AstraZeneca

Drug product	NEXIUM® 20 mg and 40 mg capsules	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Remission Rates for Once Daily Treatment with Esomeprazole 20 mg and Lansoprazole 15 mg for 6 months in Patients whose EE Has Been Healed

Study center(s)

This study was conducted at 143 centers in the US.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	18 December 2002	Therapeutic use (IV)
Last patient completed	5 January 2004	

Objectives

Primary objective: To compare remission rates through 6 months of treatment with esomeprazole 20 mg qd (E20) and lansoprazole 15 mg qd (L15), after initial healing of erosive esophagitis (EE). Remission was defined as erosive esophagitis LA Grade A-D not detected and the patient did not discontinue due to reflux symptoms.

Secondary objectives:

1. To compare endoscopic remission rates through 6 months of treatment with E20 and L15, after initial healing of EE

2. To assess symptoms in the 2 treatment groups after 1, 3, and 6 months

3. To assess the safety and tolerability of up to 6 months of treatment with E20 and L15 after initial healing of EE.

Study design

This was a multicenter, 2-part, Phase IV study, which comprised an open-label healing phase (H_{325}); and a randomized, comparative, double-blind, double-dummy, parallel-group, maintenance phase (M_{325}). Enrollment into M_{325} was from 2 sources: H_{325} and a separate EE healing study (Study 322; H_{322}) being conducted concurrently at the same study sites. All patients enrolled into H_{322} and H_{325} underwent the same screening procedures and were subject to the same entry criteria, with 1 exception—patients with LA Grade A or B erosive esophagitis were eligible only for H_{325}, while patients with LA Grade C or D were eligible only for H_{322}.

Healing phase/study:

In H_{325}, patients received esomeprazole 40 mg qd (E40) in an open-label fashion, for 4 to 8 weeks. H_{322} was a randomized, double-blind, double-dummy, parallel-group study in which patients received either E40 or lansoprazole 30 mg qd (L30) for 4 to 8 weeks. Patients in either H_{325} or H_{322} whose EE was healed at Week 4, and who reported no heartburn or acid regurgitation during the 7 days prior to the Week 4 visit, were eligible to be enrolled into M_{325}. H_{325} patients with persistent EE or symptoms at Week 4 were to be assessed again at Week 8, but were to have a repeat esophagogastroduodenoscopy (EGD) only if they were symptom-free; they were then either enrolled into M_{325} (if healed) or discontinued and treated according to routine clinical practice. H_{322} patients with persistent EE at Week 4 were to be assessed again at Week 8, and were eligible to be enrolled into M_{325} if healed and symptom-free. H_{322} patients who were healed at Week 4 but had persistent symptoms were discontinued from the study and were ineligible for M_{325}.

Maintenance phase:

There was to be no interruption of treatment as patients were re-randomized to maintenance therapy, which consisted of either E20 or L15 for up to 6 months. They were to report to the study site after 1, 3, and 6 months of maintenance treatment for symptom assessment; and were to undergo endoscopy at the 3-month and 6-month visits. Patients were instructed to contact the study center in the case of moderate or severe heartburn and/or acid regurgitation persisting over 3 consecutive days, to schedule an additional endoscopy. If EE Grade A-D was detected during any of the planned or additional endoscopies, and/or the patient discontinued due to reflux symptoms, this was classified as ‘relapse’ and the patient’s participation in the study was to be concluded.

Target patient population and sample size

Male and female patients between 18 and 75 years of age with heartburn at least 2 days per week and mild EE (LA Grade A or B) were eligible for H_{325}. Those patients whose EE was healed in H_{325} or in H_{322}, and who reported no heartburn or acid regurgitation during the previous week, were eligible for M_{325}.

It was estimated that a sample size of 495 patients per treatment group (990 patients in total) in M_{325} would be needed to detect a 10% difference in remission rates (assuming remission rates of 85% for E20 and 75% for L15) with a 5% significance level and 95% power, allowing for a dropout rate of up to 15%. The M_{325} study population was to comprise approximately 750 patients from H_{325} (pre-healing LA Grade A or B) and approximately 250 patients from H_{322} (pre-healing LA Grade C or D). Therefore, enrollment into H_{325} was to stop when approximately 750 patients had been enrolled into M_{325} from H_{325}.

