AstraZeneca

I-904-B

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Losec™

ACTIVE INGREDIENT: Omeprazole

Trial Title (number):Duodenal Ulcer Relapse During Maintenance Treatment With Omeprazole 20 mg, Omeprazole 10 mg, or Ranitidine 150 mg for Twelve Months

Development Phase: III
First Subject Recruited:
Last Subject Completed:
Approval Date: 25 May 1998

OBJECTIVES

The primary aim of this study was to compare the efficacy of Omeprazole 10 mg once daily (O.M.), Omeprazole 20 mg once daily (O.M.), or Ranitidine 150 mg at bedtime in maintaining duodenal ulcer patients in remission for twelve months.

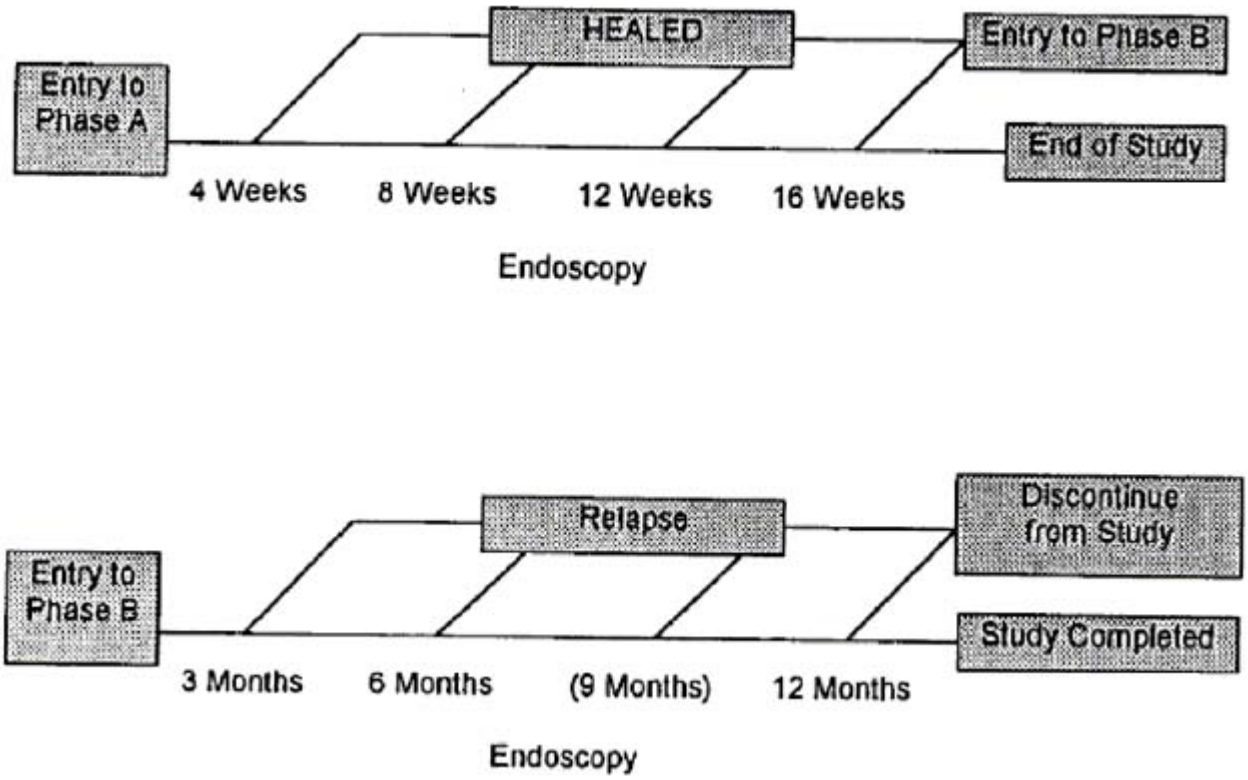
Secondary: The secondary aim of this study was to compare the safety (type and frequency of adverse events and influence on laboratory variables) and tolerability profiles of each treatment regimen in these patients.

