AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole
Study code:	D9612L00109
Date:	02 July 2008

CSR-9-01 Version 2000.02.00

SYMPATHY (Symptom Adapted Therapy)
A randomised, open, parallel-group, multi-national, multi-centre, phase IV study to evaluate the efficacy of three different subject management strategies with and without esomeprazole 20 mg during a 3 months maintenance phase following an initial 4-weeks acute treatment phase in subjects with symptoms thought to be GERD related

Study dates:	First subject enrolled: 17 Aug 2006 Last subject enrolled: 25 Dec 2006
Phase of development:	Therapeutic confirmatory (IV)
International Coordinating Investigator:	
Sponsor's Responsible Medical Officer:	

This study was performed in compliance with Good Clinical Practice (GCP).

Drug product:	Nexium®	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
Study code:	D9612L00109		
Date:	27 May 2008		

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Study centre(s)

The study was conducted in 128 centres in Germany. Identities of investigators and addresses of respective study sites are provided in Appendix 12.1 (Study information).

Publications

none

Study dates		**Phase of development**
First subject enrolled	17 Aug 2006	Phase IV
Last subject completed	02 Aug 2007	

Objectives

Primary objective was:

To compare the efficacy of three different long-term treatment strategies in primary care setting, separately within different levels of symptom load according to clinical judgement at baseline (Visit 1), in subjects with symptoms thought to be GERD-related, using the number of '*treatment failures*' as primary outcome variable.

Secondary objectives were:

1. To evaluate whether the Reflux Disease Questionnaire (RDQ) – used in primary care setting - adds value to clinical judgement in assessing baseline symptom load and thus facilitated the decision on appropriate acute and maintenance treatment strategy in subjects with reflux symptoms

2. To assess the additional impact of a concomitant low dose acetylsalicylic acid (ASA) therapy during acute and maintenance phase with regard to efficacy

3. To evaluate whether there is a difference between treatment strategies with regard to subject satisfaction during maintenance phase, using the GERD Impact Scale

4. To assess resource utilization and days absent from work due to GERD symptoms related to '*treatment failures*' during the maintenance phase.

5. To assess the impact of GERD symptoms on patient-reported utility values.

6. To assess the impact of GERD symptoms on patient-reported productivity while at work and while carrying out daily non-work activities.

Exploratory objectives were:

1. To establish cut-off scores for the RDQ that could be used to support the grading of symptom load at baseline.

2. To establish cut-off scores for the RDQ that could be used in allocating subjects to different short- and long-term treatment strategies.

3. To establish cut-off scores for the RDQ that could be used for defining treatment success.

Study design

This was a randomised, open, parallel-group, multi-national, multi-centre study which was performed in a primary care setting.

Target subject population and sample size

The target study population were subjects of either gender aged 18-50 years who sought medical advice for symptoms thought to be GERD related by primary care physicians. Subjects were to be eligible for empirical treatment for up to 16 weeks with either esomeprazole or rescue medication (antacids) according to physician's judgement. Subjects with any clinical GERD diagnosis / treatment (PPI, H_2-receptor antagonists) within the last 3 months prior to Visit 1 were not allowed to be enrolled into the study.

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

Acute phase (4 weeks):
*D*epending on the physician's treatment strategy, esomeprazole tablets 20 mg or 40 mg, were administered orally once daily in the morning prior to breakfast.

Maintenance phase (12 weeks):
Following the randomisation scheme, one of the following treatment regimens was applied:

Group (1)*:* esomeprazole tablets 20 mg were administered orally once daily in the morning prior to breakfast.

Group (2): esomeprazole tablets 20 mg could be used once daily *on-demand* (maximum 1 tablet per day).

Batch No.: HB16386A3 (expiry date: Jan 2009), HB10480A3 (expiry date: Jan 2009).