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

Healing Phase (H_{325}):

E40: Esomeprazole magnesium 40 mg once daily (40 mg oral capsule, batch number H1222-04-01-10)

GELUSIL® tablets were provided as a rescue medication for relief of GERD symptoms.

Maintenance Phase (M_{325}):

E20: Esomeprazole magnesium 20 mg once daily (20 mg oral capsule, batch numbers H1189-04-01-06 and H1189-04-01-08)
& Placebo (to match the L15 mg capsule) once daily (batch number H1480-01-01-01)

L15: Lansoprazole 15 mg once daily (15 mg oral capsule, batch number H1460-02-01-03)
& Placebo (to match the E20 mg capsule) once daily (batch number H0459-06-03-10)

Duration of treatment

E40 for 4 to 8 weeks in H_{325}; E20 or L15 for up to 6 months in M_{325}.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Remission of EE and of symptoms of heartburn and acid regurgitation during M_{325}. 'Remission' was defined as EE (LA Grade A-D) not detected and the patient did not discontinue due to reflux symptoms.
- Secondary variables:
  - Endoscopic remission rate during M_{325}. 'Endoscopic remission' was defined as EE (LA Grade A-D) not detected.

- Symptomatic remission rate during M_{325}. 'Symptomatic remission' meant that the patient did not discontinue from M_{325} due to heartburn or acid regurgitation.

- Investigator-rated severity of GERD-related symptoms (ie, heartburn, acid regurgitation, dysphagia, and epigastric pain) at Months 1, 3, and 6 of M_{325}.

Safety

Standard safety assessments included adverse event (AE) reports, clinical laboratory tests, physical examinations, and vital signs.

Statistical methods

The efficacy endpoints were analyzed using an 'intention-to-treat' (ITT) population, which included all randomized patients who had no EE, heartburn, or acid regurgitation at randomization into M_{325}, and who took at least 1 dose of E20 or L15. The primary efficacy endpoint was also analyzed using a 'per-protocol' (PP) patient population, which was a subset of the ITT population, created by excluding patients, in a blinded fashion, according to pre-defined guidelines for non-evaluability. The H_{325} safety population comprised all patients who took at least 1 dose of E40. The M_{325} safety population comprised all randomized patients who took at least 1 dose of E20 or L15.

The primary efficacy analysis was made using a log-rank test to compare E20 and L15 with respect to remission rates through Month 6, where the remission rate was estimated by the Kaplan-Meier method. In addition, the observed remission rate at Month 3 and the cumulative remission rate at Month 6 were compared using a Cochran-Mantel-Haenszel (CMH) test. The treatment groups were also compared with respect to estimated endoscopic remission rates through Month 6, using a log-rank test.

The percentage of patients who were symptom-free at Months 1, 3, and 6, as evaluated by the investigator, was analyzed using a CMH test for each symptom separately (heartburn, acid regurgitation, dysphagia, and epigastric pain), stratified by the baseline status of that symptom.

All demographic and safety parameters were summarized descriptively. No formal comparisons were made.

Patient population

Of the 1026 M_{325} patients, 759 (74.0%) were from H_{325} and 267 (26.0%) were from H_{322}. As shown in Table S1 below, the M_{325} treatment groups were generally well balanced in terms of baseline characteristics, dropouts, and eligibility for the ITT and PP populations. The most common reason for discontinuation was lack of therapeutic response (7.4% for E20 and 13.2% for L15), which was defined as endoscopic relapse (4.9% and 10.7%, respectively) and/or symptomatic relapse (5.5% and 8.0%, respectively).