METHODS

Study design

The study consisted of 2 phases: Phase A was a 4-16 week open treatment period and Phase B was a 12-month period of a randomized, double-blind, parallel group design. This particular report deals mainly with Phase B of the study. The study design is given in Figure 1.1.

Figure 1.1: Study Design



In Phase A, all qualified patients diagnosed by endoscopy to have active duodenal ulcer were treated for 4 to 8 weeks with 20 mg Omeprazole O.M. until healing (defined as complete re-epithelialization of all ulcer sites). Patients who were not healed after 8 weeks of treatment were given two 20 mg O.M. for four weeks, and if still unhealed, treatment was continued for a further 4 weeks. Any patient unhealed after 16 weeks of treatment was dropped from the study.

All patients healed and without moderate to severe epigastric pain or symptom of gastrointestinal bleeding were included in the 12-month maintenance period. These patients were randomized to receive either Omeprazole 10 mg O.M., Omeprazole 20 mg O.M. or Ranitidine 150 mg H.S.

Medical history, physical examination, endoscopy and laboratory screen were assessed at the start of Phase B. Subsequent visits were performed at 3, 6, 9, and 12 months after the start of Phase B. If moderate to severe epigastric pain or any sign of gastrointestinal bleeding recurred for three or more consecutive days during the maintenance treatment, an extra visit with endoscopy was performed to investigate if there was an ulcer. In the event of relapse (ulcer with or without symptoms) during maintenance treatment, the patient was considered a treatment failure and subsequently withdrawn from the study.

Randomization

Patients healed in the treatment phase (Phase A) and without moderate to severe pain or indication of gastrointestinal bleeding, were allocated to receive either Omeprazole 10 mg O.M., Omeprazole 20 mg

O.M., or Ranitidine 150 mg H.S. according to a computer-generated randomization list provided by Astra Hassle. The randomization was separate for each center and within blocks of consecutive patients.

Patients

Inclusion criteria

- All patients with at least one active duodenal ulcer verified by endoscopy, not more than four days prior to inclusion in the study, with width of at least 5 mm in the greater axis, underwent an open treatment regimen with 20 mg Omeprazole once daily for 4 or 8 weeks on an outpatient basis. Patients who were not healed after 8 weeks' treatment were given two 20 mg Omeprazole once daily for another 4 weeks, and if still unhealed, treatment was continued for another 4 weeks.
- Patients healed after 4 to 16 weeks treatment, and who were free from ulcer symptoms (not more than mild pain during the past two days and with no sign of gastrointestinal bleeding) were eligible for inclusion in the maintenance phase.

Exclusion criteria

Patients with any of the following conditions were not eligible for inclusion in the maintenance phase of the study:

- Patients not giving informed consent
- Age below 18 and above 80 years
- Pregnancy or lactation
- Pyloric stenosis that requires surgical treatment
- Concurrent gastric or pyloric ulcer or erosive/ ulcerative reflux esophagitis or active bleeding
- History of gastric surgery except for simple closure
- Concurrent disease or therapy which may complicate the evaluation of the drug, e.g. known liver or kidney disease, severe cardiac or pulmonary disease, suspected or confirmed malignancy
- Clinically significant abnormalities in the predrug screen, other than those directly related to the primary diagnosis
- Treatment with an investigational drug during the previous month
- Chronic alcoholism, drug abuse or any other condition associated with poor patient compliance, including patients who were not expected to cooperate
- Previous inclusion in the study

Target subject population and sample size

It was planned that 210 patients would enter the study. Sixty male and female outpatients aged 18 to 80 diagnosed by endoscopy to have duodenal ulcer four days prior to inclusion were required complete each of the three arms of Phase B according to the protocol. To provide for dropouts, a total of 210 patients were to be entered into the study. Patients who developed ulcer recurrence were withdrawn and considered as completed.

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

The investigational drug was Omeprazole, formulated as enteric-coated granules and dispensed in hard gelatin capsules, each containing 10 or 20 mg manufactured by Astra Hassle AB, Sweden. The size of the capsule was the same for the two doses.

The reference drug was Ranitidine in 150 mg tablets manufactured by Glaxo. For blinding purposes, placebo drugs (Astra Hassle AB, Sweden), containing lactose granules, identical in appearance to Omeprazole capsules and Ranitidine tablets were given.

