2.0 SYNOPSIS

Name of Company: AstraZeneca, LP (at the time study was conducted the sponsor's name was Astra Merck Inc.)	**Individual Study Table Referring to Item of the Submission N/A** **Volume: N/A** **Page: N/A**	**(For National Authority Use only) N/A**
Name of Finished Product: PRILOSEC®		
Name of Active Ingredient: omeprazole		

Title of Study: A multicenter, double-blind study to evaluate the safety and therapeutic efficacy of omeprazole 20 mg a.m. or 10 mg a.m. as compared to placebo during 12-24 months of maintenance treatment of patients with duodenal ulcer healed following 4 weeks of omeprazole 20 mg a.m.

Study Center(s): 70 investigator sites initiated.

Publication (reference): N/A

Studied Period (years): (date of first enrollment) 5/90 (date of last completed) 4/94	**Phase of development: III**

Objectives:

1. To investigate the efficacy of two oral omeprazole dosing regimens vs. placebo in the maintenance treatment of patients with active duodenal ulcer(s) healed with omeprazole 20 mg a.m.
2. To evaluate the long-term safety of continued omeprazole therapy in patients with duodenal ulcer.

Methodology: This randomized, double-blind, placebo-controlled study, conducted in three phases, was designed to investigate the safety and efficacy of 10 mg and 20 mg of omeprazole a.m. in the maintenance treatment of patients with active duodenal ulcer(s) healed with omeprazole 20 mg a.m. Eligible patients with at least one endoscopically verified active duodenal ulcer were enrolled in a one-month, open-label phase and received omeprazole 20 mg a.m. Seven hundred fifty patients with healed duodenal ulcers were to be randomized to receive either omeprazole 10 mg a.m., omeprazole 20 mg a.m., or placebo for up to two years in a double-blind fashion. The patients were stratified according to smoking status. The first year was designated maintenance phase 1 and the second year maintenance phase 2.

At weeks 6, 26, 52, and 104 of maintenance treatment, or when patients experienced three or more consecutive days of moderate to severe ulcer pain, the status of the duodenal ulcer was assessed endoscopically to determine if the ulcer had recurred. If no ulcer were found, the patient was able to remain in the study. Diary cards and Physicians Global assessment of ulcer pain relief were also collected. Adverse events were recorded throughout the study. Standard laboratory safety tests and gastric fundic biopsies for endocrine cell assessment were performed at several timepoints.

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Number of Patients (Planned and Analyzed):

Phase	Total Planned	Total Entered	Completed[1]	Efficacy: Duodenal Ulcer Status[2]	Safety: Adverse Events
Acute					
Omep. 20 mg a.m. Open-label	1000	1170	910		312
Maintenance Phase 1	750	913			
Omep. 10 mg a.m.	300	372	209	351	252
Omep. 20 mg a.m.	300	362	247	336	231
Placebo	150	179	50	165	103
Maintenance Phase 2	450-550	418			
Omep. 10 mg a.m.		172	140		113
Omep. 20 mg a.m.		206	171		141
Placebo		40	28		29

[1] Includes patients who were found to have ulcer recurrence at the Week 52 or 104 endoscopy.
[2] Number of patients regardless of maintenance phase.

Diagnosis and Main Criteria for Inclusion:
Acute phase: Males and females (either postmenopausal or on contraception) 18 years or older with endoscopic documentation of at least one duodenal or pyloric channel ulcers, 0.3 to 2.5 cm in diameter, within 7 days of start of study medication.
Maintenance phase (Weeks 1-52): Healed duodenal ulcer(s) during the acute phase of the study no more than 5 days prior to the entry into the maintenance phase. Adequate relief of ulcer pain. No severe or serious clinical or laboratory adverse events felt to be causally related to omeprazole during the acute phase of the study.
Maintenance phase (Weeks 53-104): No recurrence of duodenal ulcer(s) during the first 52-week maintenance phase.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
omeprazole 20 mg capsules, 10 mg capsules and matching placebo:
Lot numbers: C-V732, C-W554,C-W473, C-W894, C-W954, C-X456.
GELUSIL®: Lot numbers: C-V732, C-V732A, C-W474, C-X040.

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Duration of Treatment:
Phase 1 Acute healing phase, 4 weeks
Phase 2 Maintenance phase 1, weeks 1-52
Phase 3 Maintenance phase 2, weeks 53-104

Reference Therapy, Dose and Mode of Administration, Batch or Lot Number: N/A

Criteria for Evaluation:
Efficacy:
The analysis of the end-of-therapy ulcer status was performed using an intent-to-treat (ITT) patient cohort. This cohort was defined as all randomized patients who had at least one dose of their randomized study medication and had both a baseline and at least one during-treatment assessment of their ulcer status via an endoscopy. An ITT patient was included in the analysis of the final global ratings if he or she had at least one during-treatment assessment.

Safety:
Adverse Events:
Randomized patients who received at least one dose of their randomized study medication were included in the assessment of adverse events.
ECL-Cell and Fasting Serum Gastrin Evaluation:
The 335 patients who completed treatment for two years and who had a biopsy taken are reported.

Statistical Methods:
The time patients remained in duodenal ulcer remission was analyzed using the Cox proportional hazard model to test for significant differences between the onset-of-recurrence curves of the treatment groups. Baseline smoking stratum was included in the model as a stratification variable, and a test for smoking stratum by treatment group interaction was performed. The Kaplan-Meier procedure was used to estimate the onset-to-recurrence curves and to estimate the proportion of patients who were still in remission at 6, 12, and 24 months.
The global assessment of ulcer pain relief was compared between treatment groups using the Cochran-Mantel-Haenszel chi-square test, stratified by baseline smoking stratum.
Adverse event rates during maintenance phase 1 (weeks 1-52) were analyzed with Fisher's Exact test. The maintenance phase 2 incidence rates may be biased because they are based on only those patients who completed one year, and not on the randomized patients. Thus, no statistical comparisons were made.
A significance level of 0.050 was used for treatment comparisons and of 0.100 to test for interaction.

