AstraZeneca

I-653B

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Losec™

ACTIVE INGREDIENT: Omeprazole

Trial Title (number):A Randomized, Double-Blind, Parallel-group, Placebo-Controlled comparison of omeprazole 20 mg once daily, omeprazole 10 mg, and placebo in adult patients (18 – 80 years of age) with healed endoscopically-diagnosed gastro esophageal reflux disease (GERD) for 1 year or until relapse.

Development Phase: III
First Subject Recruited: 07 January 1991
Last Subject Completed: 23 June 1993
Approval Date: 17 November 1997

OBJECTIVES

Primary: To assess the proportion of patients who suffer symptomatic relapse or reflux esophagitis lesions (detected endoscopically), following successful treatment of such symptoms and lesions with omeprazole, whilst receiving omeprazole 20 mg (once daily in the morning), omeprazole 10 mg, or placebo.

Secondary: To assess the proportion of asymptomatic patients who have endoscopically-diagnosed esophagitis after 3 and 12 months treatment with omeprazole 20 mg o.m, omeprazole 10 mg o.m., or placebo.

METHODS

Study design

This was a Randomized, Double Blind, Parallel-group, Placebo Controlled comparison of omeprazole 20 mg o.m., omeprazole 10 mg, and placebo in adult patients (18 – 80 years of age) with healed endoscopically-diagnosed gastrointestinal esophagitis reflux disease (GERD) for 1 year or until relapse.

Target subject population and sample size

The patients entering the study were outpatients. One hundred and ninety-three entered the study. Patients had healed endoscopically diagnosed gastrointestinal esophagitis reflux disease (GERD), were asymptomatic (Grade 0 on patient's overall evaluation of symptoms), had normal esophageal

mucosa (Grade 0) on endoscopy, and complied (≥80% compliance) with the medication regimen in Part 1 of the Study (I-653A is described elsewhere).

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

Subjects were randomly assigned to 1 of the 3 following treatment groups. Treatments were given in double-blind fashion.

- Omeprazole 10 mg was supplied as enteric-coated granules in hard gelatine capsules (Batch numbers: H499-14-2-2 and H499-14-2-3).
- Omeprazole 20 mg was supplied as enteric-coated granules in hard gelatine capsules (Batch numbers: H431-13-2-1 and H431-13-2-2).
- Placebo was supplied as lactose in hard gelatine capsules (Batch numbers: H459-6-1-1, H459-6-1-2, H459-6-1-3, and H459-6-1-4).

Gaviscon tablets each containing alginic acid 500 mg, magnesium trisilicate 25 mg, dried aluminum hydroxide gel 100 mg, and sodium bicarbonate 170 mg, were supplied in commercial packs for symptoms relief throughout the study.

Duration of treatment

Four periods of 91 ± 14 days.

Criteria for evaluation

Efficacy:

- Esophagogastroduodenoscopy was carried at Visit 3 (Week 13) and at the final visit (Week 52 for those who completed the study). On each occasion, the state of the oesophageal mucosa, the linear extent of any esophagitis, the linear extent of any Barrett's esophagus and other abnormalities were noted. The extent of the esophagitis was recorded in the case record forms and the severity of the disease graded using the following classification:
  Grade 0 = Normal esophageal mucosa.

  Grade I = No macroscopic erosions visible. Erythema, or diffusely red mucosa; edema causing accentuated folds.

  Grade II = Isolated round or linear erosions extending from the squamocolumnar junction upwards in relation to the folds, but not involving the entire circumference.

  Grade III = Confluent erosions involving the entire circumference.

  Grade IV = Frank benign ulcer.

Barrett's esophagus was defined as the presence of columnar lined epithelium extending more than 3 cm above the proximal margin of the gastric folds (GE-junction) and around the entire circumference. The presence of hiatus hernia and other abnormalities of the stomach and duodenum were recorded.

The presence and extent of strictures was recorded using the following classification:

Grade 0 = No stricture

Grade I = Visible narrowing of the esophagus but able to pass endoscope

Grade II = Stricture present – unable to pass adult endoscope of 11 mm diameter or more (Grade II was an exclusion criteria)

- At every visit, the following symptom assessments were recorded in the case record forms (using the scale 0= no symptoms or none, 1= mild, 2= moderate, 3= severe):
  - Patient's overall evaluation of symptoms during the last 7 days
  - Heartburn
  - Regurgitation
  - Dysphagia
  - Odynophagia

The patient's predominant reflux symptom was recorded at Visit 1: heartburn, regurgitation, dysphagia, odynophagia, or other.