Criteria for evaluation

The main efficacy variable in the study was the time in remission, defined as the time between randomization and the first ulcer relapse.

RESULTS

Subject population

Patient Description

Two hundred and eleven patients were randomized to treatment, of whom 178 completed the study. Two hundred patients were included in the APT analysis and 123 patients were included in the PP analysis.

The demographic variables for the APT patients are listed in Table 5.1.2 (obtained from Phase A)

Table 5.1.2 Patient Demographics

	Omeprazole 20 mg O.M. (n=69)	Omeprazole 10 mg O.M. (n=66)	Ranitidine 150 mg O.M. (n=65)
Age (years)			
Mean	51	51	51
SD	13	12	14
min	22	25	18
max	74	77	74
Sex			
Male	55	53	53
Female	14	13	12
Race			
Oriental	69	66	65

No relevant differences were found in demographic parameters between the three treatment groups.

Efficacy

Disposition of the Patients in the Analyses

Table 5.4.1 summarizes the number of patients included in the APT analyses at each timepoint.

Table 5.4.1 Number of patients in the APT analysis, summary

	Omeprazole 20 mg O.M. (n=69)	Omeprazole 10 mg O.M. (n=66)	Ranitidine 150 mg O.M. (n=65)
Randomized	71	71	69
Month 3	38	34	29
Month 6	36	32	26
Month 9	36	31	25
Month 12	36	30	24
Total	40	41	42

Clinical Efficacy

APT Analysis – Time in Remission

Subsequent visits were performed at 3, 6, 9, and 12 months after the start of Phase B. If moderate to severe epigastric pain or any sign of gastrointestinal bleeding recurred for three or more consecutive days during maintenance treatment, an extra visit with endoscopy was performed to investigate if there was an ulcer. In the event of relapse (ulcer with or without symptoms) during maintenance treatment, patient was considered a treatment failure and subsequently withdrawn from the study.

Table 5.4.3 shows the APT patients in remission, relapsed patients and patients with unknown ulcer status at the different study visits and for the three treatment groups.

Table 5.4.3: Clinical status of APT patients at different study periods

Visit	Treatment group	In Remission		Relapse		Unknown	
		n*	%	n*	%	n*	%
Month 0	Omeprazole 20 mg O.M.	68	99	0	0	1	1
	Omeprazole 10 mg O.M.	66	100	0	0	0	0
	Ranitidine 150mg H.S.	65	100	0	0	0	0
Month 3	Omeprazole 20 mg O.M.	65	94	1	1	3	4
	Omeprazole 10 mg O.M.	59	89	7	11	0	0
	Ranitidine 150mg H.S.	50	77	15	23	0	0
Month 6	Omeprazole 20 mg O.M.	61	88	3	4	5	7
	Omeprazole 10 mg O.M.	51	77	11	17	4	6
	Ranitidine 150mg H.S.	43	66	19	29	3	5
Month 9	Omeprazole 20 mg O.M.	52	75	6	9	11	16
	Omeprazole 10 mg O.M.	47	71	12	18	7	11
	Ranitidine 150mg H.S.	37	57	21	32	7	11
Month 12	Omeprazole 20 mg O.M.	51	74	7	10	11	16
	Omeprazole 10 mg O.M.	42	64	15	23	9	14
	Ranitidine 150mg H.S.	32	49	26	40	7	11

* Outcome at Visit 6 (unscheduled) was attached to the visit with the corresponding date (this explains the different number of patients in comparison to Table 5.4.1.)

In patients treated with Omeprazole 20 mg O.M. the highest rate of patients in remission could be seen throughout the study. After 12 months of maintenance therapy 74% of patients with Omeprazole 20 mg O.M. were still in remission, whereas with Omeprazole 10 mg O.M. 64% and with Ranitidine 150 mg H.S. 49% were still in remission. A relapse was found in 10% of patients treated with Omeprazole 20 mg O.M. and 40% of patients treated with Ranitidine 150 mg H.S.