Comparator, dosage and mode of administration

Group (3): no use of esomeprazole, but subjects could use rescue medication (antacids with an acid binding capacity of < 18 mmol HCl) *as needed.*
The following rescue medication had to be used:
Germany: trade name: Gelusil Lac (maximum 4 tablets per day)
Greece: trade name: Aludrox (maximum 2 tablets per day)
Portugal: trade name: Vingel (maximum 3 tablets per day)

Batch No.: 801264 (Gelusil Lac, expiry date: Aug 2008). Gelusil Lac was the only anatacid used in the study, as subjects were only recruited in Germany.

Duration of treatment

- Esomeprazole 40 mg was allowed to be taken for a maximum of 30 days (only during the acute phase)

- Esomeprazole 20 mg was allowed to be taken for a maximum of 119 days (maximum of 30 days during the acute phase and a maximum of 89 days during the maintenance phase)

- Rescue medication was allowed to be taken for a maximum of 89 days (only during the maintenance phase).

During the maintenance phase, subjects randomised to Group (2) or (3) used study medication *on-demand* resp. *as needed*, i.e. if symptoms were present and the subject saw a need to take relief medication. Subjects stopped the (*on-demand / as needed*) intake of study medication when symptoms were adequately controlled according to subject's judgement.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable:
  - Number of 'treatment failures' within the maintenance phase. A subject was considered to be a 'treatment failure' if he / she expressed during an unscheduled visit or at the final Visit 3 that his / her treatment strategy was insufficient to control the reflux symptoms or was not willing to continue with the treatment strategy.
- Secondary outcome variables:
  - Clinical judgement of investigator regarding the severity of GERD-related symptoms (mild, moderate, severe) at Visit 1 without knowledge of RDQ results from Visit 1 and re-check of clinical judgement from Visit 1 when the subject had left the clinic, but now with additional knowledge of RDQ results from Visit 1.
  - Treatment strategy of investigator at Visit 1 regarding the use and dosing of esomeprazole in the acute and maintenance phase without knowledge of RDQ results from Visit 1 and re-check of treatment strategy from Visit 1 when the subject had left the clinic, but now with additional knowledge of RDQ results from Visit 1.
  - Type and amount of ASA medication used during acute phase, maintenance phase and in total during the study

- Dimension scores derived from the GERD Impact Scale at start and end of maintenance phase

Exploratory variables

- RDQ score calculated as a sum of selected RDQ items at Visit 1 (baseline).
- Clinical judgement of investigator regarding the severity of GERD-related symptoms (mild, moderate, severe) based on additional knowledge of RDQ results from Visit 1.
- RDQ score calculated as a sum of selected RDQ items at baseline and end of the acute / maintenance phase

Pharmacokinetics (Not applicable)

Pharmacodynamic (Not applicable)

Genetics (Not applicable)

Patient-reported outcomes (PROs)

- Parameters derived from the following four PRO questionnaires:
  - Reflux Disease Questionnaire,
  - GERD Impact Scale,
  - Work Productivity and Activity Impairment Questionnaire (WPAI-GERD),
  - European Health Status Questionnaire – 5 Dimensions (EQ-5D).

Health care resource use

- WPAI-GERD,
- EQ-5D,
- Number of days absent from work due to GERD symptoms during the maintenance phase,
- Actual and / or planned medically important procedures related to the ‘treatment failure’.

Safety

- Number and type of serious adverse events and those adverse events causing premature discontinuation from study (descriptive analysis).

Statistical methods

All statistical analyses related to efficacy were based on the intention-to-treat population(s), whereas the safety population(s) was the basis for the descriptive safety analysis.

To compare the efficacy of the three treatment regimens with regard to the primary outcome variable, i.e. the number of ‘treatment failures’ during the maintenance phase, a two-sided Fisher’s exact test was used for pair-wise comparisons. To adjust for multiplicity, the Bonferroni-Holm approach (k=3 tests) was used. This analysis was performed separately for each of the three baseline symptom load levels (‘mild’, ‘moderate’, ‘severe’) as judged by the primary care physician.