- Diary card: For the first 3 months of the study, the patient was asked to complete a diary card each day. The variables recorded were as follows: Gaviscon® consumption (daytime and nighttime) and overall severity of reflux symptoms. The following scale was used:
  0 = None =No symptoms
  1 = Mild = Aware of symptoms, easily tolerated, no interference with normal activities
  2 = Moderate = Discomfort enough to cause interference with normal activities
  3 = Severe = Incapacitating, with inability to perform normal activities

Safety:

Safety was determined by the enumeration of adverse events and withdrawals as well as laboratory assessments and physical examination.

- Laboratory assessments: Serum samples for gastrin determination and gastric biopsies for argyrophil cell determination were included as part of the safety assessment for this study. Blood samples for clinical assessment and haematology screen as well as urine samples for glucose and protein analysis were taken at entry into Part 1 (described elsewhere) and on leaving Part 2 (this study).

- Physical examination: Physical examinations were made at entry into Part 1 (described elsewhere) and on leaving Part 2 (this study).
- Adverse events reported by patients were collected at the beginning of the study and at each subsequent visit.

Statistical methods

- Analysis of relapse: Endoscopic and symptomatic remission rates with 95% confidence intervals were determined using life-table analyses. The log-rank test was used to test for differences between the groups. The main comparison was between omeprazole 20 mg and omeprazole 10 mg for endoscopic remission. In addition to the full 12 month analyses, analyses for the first 3 months were performed, as the design of the trial up to then wholly reflected routine clinical practice and patients' continuous (daily) assessment of symptoms were available form diary cards.
- Analysis of diary cards: Comparisons were made between groups using a Chi-square test.
- Predictors of outcome: To determine if any factors (variables) were predictive of a reduced risk of relapse, a logistic analysis was applied.
- Laboratory parameters: Clinical chemistry and hematology results were displayed as patients within and outside the normal range. Gastrin results expressed as changed from baseline and compared between treatment groups using the Wilcoxon Rank Sum test, adjusted for multiple comparisons.
- Changes in physical examination were recorded.
- All patients were considered for enumeration of adverse events and discontinuations.

RESULTS

Subject population

In total, 193 were randomized to 1 of 3 treatment groups: 61 in the omeprazole 10 mg o.m group, 69 in the omeprazole 20 mg group, and 63 in the placebo group. Three patients discontinued the study at an early stage with no measurements of efficacy. Table S1 below gives the disposition of all patients.

Table S1 Disposition of patients per treatment group

	Placebo	Omeprazoel 20 mg	Omeprazoel 20 mg
Randomized	63	69	61
Treated	63	69	61
Included in all patients treated analysis	62	68	60

Table S2 Patient characteristics

	Omeprazole 10 mg	Omeprazole 20 mg	Placebo	Overall
Number of patients	60	68	62	190
Age (years)				
Mean (SD)	53.4 (15.1)	53.4 (14.2)	52.6 (14.1)	53.1 (14.4)
N	60	68	62	190
Min, max	23.0, 78.4	25.9, 77.8	24.4, 79.7	23.0, 79.7
Height (cm)				
Mean (SD)	169.6 (11.1)	170.9 (9.1)	171.9 (8.0)	170.8 (9.5)
Weight (kg)				
Mean (SD)	77.5 (13.1)	75.5 (13.5)	79.6 (11.1)	77.5 (12.7)
Sex				
Male: female	44 : 16	48 : 20	48 : 14	140 : 50
Smoker				
Yes : no	15 : 45	15 : 53	12 : 50	42 : 148
Tobacco consumption				
Mean (SD)	11.4 (7.3)	13.5 (6.1)	12.6 (7.6)	12.5 (6.9)
Drinker				
Yes: no	40 : 20	48 : 20	53 : 9	141 : 49
Alcohol consumption (drinks per week)				
Up to 13	28	31	39	98
14 to 27	9	12	9	30
≥28	3	5	4	12
Number of patients with each grade of esophagitis				
Grade 0	0	0	0	
Grade 1	0	0	0	
Grade 2	43 (72%)	44 (65%)	42 (68%)	
Grade 3	14 (23%)	22 (32%)	15 (24%)	
Grade 4	3 (5%)	2 (3%)	5 (8%)	
Linear extent of esophagitis (cm)				
Mean (SD)	4.51 (2.34) (n=60)	4.72 (2.07) (n=67)	4.43 (2.17) (n=62)	
Stricture passable with an adult endoscope				
	4/60 (7%)	8/68 (12%)	4/62 (6%)	
Endoscopic evidence of Barrett's esophagus				
	5/60 (8%)	1/68 (1%)	5/62 (8%)	
Duration of most recent reflux episode (years)				
Mean (SD)	4.39 (8.43)	2.13 (2.48)	3.47 (6.02)	

