SYNOPSIS

Name of Company: Astra Merck Inc.	**Individual Study Table Referring to Item of the Submission** N/A	**(For National Authority Use only):** N/A
Name of Finished Product: PRILOSEC®	**Volume:** N/A	
Name of Active Ingredient: Omeprazole	**Page:** N/A	

Title of Study: A Double-Blind Study to Evaluate the Effects of Omeprazole and an H_2Antagonist in the Treatment of Barrett's Esophagus

Study Center(s):2 investigator sites:
UCLA Medical Center and CURE Clinic, VA Wadsworth, Los Angeles, CA 90024

Portland VA Medical Center, University of Oregon Health Sciences Center, Portland, OR 97207

Publication (reference):N/A

Studied Period (years): June 1990 to April 1994	**Phase of development: Phase IV**

Objectives:

1. To determine whether long-term therapy with omeprazole or an H_2 antagonist will alter the natural course of Barrett's esophagus and result in regression in the area of esophageal involvement.
2. To compare the general safety of long-term therapy with omeprazole and an H_2 antagonist.
3. To investigate whether treatment with long-term omeprazole therapy, as compared to treatment with an H_2 antagonist, results in:
   a. significant trophic effects on endocrine cells in the esophagus and stomach.
   b. significant alterations in the histology of the esophagus, stomach or colon (i.e. dysplasia, neoplasia).
   4. To compare the tolerability of long-term therapy with omeprazole to that of an H_2 antagonist in the treatment of Barrett's esophagus.

Methodology: Patients randomized to one of two treatment groups: omeprazole 40 mg b.i.d. for 12 months then 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months.

Number of Patients (Planned and Analyzed): The original planned enrollment was for 100 to 150 patients. There were 106 patients who were randomized into either the omeprazole or ranitidine treatment groups. All of the randomized patients received at least one dose of study drug. There were 97 patients who had scheduled endoscopies performed both at baseline and during treatment. Of these, 77 patients completed 24 months of double-blind therapy. One ranitidine patient had complete endoscopy data but discontinued after 685 days of treatment. He is considered a completer for efficacy analyses. The distribution of patients by treatment group for each of the two investigators is presented.
To be included in the analysis of a parameter, a patient had to have both a baseline and at least one during-treatment assessment, with the measurements being made during day ranges defined for each scheduled visit.

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Number of Patients Entered into Study by Investigator and Treatment Group
Double-Blind Phase

Site No.	Investigator	No. Randomized			No. with Endoscopies[1]			No. of Completers		
		Omep.	Ranit.	Total	Omep.	Ranit.	Total	Omep.	Ranit.	Total
001	W. Weinstein	34	28	62	31	26	57	25	19[2]	44
002	D. Lieberman	23	21	44	22	18	40	21	12	33
	Both centers	57	49	106	53	44	97	46	31	77

[1] Number of patients with at least one endoscopy performed six months or later after baseline.
[2] One patient had complete endoscopy data but discontinued double-blind treatment.

Diagnosis and Main Criteria for Inclusion: Males and non pregnant females of legal age with a diagnosis of Barrett's esophagus well documented by a history including biopsy evidence of columnar epithelium.

Test Product, Dose and Mode of Administration, Batch or Lot Number:
Months 0-12, omeprazole 40 mg capsules or its placebo, Lot #: C-V932, C-V932A, C-W503, C-W983, C-X023, C-X222, C-X967.
Months 13-24, omeprazole 20 mg capsule or its placebo, Lot # C-W983, C-X460, C-X904, C-X984, C-Y055, C-Y358, C-Y391, C-Y392, C-Y419, C-Y773.
Months 0-24 ranitidine 300 mg tablet or its placebo, Lot # C-V932, C-V932A, C-W503, C-W983, C-X023, C-X222, C-X460, C-X904, C-X967, C-X984, C-Y055, C-Y358, C-Y391, C-Y392, C-Y419, C-Y773.
Months 0-24 GELUSIL® Lot #: C-V932, C-V932A, C-W503, C-X023, C-W983, C-X040, C-X460, C-X966, C-X967, C-Y421

Duration of Treatment: 24 months

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

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Criteria for Evaluation:

Efficacy:

At baseline and Months 6, 12, 18, and 24 of the double-blind period, patients underwent an upper videoendoscopy to determine the extent of esophageal involvement by Barrett's esophagus and to obtain biopsies of the stomach and esophagus for histologic evaluation.