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SUMMARY

EFFICACY RESULTS:

As evidenced in the following table, the estimates of patients who remained duodenal ulcer free were highest in the omeprazole 20 mg a.m. group and lowest in the placebo group.

The analysis with the Cox proportional hazard model resulted in a significant overall treatment effect, significant differences between all pairs of treatments, and a significant effect of smoking stratum for the time-to-event curves on the time until patient was free of duodenal ulcers.

When the model with interaction was examined, there was a significant interaction between smoking stratum and treatment group (i.e., treatment group differences were not similar between smokers and non-smokers). For the omeprazole 20 mg a.m. and placebo groups, the survival estimates in the smoking stratum were slightly lower than those in the non-smoking stratum. For the omeprazole 10 mg a.m. group, the survival estimates in the smoking stratum were much lower than those in the non-smoking stratum.

Estimated Proportion (%) of Patients With and Without Duodenal Ulcer (DU)[†]
Through 6, 12, and 24 Months
Intent-to-Treat Cohort

Time Period	Omeprazole 10 mg a.m. (n = 351)			Omeprazole 20 mg a.m. (n = 336)			Placebo (n = 165)		
	No. With DU	% With DU	% Without DU	No. With DU	% With DU	% Without DU	No. With DU	% With DU	% Without DU
Month 6 (day 182)	71	21.5%	78.5%	32	10.2%	89.8%	85	55.3%	44.7%
Month 12 (day 365)	82	25.6%	74.4%	41	13.4%	86.7%	96	63.6%	36.4%
Month 24 (day 730)	100	35.4%	64.6%	45	15.5%	84.6%	105	73.4%	26.6%

[†] The Kaplan-Meier approach was used to estimate the proportion of patients who had recurred by each timepoint, and the proportion who remained ulcer free for the number of specified days or more. Patients healed within two weeks prior to the timepoint were considered DU healed up to that timepoint. Patients who recurred within two weeks after the timepoint were considered as a DU recurrence for that timepoint.

The analysis of the global ratings resulted in a significant overall treatment effect and significant differences between all pairs of treatments. The proportion of patients who were improved at the end of maintenance treatment was 58% in the omeprazole 20 mg a.m. group, 45% in the omeprazole 10 mg a.m. group, and 16% in the placebo group.

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SAFETY RESULTS: Adverse Events

Overall Summary of Adverse Events Number (%) of Patients Open-Label Phase

	Omeprazole 20 mg Open-Label (n = 1170)	
	N	(%)
With ≥ 1 Adverse Event	312	(26.7%)
With possibly, probably, or definitely drug related adverse event	80	(6.8%)
With a serious adverse event	23	(2.0%)
Discontinued due to an adverse event	28	(2.4%)

Overall Summary of Adverse Events Number (%) of Patients
Maintenance Phase 1 (Weeks 1-52)Safety Cohort

	Omeprazole 10 mg a.m. (n = 372)		Omeprazole 20 mg a.m. (n = 360)		Placebo (n = 177)	
	N	(%)	N	(%)	N	(%)
With ≥ 1 Adverse Event	252	(67.7%)	231	(64.2%)	103	(58.2%)
With possibly, probably, or definitely drug related adverse event	39	(10.5%)	40	(11.1%)	15	(8.5%)
With a serious adverse event	29	(7.8%)	31	(8.6%)	5	(2.8%)
Discontinued due to an adverse event	28	(7.5%)	20	(5.6%)	8	(4.5%)

Overall Summary of Adverse Events Number (%) of Patients
Maintenance Phase 2 (Weeks 53-104) –- Safety Cohort

	Omeprazole 10 mg a.m. (n = 372)		Omeprazole 20 mg a.m. (n = 360)		Placebo (n = 177)	
No. Entering Maintenance Phase 2	172		206		40	
	N	(%)	N	(%)	N	(%)
With ≥ 1 Adverse Event	113	(65.7%)	141	(68.4%)	29	(72.5%)
With possibly, probably, or definitely drug related adverse event	16	(9.3%)	20	(9.7%)	1	(2.5%)
With a serious adverse event	13	(7.6%)	18	(8.7%)	5	(12.5%)
Discontinued due to an adverse event	8	(4.7%)	9	(4.4%)	2	(5.0%)

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SAFETY RESULTS (cont.):

Fasting Serum Gastrin Levels

Median gastrin levels increased modestly from baseline in the omeprazole 20 and 10 mg treatment groups as compared with the placebo treatment group. Few patients had gastrin levels > 150% of the upper limit of normal.

ECL Cells:

No ECL cell dysplasia, neoplasia or carcinoids were found in any patients. In the omeprazole 20 mg a.m. group, 31% of evaluable patients displayed simple hyperplasia as compared to baseline (10%). The number of patients with simple hyperplasia in the omeprazole 10 mg a.m. and placebo treatment groups was essentially the same at baseline and after two years.

Compared to findings at baseline, micronodular hyperplasia was identified in a small number of biopsies taken after two years treatment: 4 in the omeprazole 20 mg group and 3 in the omeprazole 10 mg group. Intestinal metaplasia was observed in one patient in the 20 mg treatment group after 2 years of treatment.