress was followed by the investigator during I-635 and the first part of SOPRAN. This group of patients is referred to as the "third arm", and is included in the safety population.

Table S 1 Patient population key demographics and disposition

	Omeprazole	Surgery	Third arm	Total
No. enrolled (I-635)				344
No. randomized (I-635)	155	155	34	344
No. treated	154	144	34	332
Males / Females	115/39	110/34	24/10	225/73
Age (median, range; years)	54 (21 to 76)	50 (18 to 77)	49.5 (24 to 71)	51.5 (18 to 77)
H. pylori status at I-635 baseline (negative/positive)	124/30	101/42[a]	26/5	251/77
No. completed I-635	133	122	26	281
No. continued into SOPRAN	119	100	20	239
No. completed first 5 years SOPRAN	99	88	20	207
No. continuing into SOPRAN prolongation	78	59	0	137
No. remaining in SOPRAN at termination	71	53	0	124
No. analyzed for efficacy (ITT)	154	144	0	298
No. analyzed for safety	155	155	34	332

[a] A further 1 patient was assessed as having unknown *H. pylori* status
ITT=Intention to treat; No=Number of patients.

Efficacy results

Gastritis-related histopathology: Signs of gastritis, ie, activity, inflammation and atrophy in both treatment groups were seen mainly in patients who were *H. pylori* positive at the last investigation. There were no clinically significant differences between the treatment groups in the proportion of patients with atrophy in those remaining *H. pylori* positive throughout the study. There was an increase of inflammation severity in patients remaining *H. pylori* positive in the omeprazole group but not in the surgery group. Very few patients had or developed intestinal metaplasia and there were no clear differences from baseline to last visit in changes between the treatment groups. No patient developed any sign of dysplasia.

Table S 2 Numbers of omeprazole-treated patients by degree of gastritis at baseline and last visit by *H. pylori* status (ITT population)

H. pylori status[b]	Degree[a] of gastritis	Activity		Inflammation		Atrophy		Intestinal metaplasia	
		Baseline	Last visit	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit
Neg/Neg	None	112	115	93	105	112	115	114	116
(n=116)	Mild	4		22	10	4		2	
	Moderate			1			1		
	Severe		1		1				

Table S 2 Numbers of omeprazole-treated patients by degree of gastritis at baseline and last visit by *H. pylori* status (ITT population)

***H. pylori* status**[b]	**Degree**[a] **of gastritis**	**Activity**		**Inflammation**		**Atrophy**		**Intestinal metaplasia**	
		Baseline	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**
Pos/Pos	None	1				15	12	17	14
(n=18)	Mild	8	8	10	3	3	3	1	3
	Moderate	6	7	7	6		2		1
	Severe	3	3	1	9		1		

a Gastritis classified according to the Sydney system
b Neg/Neg = *H. pylori* negative at entry and at completion
Pos/Pos = *H. pylori* positive at entry and at completion

Table S 3 Number of surgery-treated patients by degree of gastritis at baseline and last visit by *H. pylori* status (ITT population)

***H. pylori* status**[b]	**Degree**[a] **of gastritis**	**Activity**		**Inflammation**		**Atrophy**		**Intestinal metaplasia**	
		Baseline	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**	**Baseline**	**Last visit**
Neg/Neg	None	84	85	73	81	85	86	85	86
(n=86)	Mild	2	1	12	5			1	
	Moderate			1		1			
	Severe								
Pos/Pos	None	1	1	1		17	16	18	18
(n=20)	Mild	9	13	6	10	1	2	1	1
	Moderate	7	4	10	6	2	1	1	
	Severe	3	2	3	4		1		1

a Gastritis classified according to the Sydney system
b Neg/Neg = *H. pylori* negative at entry and at completion
Pos/Pos = *H. pylori* positive at entry and at completion

Argyrophil cell hyperplasia was seen in only a minority of patients, but was more common in patients treated with maintenance omeprazole and in patients remaining *H. pylori* positive throughout the study. Micronodular hyperplasia was observed in both treatment groups but no changes beyond micronodular hyperplasia were observed in any of the groups.

Table S 4 Number of omeprazole-treated patients by degree of argyrophil cell hyperplasia (ITT population)

Degree[a]	Baseline	Years in study					End of study
		1	3	5	7	10	
Total	153	138	129	125	109	90	36
Normal	148	131	118	113	91	68	30
Diffuse	2	3	3	3	5	4	
Linear		1	3	3	4	7	2
Micronodular	3	3	5	6	9	11	4