The esophagus was divided into segments as measured from the incisors. The distance from the incisors to the most proximal extent of Barrett's epithelium is referred to as the "upper margin" distance. The distance from the incisors to the most distal portion of the major squamocolumnar junction is referred to as the "lower margin" distance. The portion of the esophagus between the upper and lower margins was considered one segment. The portion of the esophagus distal to the lower margin was divided into segments by withdrawing the endoscope 2 cm at a time starting at the lower esophageal sphincter (LES) and ending at the lower margin. Each segment was assigned a score according to the estimated proportion within the segment that is lined with Barrett's epithelium. The original scoring system, comprised of integer scores from 1 to 5, was as follows:

1 = no involvement of Barrett's epithelium
2 = ≤25% of area involved
3 = >25% to ≤75% of area involved
4 = >75% to ≤99% of area involved
5 = 100% of area involved.

The data were used to derive the following six parameters, three relating to length and three a function of the lengths multiplied by the involvement scores.

Barrett's lengths (cm):

lower margin minus upper margin distance
LES minus lower margin distance
total length (LES minus upper margin distance)

Barrett's involvement:

lower to upper margin involvement:
calculated as (lower margin minus upper margin distance) multiplied by the score
LES to lower margin involvement:
calculated as the sum of (segment lengths between the LES and lower margin multiplied by the score per segment)
[This parameter was not specified in the protocol.]
Total esophageal involvement:
calculated as lower to upper margin involvement + LES to lower margin involvement.

If the area between the LES and lower margin was confluent, then the LES to lower margin involvement was calculated as:

(LES minus lower margin distance) multiplied by the involvement score

Of primary interest is the total length of Barrett's esophagus (i.e., LES minus upper margin distance) and the total esophageal involvement.

Squamous Islands in Barrett's Epithelium

The number of squamous islands within the Barrett's epithelium was recorded at each endoscopy. As stated in the protocol, regression was considered to have occurred if a patient developed at least two islands of squamous mucosa, each ≥0.5 cm in greatest diameter, completely surrounded by pink Barrett's epithelium. Since only the diameter of the largest and smallest islands were recorded in the case report form, the definition was modified such that the largest diameter was at least 0.5 cm in greatest diameter. Prior to analysis, regression was also defined removing the restriction that the diameter of the largest island be at least 0.5 cm. Only patients with no squamous islands at baseline were included in the analyses of the regression.

Safety:

All 106 patients who had taken at least one dose of study medication were included in the evaluation of clinical and laboratory adverse events. Thus, patients who were lost to follow-up or who withdrew from the study early were included in the adverse event summaries. If no adverse events were recorded for those patients, it was assumed that they did not have any adverse events.

Serum Gastrin Levels

Postprandial serum gastrin levels were measured at study entry and every six months thereafter in the double-blind phase.

Esophageal Mucosa

Biopsies of the esophagus were obtained at study entry and every six months thereafter in the double-blind phase. The mucosa was categorized as normal, Barrett's metaplasia, indeterminate, low grade dysplasia, high grade dysplasia, or carcinoma.

Colon Polyps

A colonoscopy was performed at baseline and at Month 24 of the double-blind period. The protocol specified that pre-neo-plastic lesions exceeding 3 mm in diameter were to be removed.