Approximately 7.600 subjects needed to be enrolled into the study at Visit 1 to be able to randomise about 6.400 subjects leading to approximately 6.000 evaluable subjects [mild cases: ~ 900; moderate cases: ~ 3.600; severe cases: ~ 1.500] with data available up to Visit 3.

Taking other assumptions into account, the following subject numbers were expected within each of the three levels of baseline symptom load: ~300 subjects per treatment regimen of 'mild' severity, ~ 1.200 subjects per treatment regimen of 'moderate' severity and ~ 500 subjects per treatment regimen with 'severe' symptoms.

A sample size of ~ 300 subjects [the smallest assumed number within treatment regimens during the maintenance phase] in each of Group (1) and Group (2) [the groups with the smallest assumed treatment difference in the number of '*treatment failures*'] should lead to a power of more than 80% with a significance level $\alpha = 0.017$ [the significance level of the 3rd test in the Bonferroni-Holm procedure] using a two-sided Fisher's exact test.

Subject population

The number of participating subjects was reduced from the initially planned approximately 6400 randomised subjects to 440 enrolled subjects, respectively, 372 randomised subjects due to early stop of recruitment.The reason for this change was the unanticipated low rate of recruitment of patients with mild symptoms (approximately 8% in December 2006 compared to the expected 15%) that made achievement of the initial aims of the study i.e. including 300 patients with mild symptoms unattainable.

Subject population of the acute phase

At the beginning of the acute phase the subjects were either given 20 or 40 mg esomeprazole by the investigator, based on the routine clinical judgement. Table S1 provides an overview of subject population and disposition at the beginning of the acute phase.

Table S1 Subject population and disposition (acute phase)

		Esomeprazole 20 mg		Esomeprazole 40 mg		Total	
Population							
n enrolled						440	
Demographic characteristics (ITTa: n=411)							
Sex (n (%) of subjects)	Male	132	(53.0%)	74	(45.7%)	206	(50.1%)
	Female	117	(47.0%)	88	(54.3%)	205	(49.9%)
Age (years)	Mean (SD)	40.0	(8.7)	39.9	(9.5)	39.9	(9.0)
	Range	18 to 72		18 to 73		18 to 73	
Race (n (%) of subjects)	Caucasian	246	(98.8%)	162	(100.0%)	408	(99.3%)
	Oriental	3	(1.2%)	0	(0.0%)	3	(0.7%)
Baseline characteristics							
Duration of reflux disease [years]	Mean (SD)	4.8	(6.4)	5.1	(7.1)	4.9	(6.7)
History of reflux disease	n (%)	131	(52.6%)	105	(64.8%)	236	(57.4%)
Surgery in upper gastrointestinal tract	n (%)	4	(1.6%)	1	(0.6%)	5	(1.2%)
Previous eradication therapy	n (%)	15	(6.0%)	11	(6.8%)	26	(6.3%)
Disposition (acute phase)							
n (%) of subjects in the ITTa data set who	Completed	225	(90.4%)	142	(87.7%)	367	(89.3%)
	discontinued	24	(9.6%)	20	(12.3%)	44	(10.7%)
n analysed for safety[a]		257		167		424	
n analysed for efficacy (ITTa)		249		162		411	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITTa=intention-to treat data set of acute phase; N=Number

The number of female subjects was comparable to the number of male subjects in both treatment groups. Almost all subjects were of Caucasian race. There were no relevant differences in demographic and baseline characteristics.

Disease data showed a slightly higher incidence and longer duration of gastro-oesophageal reflux disease (GERD) in the 40 mg treatment group.

Efficacy results of the acute phase

Additional knowledge of the Visit 1 RDQ results led to minor changes in clinical judgement and preferred treatment strategy. Change in clinical judgement occurred for 42/411 subjects (10.2%), whereas treatment strategy was changed in 20/411 subjects (4.9%) for the acute phase and in 23/411 subjects (5.6%) for the maintenance phase. Table S2 provides a detailed overview of changes in clinical judgement and treatment strategy for the acute and maintenance phase.