a Argyrophil cell hyperplasia classified according to Solcia et al 1988

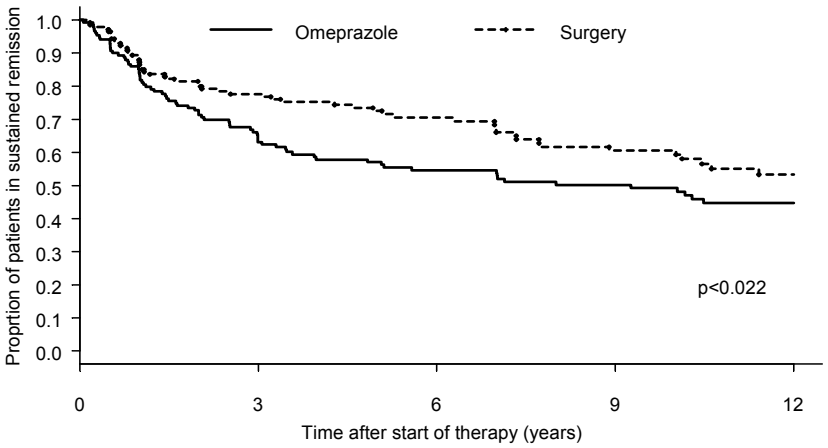
Table S 5 Number of surgery-treated patients by degree of argyrophil cell hyperplasia (ITT population)

Degree[a]	Baseline	Years in study					End of study
		1	3	5	7	10	
Total	137	120	113	114	92	79	26
Normal	133	118	109	112	87	74	23
Diffuse	1		1	2	1	1	1
Linear			1		1	2	1
Micronodular	3	2	2		3	2	1

a Argyrophil cell hyperplasia classified according to Solcia et al 1988

Treatment failure: The treatment in the surgery group was more effective than the treatment in the omeprazole group in keeping patients in sustained remission with regard to time to treatment failure (p=0.022; Figure S 2).

Figure S 2 Proportion of patients in maintained remission (ITT analysis set)



The point prevalence of recurrences of reflux disease (esophagitis and/or symptoms) was similar (approximately 10% in) in the 2 treatment groups for up to 10 years.

Endoscopy: recurrences of esophagitis at the pre-scheduled endoscopies were almost exclusively of modified Savary-Miller grade 2 (=isolated erosion) only. The presence of stricture observed at entry was 6% and 8% in the omeprazole and surgical groups respectively, and decreased to 1 to 2%, at the last endoscopy. Reported Barrett's esophagus (endoscopic assessment) at entry was 17% and 15% in the omeprazole and surgical group, respectively, and 22% and 24%, respectively, at last endoscopy. Hiatal hernia was observed in 92% of the patients at entry in both groups, and decreased to 80% and 29% in the omeprazole and surgical group, respectively, after 10 years.

Reflux and postoperative symptoms: reflux-related symptoms decreased markedly and remained infrequent over the years in both treatment groups. There was numerically more reduction of heartburn and regurgitation in the surgery group than in the omeprazole group. Symptoms such as flatulence and impaired ability to belch or vomit were more common in the surgical group and remained at the same level over the years of follow-up.

Intra-esophageal pH monitoring: esophageal acid exposure was significantly reduced in both treatment groups, and remained so throughout the observation period. The reduction of esophageal pH was more pronounced in the surgery group than in the omeprazole group after 1 year of treatment.

Manometry: lower esophageal sphincter (LES) pressure increased significantly after surgery and remained stable throughout the study; there was no significant change in LES function over time in the omeprazole group.

Patient reported outcomes:

The patient-reported gastrointestinal symptoms were generally mild. Patients in both treatment groups reported a well-being comparable to a normal population at 2 months and during the follow-up years.

Safety results

Adverse events: A few patients in the omeprazole group experienced AEs which resulted in either temporary (5 patients) or permanent (21 patients) discontinuation of omeprazole. There were numerically more SAEs in the surgical group than in the omeprazole group (92 in the surgery group and 83 in the omeprazole group; Table S 6).

Table S 6 Number (%) of patients who had at least one AE in any category (Safety population)

AE category	Run in (n=344)	Omeprazole (n=155[a])	Surgery (n=155[a])	3rd arm (n=34[b])
Any SAE	2 (1)	83 (54)	92 (59)	21 (62)
Any AE leading to temp drug stop	0 (0)	5 (3)	n.a.	n.a.
Any AE leading to perm drug stop	1 (0)	21 (14)	n.a.	n.a.
Any SAE with outcome = death	0 (0)	17 (11)	8 (5)	0 (0)

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.

a In the omeprazole group, 154 pts received randomized treatment and the corresponding number for the surgery group was 144 pts.

b All pts in the 3rd arm received anti-reflux surgery

n.a. Not applicable for the surgery group

SAEs belonging to the system organ classes (SOCs) of infection, procedural complications or gastrointestinal disorders were more common in the surgical group. There were numerically more SAEs within the SOC of cardiac disorders, including SAEs with a fatal outcome, in the omeprazole group (17 patients compared to 8 patients in the surgery group). However, there were 6 patients with a history of myocardial infarction at entry in the omeprazole group while there was no such patients in the surgery group.

Laboratory safety variables: There were no unexpected differences in laboratory variables, including B12, S-Ferritin or S-Gastrin, between the 2 treatment groups and no clinically significant changes over time in other laboratory variables.