ECL Cell Histology

At each endoscopy visit, performed at baseline and Months 6, 12, 18, and 24 of the double-blind period, biopsies of the esophagus and stomach were obtained to evaluate for qualitative changes in endocrine cells.

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SUMMARY

EFFICACY RESULTS:

All Patients With Available Data

Barrett's Involvement and Length

During treatment, the decreases from baseline in total esophageal involvement and the LES to lower margin involvement were significantly greater in the omeprazole group at all months of evaluation. Between 74% and 87% of the omeprazole patients (median decreases between 0.8 and 1.3) had reductions from their baseline total involvement compared with between 33% and 61% of the ranitidine patients (median decreases between 0 and 0.5).

Across the various time points, between 36% and 65% of the omeprazole patients (median decreases between 0 and 1 cm) had reductions from their baseline total length compared with between 27% and 42% of the ranitidine patients (median decreases 0 cm). At Month 24, the analysis of the LES to lower margin distance resulted in a significantly greater decrease in the omeprazole group when compared with the ranitidine group.

The change from baseline in the total length in the "available data" analysis was not significant. A significantly greater decrease in total length in the omeprazole treatment group relative to the ranitidine treatment group is observed in months 12 and 24 of the "all patients treated analysis."

Squamous Islands

At baseline, there was no significant difference between treatment groups in the distribution of the number of squamous islands. There were significant differences between the treatment groups at Months 12, 18, and 24. Between 62% and 73% of the omeprazole patients and between 22% and 35% of the ranitidine patients had increases from baseline in their number of squamous islands.

At all months of evaluation, significantly more omeprazole patients had two or more squamous islands (range: 58%-69%) when compared with the ranitidine patients (range: 7%-28%). This was also true when the diameter restriction was imposed, where the percentages of patients with at least two squamous islands ranged from 50% to 65% in the omeprazole group and from 7% to 17% in the ranitidine group.

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Means and Median Changes[1] from Baseline for Barrett's Total Involvement
Patients with Available Data -- Double-Blind Phase

	Month	Barrett's Involvement	Omeprazole	Ranitidine	P-Value[2]
Total Esophageal Involvement[3]					
	baseline	No. of patients	53	44	
		mean	5.1	4.6	
		std. dev.	3.3	3.2	
		median	4.0	3.4	0.380
		range	0.8, 13.5	1.5, 17.5	
	6	No. of patients	53	44	
		mean	4.2	4.5	
		std. dev.	2.8	3.1	
		median	3.3	3.5	
		range	0.5, 11.5	1.3, 18.0	
		mean change	-0.9	-0.1	
		std. dev.	1.1	0.7	
		median change	-0.8	0.0	<0.001*
		range	-3.5, 1.0	-1.8, 1.5	
	12	No. of patients	50	40	
		mean	4.0	4.5	
		std. dev.	2.9	3.3	

1 A negative change indicates a decrease from baseline.

2 Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.

3 The lower to upper margin involvement + sum(segment lengths between lower esophageal sphincter and lower margin multiplied by Barrett's score per segment).

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Means and Median Changes[1] from Baseline for Barrett's Involvement
Patients with Available Data -- Double-Blind Phase (cont.)

	Month	Barrett's Involvement	Omeprazole	Ranitidine	P-Value[2]
Total Esophageal Involvement[3] (continued)					
		median	3.0	3.5	
		range	0.3, 11.0	1.0, 18.0	
		mean change	-1.2	0.0	
		std. dev.	1.5	0.9	
		median change	-1.3	0.0	<0.001*
		range	-5.0, 4.0	-2.0, 1.5	
	18	No. of patients	49	37	
		mean	3.9	4.2	
		std. dev.	2.8	3.0	
		median	3.0	3.5	
		range	0.3, 10.5	1.5, 16.0	
		mean change	-1.4	-0.2	
		std. dev.	1.4	1.1	
		median change	-1.0	0.0	<0.001*
		range	-5.5, 1.5	-2.8, 1.8	

1 A negative change indicates a decrease from baseline.
2 Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.
3 The lower to upper margin involvement + sum(segment lengths between lower esophageal sphincter and lower margin multiplied by Barrett's score per segment).