Time in remission was defined as the time between randomization and first ulcer relapse. Comparison of the time in remission between the three treatment groups was investigated using a Cox proportional hazards analysis. Predictor variables used in the model included treatment group with the following control variables: age, sex, ulcer size at baseline (ordinal coded as the distribution was rather right-tailed), previous ulcer treatment and duration of peptic ulcer disease (data from Phase A of the study). For the treatment groups a dummy coding was added so that the resulting p-values and risk ratios for the two Omeprazole groups could be seen in comparison to the Ranitidine group.

After calculating the previously described full model a reduced model with only the significant variables (p-value<0.05) was calculated. For both models the relevant statistical information are given below.

Table 5.4.4: Cox Proportional Hazards Model for time in remission for APT patients - full model

Cox Proportional Hazards Model - Analysis of Maximum Likelihood Estimates						
Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
Omeprazole 20mg OM [yes]	**1**	**-1.780939**	**0.44168**	**16.25838**	**0.0001**	**0.168**
Omeprazole 10mg OM [yes]	**1**	**-0.924139**	**0.34760**	**7.06839**	**0.0078**	**0.397**
Gender [female]	1	-0.124353	0.39079	0.10126	0.7503	0.883
Age	1	0.007839	0.01084	0.52268	0.4697	1.008
Ulcer size at baseline [> 10 mm]	1	0.395069	0.30772	1.64832	0.1992	1.484
Duration of ulcer disease [1-5 years]	1	0.189057	0.41729	0.20526	0.6505	1.208
Duration of ulcer disease [>5 years]	1	0.344187	0.38751	0.78889	0.3744	1.411
Previous ulcer treatment [yes]	1	0.562314	0.39959	1.98024	0.1594	1.755

Parameter estimates for the treatment Omeprazole 20 mg O.M. and 10 mg O.M. are statistically significant with p=0.0001 and 0.0078 respectively, indicating that the time in remission is significantly longer for both the Omeprazole treatment groups than for the Ranitidine group. The risk ratio for Omeprazole 20 mg O.M. is 0.168, indicating that the risk for a relapse for patients treated with Omeprazole 20 mg O.M. is only 16.8% of those for patients treated with Ranitidine 150 mg H.S. The risk ratio for Omeprazole 10 mg O.M. is 0.397, indicating that the risk for relapse for patients treated with Omeprazole 10 mg O.M. is only 39.7% of those for patients treated with Ranitidine 150 mg H.S.

Table 5.4.5: Cox Proportional Hazards Model for time in remission for APT patients - reduced model

Cox Proportional Hazards Model - Analysis of Maximum Likelihood Estimates						
Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Risk Ratio
Omeprazole 20mg OM	**1**	**-1.571134**	**0.42610**	**13.59573**	**0.0002**	**0.208**
Omeprazole 10mg OM	**1**	**-0.690550**	**0.32440**	**4.53125**	**0.0333**	**0.501**

The reduced model shows similar results as the full model and the risk ratios are only slightly higher. A comparison of the two omeprazole regimens showed, in both models, no significant differences between the 20 mg and 10 mg treatment (full model: p=0.062; reduced model: p=0.055).

Safety results

Clinical examinations

Endoscopic findings of Safety Analysis patients are given in Table 5.5.1

Table 5.5.1: Endoscopic findings of Safety Analysis patients.

		Abnormal findings							
		Oesophagus		Stomach		Duodenum		Others	
Visit	Treatment Group	n	%	n	%	n	%	n	%
Month 3	Omeprazole 20 mg O.M.	2	3	14	22	0	0	19	30
	Omeprazole 10 mg O.M.	1	2	11	20	0	0	17	30
	Ranitidine 150mg H.S.	0	0	9	19	1	2	8	17
Month 6	Omeprazole 20 mg O.M.	1	2	14	24	0	0	10	17
	Omeprazole 10 mg O.M.	0	0	8	16	0	0	9	18
	Ranitidine 150mg H.S.	0	0	7	17	0	0	9	22
Month 9*	Omeprazole 20 mg O.M.	0	0	0	0	0	0	0	0
	Omeprazole 10 mg O.M.	0	0	1	100	0	0	0	0
	Ranitidine 150mg H.S.	0	0	0	0	0	0	0	0
Month 12	Omeprazole 20 mg O.M.	1	2	12	23	1	2	12	23
	Omeprazole 10 mg O.M.	0	0	11	24	3	7	6	13
	Ranitidine 150mg H.S.	1	3	9	24	5	14	5	14

* At visit (Month 9) no endoscopy was planned.