Table S1 Patient population and disposition

	Study phase:	Healing (H_{325})	Maintenance (M_{325})		
	Treatment:	E40	E20	L15	Total M_{325}
Patient disposition					
N enrolled (N planned)		1171 (1000)	512 (495)	514 (495)	1026 (990)
Completed phase: n (%)		759 (64.8%)	400 (78.1%)	380 (73.9%)	780 (76.0%)
N analyzed for safety[a]		1170 (99.9%)	510 (99.6%)	514 (100%)	1024 (99.8%)
N analyzed for efficacy (ITT[b])		NA	501 (97.9%)	500 (97.3%)	1001 (97.6%)
N analyzed for efficacy (PP[c])		NA	445 (86.9%)	448 (87.2%)	893 (87.0%)
Demographic characteristics (H_{325} safety population/M_{325} ITT population)					
Gender: n (%)	Male	612 (52.3%)	297 (59.3%)	293 (58.6%)	590 (58.9%)
	Female	558 (47.7%)	204 (40.7%)	207 (41.4%)	411 (41.1%)
Age in years:	Mean (SD)	46.1 (12.8)	47.5 (12.3)	47.9 (13.3)	47.7 (12.8)
	Range	18 - 76	18 - 75	18 - 78	18 - 78
Race: n (%)	Caucasian	858 (73.3%)	391 (78.0%)	386 (77.2%)	777 (77.6%)
	Black	94 (8.0%)	28 (5.6%)	32 (6.4%)	60 (6.0%)
	Oriental	9 (0.8%)	1 (0.2%)	6 (1.2%)	7 (0.7%)
	Other	209 (17.9%)	81 (16.2%)	76 (15.2%)	157 (15.7%)
Baseline characteristics (H_{325} safety population/M_{325} ITT population)					
Pre-healing LA Grade	A	613 (52.4%)	178 (35.5%)	194 (38.8%)	372 (37.2%)
	B	557 (47.6%)	202 (40.3%)	175 (35.0%)	377 (37.7%)
	C	0	98 (19.6%)	109 (21.8%)	207 (20.7%)
	D	0	23 (4.6%)	22 (4.4%)	45 (4.5%)
GERD history: n (%)	<1 year	115 (9.8%)	48 (9.6%)	36 (7.2%)	84 (8.4%)
	1-5 years	584 (49.9%)	241 (48.1%)	221 (44.2%)	462 (46.2%)
	>5 years	471 (40.3%)	212 (42.3%)	243 (48.6%)	455 (45.5%)
EE history: n (%)	Yes	322 (27.5%)	153 (30.5%)	148 (29.6%)	301 (30.1%)
	No	848 (72.5%)	348 (69.5%)	352 (70.4%)	700 (69.9%)
H. pylori serology: n (%)	Negative	1017 (86.9%)	446 (89.0%)	442 (88.4%)	888 (88.7%)
	Positive	147 (12.6%)	53 (10.6%)	57 (11.4%)	110 (11.0%)

[a] The H_{325} and M_{325} safety populations comprised all patients who took at least 1 dose of study medication in H_{325} or M_{325}, respectively.

[b] Number of M_{325} patients who had no EE, heartburn, or acid regurgitation at randomization, and who took at least 1 dose of E20 or L15.

[c] Number of M_{325} patients who were considered to have adequately met certain pre-specified criteria for protocol compliance.

H_{325} Healing phase of Study 325; M_{325} Maintenance phase of Study 325; E40 esomeprazole 40 mg qd; E20 esomeprazole 20 mg qd; L15 lansoprazole 15 mg qd; ITT Intention-to-treat population; PP Per-protocol population; NA Not applicable

The majority of the patients were male, Caucasian, less than 65 years old, and *H. pylori* negative. Prior to the healing phase/study, most patients had LA Grade A or B esophagitis, moderate to severe heartburn and acid regurgitation, no or mild dysphagia, and no or mild epigastric pain. The study population was therefore representative of the intended target patient population.

Efficacy results

As shown in Table S2 below, the E20 treatment group was associated with a significantly higher estimated remission rate through Month 6 than the L15 treatment group. The data for the secondary outcome measures provided further evidence of the relative efficacy of E20 compared to L15 in maintaining EE healing.

Table S2 Summary of efficacy results (ITT population)

	E20		L15		p-value
Outcome variable	**N**	**%**	**N**	**%**	**(E20 vs L15)**
Primary variable					
Estimated endoscopic and symptomatic remission rate through Month 6[a]	501	84.8%	500	75.9%	0.0007
Secondary variables					
Estimated endoscopic remission rate through Month 6[a]	501	86.9%	500	77.8%	0.0003
Observed cumulative endoscopic and symptomatic remission rate through Month 6[b]	501	86.2%	500	77.6%	<0.0001
Observed endoscopic relapse rate through Month 6	501	11.6%	500	20.0%	NT
Observed symptomatic relapse rate through Month 6	501	5.6%	500	7.6%	NT
Percentage of patients with no GERD-related symptoms (per investigator) at Month 6:[c]					
Heartburn	462	82.9%	466	79.2%	0.1490
Acid regurgitation	462	86.8%	466	85.8%	0.6708
Dysphagia	462	97.6%	466	96.4%	0.2685
Epigastric pain	462	91.6%	466	89.5%	0.2634