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Means and Median Changes[1] from Baseline for Barrett's Involvement
Patients with Available Data -- Double-Blind Phase (cont.)

	Month	Barrett's Involvement	Omeprazole	Ranitidine	P-Value[2]
Total Esophageal Involvement[3] (continued)					
	24	No. of patients	46	31	
		mean	3.6	4.2	
		std. dev.	2.6	1.7	
		median	2.9	3.0	
		range	0.3, 10.0	1.0, 16.0	
		mean change	-1.8	-0.2	
		std. dev.	1.5	1.0	
		median change	-1.3	-0.5	<0.001*
		range	-5.5, 0.8	-2.3, 2.3	

[1] A negative change indicates a decrease from baseline.
[2] Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.
[3] The lower to upper margin involvement + sum(segment lengths between lower esophageal sphincter and lower margin multiplied by Barrett's score per segment).

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Medians and Median Changes From Baseline[1] in Number of Squamous Islands Patients with Available Data -- Double-Blind Phase

Month		Omeprazole	Ranitidine	P-Value[2]
Baseline	no. of patients	53	44	
	median	1.0	1.0	0.434
	range[3]	0, 17 [10]	0, 12 [11]	
6	no. of patients	53	44	
	median	3.0	2.0	
	range	0, 13 [11]	0, 17 [10]	
	median change	2.0	0.0	0.062
	range	-7, 13 [10]	-8, 10 [10]	
12	no. of patients	50	40	
	median	3.0	1.0	
	range	0, 28 [10]	0, 32 [15]	
	median change	1.0	0.0	<0.001*
	range	-5, 28 [10]	-6, 28 [4]	
18	no. of patients	49	37	
	median	3.0	1.0	
	range	0, 59 [10]	0, 17 [10]	
	median change	2.0	0.0	<0.001*
	range	-3, 59 [10]	-6, 6 [5]	
24	no. of patients	46	31	
	median	3.0	1.0	
	range	0, 10 [10]	0, 33 [14]	
	median change	2.0	0.0	0.004*
	range	-7, 10 [10]	-7, 21 [6]	

1 A negative change indicates a decrease from the baseline count of squamous islands.
2 Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.
3 The numbers in brackets represent the second largest value.

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SAFETY RESULTS:

Clinical Adverse Events

The summary of overall clinical adverse events occurring during the double-blind portion of the study, regardless of drug relationship, is presented. During the double-blind phase, 14 patients who received omeprazole and 17 who received ranitidine had clinical adverse events that were considered serious. Three omeprazole patients died. None of the deaths were characterized by the investigator as related to study medication. There were 7 omeprazole patients and 14 ranitidine patients who discontinued the double-blind portion of the study due to clinical adverse events. Significantly more patients in the ranitidine group discontinued the double-blind treatment due to adverse events (29%) when compared with the omeprazole group (12%). There were significant differences between treatment groups in the occurrence rates of four clinical adverse events: edema/swelling (0% vs. 8%), esophagitis (0% vs. 16%), reflux esophagitis (2% vs. 12%), and esophageal ulcer (0% vs. 8%). In all instances, the higher incidence rates were in the ranitidine group. Also, significantly more ranitidine patients reported an adverse event of the digestive system (76%) when compared with the omeprazole patients (56%).

Laboratory Adverse Events

The summary of overall laboratory adverse events occurring during the double-blind portion of the study, regardless of drug relationship, is listed. One ranitidine patient experienced a serious laboratory adverse event. There were no significant differences between treatment groups in the occurrence rates.

Gastrin Levels

Patients in the omeprazole group had significantly greater increases from their baseline gastrin levels when compared with the ranitidine group.