Years since esophagitis first diagnosed			
Mean (SD)	1.16 (2.59) (n=52)	1.69 (4.32) (n=55)	1.19 (2.31) (n=57)
Heartburn, N (%)			
None	1 (2)	4 (6)	3 (5)
Mild	17 (28)	20 (29)	16 (26)
Moderate	31 (51)	39 (43)	30 (48)
Severe	11 (18)	15 (22)	13 (21)
Regurgitation, N (%)			
None	14 (23)	19 (28)	18 (29)
Mild	29 (48)	25 (36)	27 (44)
Moderate	15 (25)	23 (34)	14 (23)
Severe	2 (3)	1 (1)	3 (5)
Dysphagia, N (%)			
None	38 (62)	44 (65)	42 (68)
Mild	13 (22)	9 (13)	12 (19)
Moderate	5 (8)	5 (7)	5 (8)
Severe	4 (7)	10 (15)	3 (5)
Odynophagia, N (%)			
Yes	15 (25)	18 (26)	18 (29)
No	45 (75)	50 (74)	44 (71)
Patients overall symptom evaluation, N (%)			
None	0	0	0
Mild	20 (33)	21 (31)	22 (35)
Moderate	39 (48)	38 (56)	27 (44)
Severe	11 (18)	9 (13)	13 (21)
Predominant symptom, N (%)			
Heartburn	44 (76)	47 (69)	47 (78)
Regurgitation	8 (14)	11 (16)	7 (12)
Dysphagia	3 (5)	6 (9)	3 (5)
Odynophagia	3 (5)	3 (4)	2 (3)
Other	1 (2)	1 (1)	1 (2)

A total of 117 patients discontinued treatment; the majority due to a deterioration of reflux esophagitis.

Thirty patients were withdrawn from the study because of non-compliance with either the medication regimen or clinic visits, 10 from the omeprazole 20 mg group, 11 from the omeprazole 10 mg group, and 9 from the placebo group.

Efficacy results

Endoscopic assessments at the final visit, key findings:

- For the patients who relapsed, the severity of esophagitis was comparable between the omeprazole groups whereas the patients in the placebo group tended to have a more severe grade of esophagitis. A similar pattern was seen in the extent of esophagitis.
- For the patients who did not relapse, there was little difference between the 2 omeprazole groups. In the 10 mg group, 93% had grade 0 esophagitis at their final visit, compared to 83% of the 20 mg group. Only 3 patients on placebo had final visit endoscopy data. No statistical tests were performed on the data, due to the small sample sizes with the subgroups.

Results for endoscopic assessments at the final visit are presented in Table S3.

Table S3 Endoscopic assessment at final visit

	Relapse patients			Non-relapse patients		
	Omeprazole			Omeprazole		
	10 mg	20 mg	Placebo	10 mg	20 mg	Placebo
Esophagitis grade, N (%)						
0	2 (8)	3 (16)	2 (4)	25 (93)	34 (83)	2
1	1 (4)	2 (11)	1 (2)	2 (7)	7 (17)	1
2	21 (84)	11 (58)	39 (78)	0	0	0
3	1 (4)	3 (16)	5 (10)	0	0	0
4	0	0	3 (6)	0	0	0
Extent of esophagitis (cm)						
Mean (SD)	2.92 (1.74)	2.13 (1.43)	3.97 (2.34)	0.07 (0.38)	0.30 (0.79)	1.00 (1.73)
N	24	19	49	27	40	3
Min, max	0, 6	0, 5	0, 10	0, 2	0, 3	0, 3
Stricture grade: n (%)						
0	24 (96)	18 (100)	47 (96)	26 (96)	41 (100)	3
1	1 (4)	0	2 (4)	1 (4)	0	0
2	0	0	0	0	0	0
Evidence of Barrett's esophagus						
Yes	1	3 (16)	5 (10)	2 (7)	1 (2)	0
No	24	16 (84)	45 (90)	25 (93)	40 (98)	3
If yes, extent (cm)						
Mean (SD)	9	4.0 (1.0)	6.7 (2.9)	6 (0)	4	---
N	1	3	3	2	1	0
Min, max	9	3, 5	5, 10	6	4	
Nature						
Confluent	1	1	3	2	1	0
Patchy	0	2	1	0	0	0
Histologically proven						
Yes	1	0	4	0	0	0
No	0	2	1	2	1	0
Hiatus hernia						
Yes	9 (36)	9 (50)	16 (33)	10 (37)	17 (41)	0
No	16 (64)	9 (50)	33 (67)	17 (63)	24 (59)	2
Stomach and duodenum normal						
Yes	22 (88)	18 (95)	47 (96)	26 (100)	38 (95)	2
No	3 (12)	1 (5)	2 (4)	0	2 (5)	1