Table S2 Re-evaluation of clinical judgement and treatment strategy based on Visit 1 RDQ results

		Clinical judgement with RDQ results					
		Mild (n=47)		Moderate (n=260)		Severe (n=104)	
		n	%	n	%	n	%
Clinical judgement without RDQ results	Mild (n=45)	38	(9.2%)	6	(1.5%)	1	(0.2%)
	Moderate (n=264)	8	(1.9%)	242	(58.9%)	14	(3.4%)
	Severe (n=102)	1	(0.2%)	12	(2.9%)	89	(21.7%)

Acute phase		Treatment strategy with RDQ results			
		Esomeprazole 20 mg (n=243)		Esomeprazole 40 mg (n=168)	
		n	%	n	%
Treatment strategy without RDQ results	Esomeprazole 20 mg (n=249)	236	(57.4%)	13	(3.2%)
	Esomeprazole 40 mg (n=162)	7	(1.7%)	155	(37.7%)

Maintenance phase		Treatment strategy with RDQ results					
		Esomeprazole 20 mg daily (n=95)		Esomeprazole 20 mg on demand (n=289)		Rescue medication (n=27)	
		n	%	n	%	n	%
Treatment strategy without RDQ results	Esomeprazole 20 mg daily (n=88)	84	(20.4%)	4	(1.0%)		
	Esomeprazole 20 mg on demand (n=293)	10	(2.4%)	280	(68.1%)	3	(0.7%)
	Rescue medication (n=30)	1	(0.2%)	5	(1.2%)	24	(5.8%)

The low rate of change in clinical judgement indicates that RDQ results were well associated with clinical judgment. This applied to the total score as well as each item of the RDQ score. However, the ranges of RDQ overlapped extensively between the different clinical categories. Table S4 shows the RDQ scores associated with the clinical judgement at Visit 1. As there was a good association the need for re-evaluation of the GERD severity was meagre. Table S3 shows the RDQ scores associated with the clinical judgement at Visit 1.

Table S3 Relation of clinical judgement to RDQ score at Visit 1

RDQ score at Visit 1		Clinical judgment at Visit 1 without RDQ results mild (n=45)	moderate (n=264)	severe (n=102)
Acid regurgitation	Mean (SD)	10.6 (5.0)	13.4 (5.7)	16.6 (5.9)
	Range	4 to 24	4 to 24	4 to 24
Heartburn	Mean (SD)	10.1 (5.1)	12.5 (5.8)	15.7 (6.4)
	Range	4 to 23	4 to 24	4 to 24
Dyspepsia	Mean (SD)	10.0 (4.7)	13.1 (5.2)	16.4 (5.9)
	Range	4 to 22	4 to 24	4 to 24
GERD	Mean (SD)	20.7 (8.6)	25.9 (9.1)	32.3 (10.8)
	Range	8 to 47	8 to 48	8 to 48
total score	Mean (SD)	30.7 (11.8)	39.0 (11.9)	48.7 (14.6)
	Range	12 to 65	12 to 72	12 to 72
total score Esomeprazole 20 mg	n (%)	44 (97.8%)	189 (71.6%)	16 (15.7%)
	Mean (SD)	30.7 (11.9)	40.2 (12.2)	45.1 (15.5)
total score Esomeprazole 40 mg	n (%)	1 (0.2%)	75 (28.4%)	86 (84.3%)
	Mean (SD)	33.0	35.9 (10.6)	49.4 (14.4%)

5/249 (1.9%) and 2/162 (1.2%) subjects in the 20 and 40 mg group, respectively, took ASA as concomitant medication. In most cases the indication was prophylaxis in the context of cardio- and cerebrovascular diseases.