\- Outcome of Visit 6 was attached to Month "x" if: ABS[ENDODATE(Visit6)-(DATE(Visit x-1) + 91.3)]≤10

Adverse Events

Adverse events were recorded in response to spontaneous reports by the patients and open questioning at all visits. The data presented is based on all patients who received at least one dose of study medication. A summary of AEs is presented in Table 5.5.3 and Table 5.5.4 presents more detailed adverse event information.

Table 5.5.3: Adverse event summary

	Omeprazole 20 mg (n=71)		Omeprazole 10 mg (n=67)		Ranitidine 150 mg (n=65)	
	n	%	n	%	n	%
No. of patients reporting AEs (n,%)	36	51	36	54	34	52
No. of patients with serious AEs (n,%)	2	3	2	3	5	8
No. of patients discontinuing study due to AEs (n,%)	3	4	3	4	6	9
No. of patients wth sever AEs (n,%)	4	6	1	1	5	8
No. of AEs reported (n,%)	97		68		72	

Table 5.5.4: Number of patients reporting each adverse event

	Omeprazole 20 mg		Omeprazole 10 mg		Ranitidine 150 mg		Total
Preferred Term	n	%	n	%	n	%	n
Gastrointestinal symptoms							
Epigastric pain/ discomfort/ burning	16	22.5	13	19.4	18	27.7	47
Stools loose/ Diarrhoea/ watery stools	8	11.3	10	14.9	2	3.1	20
Bloating/ Fullness abdominal/ distension	1	1.4	3	4.5	4	6.2	8
Melaena	0	0	0	0	4	6.2	4
Vomiting	3	4.2	0	0	0	0	3
Flatulence	2	2.8	0	0	0	0	2
Abdominal pain/ cramp	1	1.4	1	1.5	0	0	2
Constipation	0	0	1	1.5	0	0	1
Haemorrhoids	1	1.4	0	0	0	0	1
Nausea	1	1.4	0	0	0	0	1
TOTAL	33	46.5	28	41.8	28	43.1	89
Respiratory symptoms							
Coughing/ Common cold/ Nasal irritation/ Pharyngitis/ Hiccup/Sinusitis/ Breath shortness	18	25.3	11	16.4	4	6.2	33
Infection	1	1.4	1	1.5	0	0	2
TOTAL	19	26.8	12	17.9	4	6.2	35
Cardiovascular symptoms							
Hypertension/ Blood pressure increased	3	4.2	2	3.0	1	1.5	6
Palpitation	0	0	0	0	2	3.1	2
Chest pain	1	1.4	0	0	1	1.5	2
TOTAL	4	5.6	2	3.0	4	6.2	10
Genitourinary symptoms							
Dysuria/ Urine volume deficient	1	1.4	1	1.5	2	3.1	4
Vaginal haemorrhage	0	0	0	0	1	1.5	1
Urinary tract infection	0	0	1	1.5	0	0	1
Hepatorenal syndrome	1	1.4	0	0	0	0	1
TOTAL	2	2.8	2	3.0	3	4.6	7