Esophageal Mucosa

There were no significant differences between treatment groups in the distribution of mucosa scores at either baseline or during treatment. The majority of the patients had Barrett's metaplasia at baseline; seven patients had low grade dysplasia. During treatment with omeprazole, two patients developed low grade and two developed high grade dysplasia. During treatment with ranitidine, five patients developed low grade dysplasia, only one of which also had low grade dysplasia at baseline. No patients developed esophageal carcinoma.

Colon Polyps

The summary table for the number of colon polyps >3 mm in diameter follows. At baseline, there was no significant difference between treatment groups in the distribution of the number of large colon polyps. There was no significant difference between treatment groups, where between 70% and 80% of the patients in each treatment group had no colon polyps >3 mm.

ECL Cell Histology

Enterochromafin like cells (ECL) were stained and evaluated in corpus gastric biopsies at baseline and every 6 months. Two patients on omeprazole exhibited micronodular ECL cell hyperplasia as well as two patients on ranitidine. No ECL cell micronodular hyperplasia was found in biopsies from the last visit. The esophageal ECL cell data have not been analyzed and are not included in this report.

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SAFETY RESULTS (continued):

Atrophic Gastritis and Intestinal Metaplasia

Corpus and antrum biopsies were stained and evaluated for gastritis/atrophic gastritis and intestinal metaplasia. No significant differences between omeprazole and ranitidine treated patients with respect to corpus atrophic gastritis or corpus intestinal metaplasia were observed.

Overall Summary of Clinical Adverse Events
Double-Blind Phase

Clinical Adverse Events	Omeprazole (n = 57)	Ranitidine (n = 49)	P-Value[1]
≥1 adverse event	54 (95%)	46 (94%)	1.000
≥1 serious adverse event	14 (25%)	17 (35%)	0.289
Discontinued due to adverse event	7 (12%)	14 (29%)	0.050*

[1] Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.

Overall Summary of Laboratory Adverse Events
Double-Blind Phase

Laboratory Adverse Events	Omeprazole (n = 57)	Ranitidine (n = 49)	P-Value[1]
≥1 adverse event	11 (19%)	10 (20%)	1.000
≥1 serious adverse event	0 (0%)	1 (2%)	0.462
Discontinued due to adverse event	0 (0%)	0 (0%)	1.000

[1] Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.

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Number (%) of Patients by Status at End of Double-Blind Phase
All Randomized Patients

	Omeprazole (n = 57)	Ranitidine (n = 49)	P-Value[1]
Patients Completing	46 (81%)	30 (61%)	--
Patients Discontinued	11 (19%)	19 (39%)	0.032*
adverse event related to GERD	1 (2%)	12 (24%)	<0.001*
adverse event unrelated to GERD	6 (11%)	1 (2%)	0.120
malignancy developed	0 (0%)	1 (2%)	0.462
lost to follow-up	2 (4%)	2 (4%)	1.000
protocol deviation	1 (2%)	2 (4%)	0.595
patient uncooperative	1 (2%)	1 (2%)	1.000

[1] Significant difference ($p \leq 0.05$) between treatment groups is indicated by *.

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Number (%) of Patients with Colon Polyps >3 mm in Diameter Double-Blind Phase

Month	No. of Colon Polyps >3 mm	Omeprazole	Ranitidine
baseline	No. of patients	46	39
	0	40 (87%)	27 (69%)
	1	3 (7%)	8 (21%)
	2	2 (4%)	3 (8%)
	5	1 (2%)	0 (0%)
	6	0 (0%)	1 (3%)
	[median]	[0.0]	[0.0]
24	No. of patients	46	39
	0	37 (80%)	28 (72%)
	1	6 (13%)	8 (21%)
	2	2 (4%)	2 (5%)
	3	1 (2%)	0 (0%)
	4	0 (0%)	1 (3%)
	[median]	[0.0]	[0.0]