Safety results of the acute phase

AEs occurring prior to Visit 2 (acute phase) and after Visit 2 (maintenance phase) were evaluated separately. Table S4 and Table S5 show the numbers (%) of subjects with AEs during the acute phase by categories and by system organ class.

Table S4 Number of subjects who had an AE in any category during the acute phase

Category of AE	Number of subjects who had an AE in each category[a]	
	Esomeprazole 20mg (n=257)	Esomeprazole 40mg (n=167)
Serious adverse event	1	1
Serious adverse event leading to death	---	---
Serious adverse event not leading to death	1	1
Discontinuation of study treatment due to an AE	2	3
Other significant AE	---	---
	Total number of AEs	
Any AE	8	6
Serious adverse event	4	1
Other significant AE	---	---

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

The number of subjects with AEs ordered by system organ class are summarised below.

Table S5 Number of subjects per treatment group who had at least one AE in any SOC, sorted by decreasing order of frequency

	Esomeprazole 20mg (n=257)	Esomeprazole 40mg (n=167)
	n	n
Subjects with AEs	4	6
System organ class		
Gastrointestinal disorders	2	
Infections and infestations		2
Skin and subcutaneous tissue disorders	1	1
Injury, poisoning and procedural complications	1	
Cardiac disorders		1
Musculoskeletal and connective tissue disorders		1
Nervous system disorders		1
General disorders and administration site conditions	1	

More than one entry per subject possible.

Overall, the number of subjects with AEs during the acute phase was low. Two SAEs (traffic accident, tachyarrhythmia) were reported that were not drug related. The number of subjects experiencing AEs in the various system organ classes was too low to exhibit any distinct pattern (i.e. no preferred term occurred more than once). No subject deaths were reported during the course of the acute phase of the study.

Subject population of the maintenance phase

After the acute phase, all subjects with treatment success were randomised to maintenance therapy with either 20 mg esomeprazole daily, 20 mg esomeprazole on demand or rescue medication with antacids (Gelusil Lac®).

Table S6 provides an overview of subject population entering the maintenance phase.

Table S6 Subject population and disposition (maintenance phase)

		Esomeprazole 20 mg daily		Esomeprazole20 mg on demand		No Esomeprazole	
Population							
n analysed (ITTm)		109		133		124	
Demographic characteristics							
Sex (n (%) of subjects)	Male	53	(48.6%)	66	(49.6%)	69	(55.6%)
	Female	56	(51.4%)	67	(50.4%)	55	(44.4%)
Age (years)	Mean (SD)	39.8	(9.8%)	38.8	(9.7%)	40.4	(8.4%)
	Range	18 to 72		18 to 73		18 to 61	
Race (n (%) of subjects)	Caucasian	108	(99.1%)	132	(99.2%)	122	(98.4%)
	Oriental	1	(0.9%)	1	(0.8%)	2	(1.6%)
Baseline characteristics							
Duration of reflux disease [years]	Mean (SD)	6.2	(7.7)	4.3	(5.9)	4.6	(6.1)
History of reflux disease	n (%)	54	(49.5%)	70	(52.6%)	76	(61.3%)
Surgery in upper gastrointestinal tract	n (%)	1	(0.9%)			2	(1.6%)
Previous eradication therapy	n (%)	5	(4.6%)	2	(1.5%)	6	(4.8%)
Disposition (maintenance phase)							
n (%) of subjects in the ITTm data set who	completed	106	(97.2%)	131	(98.5%)	117	(94.4%)
	discontinued	3	(2.8%)	2	(1.5%)	7	(5.6%)
n analysed for safety[a]		111		135		126	
n analysed for efficacy (ITTm)		109		133		124	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITTm=intention-to treat data set of maintenance phase; N=Number

At Visit 2, the efficacy parameters based on the RDQ, GIS, WPAI and EQ-5D questionnaires at baseline of the maintenance phase were well balanced across all treatment groups.