Muscoskeletal symptoms							
Musculoskeletal pain	7	9.9	3	4.5	7	10.8	17
Malaise/ weakness	1	1.4	0	0	3	4.6	4
Toothache/ loss	2	2.8	0	0	0	0	2
Fever	5	7.0	5	7.5	4	6.2	14
Headache	2	2.8	1	1.5	2	3.1	5
TOTAL	17	23.9	9	14.3	16	24.6	42
Skin disorders							
Tinea versicolor / Lichen planus-like dermatitis/ Boils/ rash/ warts	4	5.6	1	1.5	3	4.6	8
Wound infection/ Injury	0	0	2	3.0	0	0	2
Hypersensitivity reaction	1	1.4	0	0	0	0	1
TOTAL	5	7.0	3	4.5	3	4.6	11
Sensory / neural symptoms							
Euphoria	1	1.4	0	0	1	1.5	2
Dizziness	1	1.4	0	0	0	0	1
Anorexia	0	0	0	0	1	1.5	1
Hungry	0	0	0	0	1	1.5	1
Insomnia	1	1.4	0	0	0	0	1
Poor memory	0	0	1	1.5	0	0	1
Sensory disturbance	1	1.4	0	0	0	0	1
Conjunctivitis	1	1.4	0	0	0	0	1
TOTAL	5	7.0	1	1.5	3	4.6	9
Weight decrease	1	1.4	0	0	0	0	1
Bilirubin increased/ Jaundice	0	0	2	3.0	0	0	2
Anaemia / Haemoglobin decreased	0	0	0	0	2	3.1	2
Leukocytosis / WBC increased	0	0	2	3.0	0	0	2
SGOT increased	0	0	1	1.5	0	0	1
SGPT increased	0	0	1	1.5	0	0	1
Hyperglycaemia	0	0	0	0	1	1.5	1
Phosphatase alkaline increased	0	0	1	1.5	0	0	1

Table 5.5.5: Serious adverse events

Patient	Visit	Adverse Event	Treatment	Action taken regarding study drug	Other action taken
10025	2.1	Hepato-renal syndrome	Omeprazole 20 mg	Stopped	Brought to emergency room
20002	5	Flank pain	Ranitidine 150 mg	Stopped	Hospitalized
20016	4	Epigastric pain/fever	Omeprazole 10 mg	Stopped	Hospitalized
20024	1.2	Epigastric discomfort	Ranitidine 150 mg	No change	Elective cholecystectomy
20028	1.2	Persistent post-prandial vomiting	Omeprazole 20 mg	Stopped	Surgery recommened
20032	1.2	Hepatitis	Omeprazole 10 mg	Stopped	Hospitalized
20033	1.2	Chest pain/palpitation	Ranitidine 150 mg	No change	Hospitalized
30012	3	Anorexia/weakness	Ranitidine 150 mg	Stopped	Hospitalized
30013	2	Palpitation	Ranitidine 150 mg	No change	Hospitalized

Overall Results

The number and percentage of patients reporting adverse events were similar in the three treatment groups. The most common adverse events were epigastric pain, fever, coughing and loose stools and diarrhea.

More patients, however, in the Ranitidine treatment group (5, 8%) had serious adverse events compared with the Omeprazole 20 mg (2, 3%) and Omeprazole 10 mg (2, 3%) treatment groups. Reported serious adverse events also differed among centers with Centers 2 and 3 accounting for a majority of the serious adverse event reported (4 each) with Center 1 reporting 1 serious adverse event.

The number of patients with severe AEs and the number of AEs reported were significantly lower in the Omeprazole 10 mg (1, 1%; 68) treatment group than in the Omeprazole 20 mg (4, 6%; 97) and the Ranitidine (5, 8%; 72) treatment groups.

No other differences regarding the type of adverse events in the three groups were noted.
Additional safety information is presented in Table 5.5.6.

Table 5.5.6 Long-term omeprazole study data (Study I-904b) (data from maintenance phase only)

Trial	Treatment	dose (mg)	Planned duration (months)	N	Average days of treatment	Total exposure (pt-yrs)	% dropouts	# CV SAEs	# deaths all cause	# deaths CV	# MIs	# MI fatal	# deaths or MIs	# Non heam. stroke
I-904b	Omeprazole	10 mg O.M.	12	71	385	74.8	18.3	0	0	0	0	0	0	0
	Omeprazole	20 mg O.M.	12	71	385	74.8	15.5	0	0	0	0	0	0	0
	Ranitidine	150 mg H.S.	12	69	378	71.4	13.0	0	0	0	0	0	0	0

(mg milligram; N number of patient; CV Cardiovascular; SAE Serious adverse event; MI Myocardial infarction.)

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical

use. Before prescribing Prilosec™ (omeprazole), Healthcare Professionals should view their specific country information.