[a] Kaplan-Meier estimate of remission; p-value is from a log-rank test.
[b] p-value is from a Cochran-Mantel-Haenszel (CMH) test.
[c] p-values are from a CMH test, stratified by the status (present/absent) of the symptom at randomization.
E20 esomeprazole 20 mg qd; L15 lansoprazole 15 mg qd; ITT Intention-to-treat; NT Not statistically tested

Safety results

All 3 treatments were well tolerated. E20 and L15 were generally comparable with respect to the type, frequency, and severity of AEs (see Table S3 and Table S4). Of the 15 serious adverse events (SAEs) for E20 and L15 groups in the maintenance phase M_{325}, 8 in the E20 group and 5 in the L15 group were treatment-emergent. None of these SAEs were considered by the investigators to be attributable to study medication. The incidence of attributable AEs was also higher in the E20 group, but a review of all AEs did not raise any safety concerns. There were no deaths.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety populations)

Category of Adverse Event	E40 (N=1170)	E20 (N=510)	L15 (N=514)
	Number (%) of patients who had an adverse event in each category[a]		
Any adverse events	327 (27.9%)	253 (49.6%)	234 (45.5%)
Serious adverse events			
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	8 (0.7%)	10 (2.0%)	5 (1.0%)
Treatment-emergent serious adverse events[c]	8 (0.7%)	8 (1.6%)	5 (1.0%)
Discontinuations of study treatment due to adverse events (DAEs)	33 (2.8%)	16 (3.1%)	20 (3.9%)
Attributable adverse events	63 (5.4%)	41 (8.0%)	30 (5.8%)
	Total number of adverse events[b]		
Adverse events	584	529	524
Serious adverse events	17	12	6
DAEs	57	30	25
Attributable adverse events	94	58	45

[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] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

[c] Treatment-emergent SAEs were considered to be those SAEs occurring either during H_{325} (E40) or during M_{325} (E20 and L15). Patients who had an SAE in H_{325} that continued in M_{325} were not counted in M_{325}.

E40 esomeprazole 40 mg qd; E20 esomeprazole 20 mg qd; L15 lansoprazole 15 mg qd

Table S4 Number (%) of patients on each of the 3 study treatments with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized over the two M_{325} treatment groups (safety populations)

Adverse event (preferred term)	Number (%) of patients who had an adverse event		
	E40 (N=1170)	E20 (N=510)	L15 (N=514)
Diarrhea	29 (2.5%)	17 (3.3%)	26 (5.1%)
Gastritis	14 (1.2%)	22 (4.3%)	18 (3.5%)
Nausea	21 (1.8%)	10 (2.0%)	17 (3.3%)
Upper respiratory tract infection	11 (0.9%)	12 (2.4%)	13 (2.5%)
Headache	41 (3.5%)	16 (3.1%)	9 (1.8%)
Gastritis erosive	7 (0.6%)	14 (2.7%)	10 (1.9%)
GI Tract mucosal discoloration	15 (1.3%)	14 (2.7%)	10 (1.9%)
ALT increased	7 (0.6%)	10 (2.0%)	14 (2.7%)
Barrett's esophagus	9 (0.8%)	11 (2.2%)	11 (2.1%)
Sinusitis	5 (0.4%)	7 (1.4%)	14 (2.7%)
Flatulence	16 (1.4%)	13 (2.5%)	6 (1.2%)
Abdominal distension	14 (1.2%)	7 (1.4%)	11 (2.1%)
Abdominal pain	15 (1.3%)	6 (1.2%)	11 (2.1%)
Abdominal pain upper	9 (0.8%)	11 (2.2%)	5 (1.0%)

a Events with a total frequency of ≥2% for any treatment are included in this table.

E40 esomeprazole 40 mg qd; E20 esomeprazole 20 mg qd; GI gastrointestinal; L15 lansoprazole 15 mg qd; M_{325} Maintenance phase of Study 325.

With regard to the other safety variables, none of the clinical laboratory test results or vital signs data raised any safety concerns.

Date of the report

21 June 2004