Efficacy results of the maintenance phase

Primary efficacy variable: Treatment failures were substantially more frequent in the group with rescue medication compared to the other groups receiving esomeprazole. Treatment failures were distributed in the following way among the three treatment groups of the maintenance phase: Esomeprazole 20 mg daily – 8/109 subjects (7.3%); Esomeprazole 20 mg on demand – 5/133 subjects (3.8%); rescue medication – 44/124 subjects (35.5%) .

On average, treatment failures were more frequent in subjects with initial clinical judgement "severe". This concerned especially treatment with rescue medication. Table S7 summarises the incidence of treatment failures during the maintenance phase by clinical judgement at baseline and compares the rate of treatment failures using the two-sided Fisher's exact test. The Bonferroni-Holm significance level correction was applied. As a consequence the p-value of 0.0391 in Table S7 regarding subjects with mild baseline symptoms is not significant. A possible explanation could be

the low rate of subjects with clinical judgement "mild" (6.4%) in the esomeprazole 20 mg daily group compared to the on demand (12.8%) and no esomeprazole group (12.9%).

Table S7 Treatment failure during maintenance phase by clinical judgement at baseline

	Esomeprazole 20 mg daily (n=109)		Esomeprazole 20 mg on demand (n=133)		No Esomeprazole (n=124)	
	n/N	**%**	**n/N**	**%**	**n/N**	**%**
Mild (n =40)	0/7	(0.0%)	1/17	(5.9%)	6/16	(37.5%)
Moderate (n = 239)	5/76	(6.6%)	2/84	(2.4%)	25/79	(31.6%)
Severe (n = 87)	3/26	(11.5%)	2/32	(6.3%)	13/29	(44.8%)
Group comparison using two-sided Fisher's exact test						
Mild	**vs.**	**p-value**	**vs.**	**p-value**	**vs.**	**p-value**
Esomeprazole 20 mg daily		-		1.0000		0.1243
Esomeprazole 20 mg on demand		1.0000		-		0.0391
Moderate	**vs.**	**p-value**	**vs.**	**p-value**	**vs.**	**p-value**
Esomeprazole 20 mg daily		-		0.2582		0.0001
Esomeprazole 20 mg on demand		0.2582		-		<0.0001
Severe	**vs.**	**p-value**	**vs.**	**p-value**	**vs.**	**p-value**
Esomeprazole 20 mg daily		-		0.6482		0.0083
Esomeprazole 20 mg on demand		0.6482		-		0.0007

Compared to Visit 2, the three dimension scores of the GERD Impact Scale (GIS) showed minor changes at the end of the maintenance phase at Visit 3. The most noticeable changes concerned the scores "Upper GI symptoms" and "Other acid related GI symptoms" in subjects with clinical judgement "severe" in the group with rescue medication. In these subjects, the score of this item deteriorated by approximately 7.0 to 8.5%, whereas all other changes were about 5% or less.

Symptom load in terms of dimension scores derived from the GERD impact scale (GIS) increased in the treatment group with rescue medication and remained constant in both esomeprazole treatment groups (Table S8).

Table S8 Change in dimension scores derived from the GERD Impact Scale between Visit 2 and Visit 3: Impact of treatment strategy on symptom load assessed by GIS

Dimension		Esomeprazole 20 mg daily (n=109)	Esomeprazole 20 mg on demand (n=133)	No Esomeprazole (n=124)
Upper GI symptom	Mean (SD)	0.1 (0.5)	0.0 (0.6)	-0.2 (0.8)
	Range	-2.7 to 1.0	-2.3 to 3.0	-3.0 to 3.0
Other acid related GI symptoms	Mean (SD)	0.0 (0.5)	-0.0 (0.6)	-0.1 (0.8)
	Range	-2.5 to 2.5	-3.0 to 2.0	-3.0 to 3.0
Impact of symptoms on life	Mean (SD)	0.0 (0.4)	0.0 (0.5)	-0.1 (0.7)
	Range	-3.0 to 1.5	-3.0 to 3.0	-3.0 to 3.0

There was an insufficient number of cases to conclude on the additional impact of ASA on efficacy. 3/109 (2.8%), 2/133 (1.5%) and 1/124 (0.8%) subjects in the treatment groups with 20 mg esomeprazole daily, esomeprazole on demand and antacid rescue medication took ASA as concomitant medication during the maintenance phase. In most cases the indication was prophylaxis in the context of cardio- and cerebrovascular diseases.