Endoscopic assessment at 3 month, key findings:

- The 2 omeprazole groups were comparable, with 67% of the 10 mg group and 76% of the 20 mg group having grade 0 esophagitis. In comparison, only 20% of the placebo group had grade 0 esophagitis.

Endoscopic grades at month 3 and at the final visit, key findings:

- Endoscopic grades were comparable between the 2 omeprazole groups at month 3 and month 12.
- After 3 months, 41 (68%) patients on omeprazole 10 mg were in endoscopic remission compared with 52 (76%) on omeprazole 20 mg and 14 (23%) on placebo. There was no significant difference between the 2 omeprazole groups but each had statistically higher percentage of endoscopic remission compared to placebo ($p<0.0001$).
- At the final visit, 30 (50%) patients on omeprazole 10 mg were in endoscopic remission compared with 46 (68%) patients on omeprazole 20 mg and 6 (10%) patients on placebo. There was no significant difference between the 2 omeprazole groups but each had statistically higher percentage of endoscopic remission compared to placebo ($p<0.0001$).

Endoscopic relapse, key findings

- Endoscopic relapse, defined as a relapse from grade 2 to grade 4, was observed in 51% of omeprazole 10 mg patients compared to 29% of the omeprazole 20 mg patients and 96% of the placebo patients. There was no significant difference between the 2 omeprazole groups but each had statistically lower percentage of endoscopic relapse compared to placebo ($p<0.0001$).

Clinical symptom assessment, key findings:

- Symptoms at visit 3 – The 2 omeprazole groups were comparable, with 67% (10 mg) and 78% (20 mg) reporting no symptoms overall. In the placebo group, 42% reported no symptoms overall with the most commonly reported symptom being heartburn.
- Symptoms at the final visit, relapsed patients – the most common symptom in all 3 groups was heartburn. Overall, 24% of the 10 mg group, 33% of the 20 mg group, and 21% of the placebo group reported no symptoms.
- Symptoms at the final visit, non-relapsed patients – 81% of the 10 mg group and 89% of the 20 mg group reported no symptoms at all. Only 6 of the placebo patients were classified as non-relapse patients, 3 of whom gave an overall evaluation of no symptoms.

Safety results

Laboratory examination, key findings:

- For haematological and biochemical blood screen, no clinically significant results or results necessitating withdrawal from the study were found.
- For urine analysis on entry, traces of protein were reported in 11 patients and traces of glucose in 2 patients. Positive results were reported in 1 patient (protein and glucose) with known diabetes mellitus.

Adverse events, key findings:

- In general, the nature and incidence of adverse events were comparable across the treatment groups.
- Seven serious adverse events, 3 of which led to withdrawal, were reported during the course of the study. None were considered to be causally related to the study medication.

- Nine patients discontinued treatment due to an adverse event including 3 who suffered serious adverse events as noted above.

Additional safety information is presented in Table S4

Table S4 Long-term omeprazole study data

Trial	Treatment	Omep 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-653B	Omeprazole 10 mg	10	12	61	247.0	41.3	52.5	1	0	0	0	0	0	0
	Omeprazole 20 mg	20	12	69	263.0	49.7	40.6	0	0	0	0	0	0	0
	Placebo		12	63	113.0	19.5	90.5	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 Losec™ (omeprazole), Healthcare Professionals should view their specific country information.