At each visit, planned or performed medically important procedures related to a ‘treatment failure’ were recorded. Regarding the whole maintenance phase, the rate of subjects with additional medical procedures tended to be slightly higher in the group with 20 mg esomeprazole daily compared to the other groups, despite a markedly higher rate of treatment failures in the group with rescue medication. Intake of follow-up medication indicates that subjects with treatment failures in the rescue medication group switched immediately back to esomeprazole as the most frequent measure (see also discussion in Section 9.1). Table S9 shows the number of subjects with additional medically important procedures.

Table S9 Measures and examinations performed in relation to 'treatment failure'

Measures and examinations performed until end of study	Esomeprazole 20 mg daily (n=109)		Esomeprazole 20 mg on demand (n=133)		No Esomeprazole (n=124)	
	n	%	n	%	n	%
Visit at a family doctor	33	(30.3%)	38	(28.6%)	33	(26.6%)
Visit at an other doctor	16	(14.7%)	10	(7.5%)	13	(10.5%)
Endoscopy	4	(3.7%)	1	(0.8%)	3	(2.4%)
Biopsy	3	(2.8%)	1	(0.8%)	1	(0.8%)
HP-Test	3	(2.8%)	2	(1.5%)	2	(1.6%)
X-Ray examination	5	(4.6%)	4	(3.0%)	4	(3.2%)

Group differences in work productivity during the maintenance phase were minor. However, most WPAI items indicated the worst work productivity was in the treatment group with rescue medication. No systematic relationship between the change in WPAI score and the severity at baseline emerged (Table S10).

Table S10 WPAI change between begin and end of the maintenance phase by symptom severity at baseline*

		Mild*	Moderate*	Severe*	Total*
Number of hours absent from work	Mean (SD)	2.4 (8.3)	0.7 (12.5)	-1.8 (10.8)	0.5 (11.8)
	Range	-8.0 to 38.5	-40.0 to 42.0	-39.0 to 36.0	-40.0 to 42.0
Reduced productivity while at work (percentage points)	Mean (SD)	0.3 (10.2)	-0.9 (12.1)	5.2 (14.4)	0.5 (12.6)
	Range	-20.0 to 20.0	-60.0 to 30	-20.0 to 50.0	-60.0 to 50.0
Reduced productivity while carrying out daily activities (percentage points)	Mean (SD)	-2.0 (11.1)	-0.9 (17.7)	3.4 (16.3)	0.0 (16.8)
	Range	-30.0 to 20.0	-80.0 to 100.0	-40.0 to 60.0	-80.0 to 100.0
Number of work hours lost due to reduced productivity	Mean (SD)	0.4 (4.5)	-0.4 (4.6)	1.9 (5.3)	0.1 (4.7)
	Range	-12.0 to 8.0	-23.5 to 13.4	-8.4 to 16.2	-23.5 to 16.2
Work productivity score**	Mean (SD)	7.6 (20.9)	0.5 (30.6)	-0.5 (33.7)	1.3 (30.1)
	Range	-20.0 to 79.4	-100.0 to 100.0	-100.0 to 93.1	-100.0 to 100.0

* severity level as clinically judged by the PCP: Mild (n=45), Moderate (n=264),Severe (n=102), Total (n=411) at Visit 1.
**WPS = [(Q2 + Q5/10 * Q4) / (Q2 + Q4)] * 100 (see Table 11.2 (ITTm) – 5)

Table S11 compares the development of working productivity during the maintenance phase in subjects with treatment success to those with failure. Taking into account baseline values at Visit 2 as covariate, ANOVA analysis shows significantly better development of working productivity in the subgroup with treatment success compared to that with treatment failures for all analysed variables.

Table S11 WPAI and WPAI change (Visit 2-Visit 3) during the maintenance phase by treatment success

		treatment success**	treatment failure	ANOVA p-value/*
		Mean (SD)	Mean (SD)	
Number of hours absent from work	Visit 3	2.8 (9.0)	3.8 (11.0)	0.433
	Change	0.4 (11.6)	1.0 (12.8)	<0.0001*
Reduced productivity while at work (percentage points)	Visit 3	4.5 (10.5)	10.5 (13.9)	<0.0001
	Change	-1.0 (11.9)	8.9 (13.3)	<0.0001*
Reduced productivity while carrying out daily activities (percentage points)	Visit 3	4.9 (12.0)	20.2 (23.9)	<0.0001
	Change	-1.9 (14.4)	11.8 (24.3)	<0.0001*
Number of work hours lost due to reduced productivity	Visit 3	1.6 (4.1)	4.1 (6.2)	<0.0001
	Change	-0.5 (4.4)	3.7 (5.4)	<0.0001*
Work productivity score***	Visit 3	11.6 (23.3)	20.7 (27.6)	n.d.
	Change	-0.8 (29.7)	14.1 (29.8)	n.d.

* One-way ANOVA for differences in change between the groups between Visit 2 and Visit 3 without/ with baseline value at Visit 2 as covariate marked by *.

** treatment failure/success as documented in the CRF, n.d. not determined

*** WPS = [(Q2 + Q5/10 * Q4) / (Q2 + Q4)] * 100 (see Table 11.2 (ITTm) – 5)

Safety results of the maintenance phase

Table S12 and Table S13 show the number (%) of subjects with AEs during the maintenance phase by categories and by system organ class.

Table S12 Number of subjects who had at least 1 AE in any category, and total numbers of AEs during the maintenance phase

Category of AE	Number of subjects who had an AE in each category[a]		
	Esomeprazole 20 mg daily (n=111)	Esomeprazole 20 mg on demand (n=135)	No Esomeprazole (n=126)
Any AE	5	4	2
Serious adverse event	2	1	0
Serious adverse event leading to death	---	---	---
Serious adverse event not leading to death	2	1	0
Discontinuation of study treatment due to an AE	0	0	0
Other significant AE	---	---	---
	Total number of AEs		
Any AE	7	4	2
Serious adverse event	4	1	0
Other significant AE	---	---	---

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Overall, the number of subjects with AEs was low and no distinct pattern was seen. No deaths were reported and there were no discontinuations of study treatment due to AEs in any group. SAEs were reported by 2 subjects in esomeprazole 20 mg daily group and by 1 subject in the esomeprazole 20 mg on demand group. None of the SAEs was considered drug related.

Table S13 Number (%) of subjects per treatment group with AEs in system organ class (SOC), sorted by decreasing order of frequency

	Esomeprazole 20 mg daily (n=111) n (%)	Esomeprazole 20 mg on demand (n=135) n (%)	No Esomeprazole (n=126) n (%)
Subjects with AEs	5 (4.5%)	4 (3.0%)	2 (1.6%)
System organ class			
Gastrointestinal disorders	2 (1.8%)		1 (0.8%)
Infections and infestations	1 (0.9%)		1 (0.8%)
Injury, poisoning and procedural complications	1 (0.9%)		
Musculoskeletal and connective tissue disorders		1 (0.7%)	
Psychiatric disorders		1 (0.7%)	
Reproductive system and breast disorders	1 (0.9%)		
Respiratory, thoracic and mediastinal disorders		1 (0.7%)	
Vascular disorders		1 (0.7%)	

More than one entry per subject possible.