Drug product:	Omeprazole	**SYNOPSIS**	
Drug substance(s):	Omeprazole		
Edition No.:	1		
Study code:	D9584C00003		
Date:	5 January 2006		

A histopathological evaluation of Helicobacter pylori eradication in patients treated in long-term compassionate use study with omeprazole (Losec®). An open study using two antibiotics with omeprazole for seven days or omeprazole alone and with long-term follow up.

Abbreviated Clinical Study Report

Publications

None at the time of this report

Study dates

First subject enrolled *10 March 1997*

Last subject completed *8 January 2004*

Phase of development

Therapeutic confirmatory (III)

Objectives

The primary objective is to evaluate histopathology (gastritis) changes in the antrum and corpus mucosa after the eradication of *H. pylori*, using triple therapy, in patients continuously treated with omeprazole for one year or more.

The secondary objective is to estimate *H. pylori* eradication rate in patients treated with long-term omeprazole maintenance therapy.

Study design

This was an open study following patients previously included in study I-565. In study I-565 patients with confirmed peptic ulcer or reflux esophagitis refractory to H_2-receptor antagonists were included. *H.pylori* positive and *H.pylori* negative patients were included in the present study.

After informed consent was obtained, *H. pylori* positive patients were treated for *H. pylori* eradication. If patients were hypersensitive to amoxycillin (or penicillin) the treatment "arm" with metronidazole was used. If patients were still *H. pylori* positive at the 3 month visit, they were offered the same eradication treatment once more. In patients given *H. pylori* eradication therapy the dose of omeprazole had to be a minimum of 20 mg twice daily (BID) during the 7 days of eradication treatment and continued after this week with the same dose of omeprazole as prior to the eradication treatment. *H. pylori* negative patients continued on the current omeprazole maintenance dose.

Serology, histopathology, HUT-test and/or ^{13}C-urea breath test (UBT) were used to detect *H. pylori.* All patients, *H.pylori* negative and positive, maintained on long-term omeprazole treatment. Both groups were followed with histopathological evaluation until the cut off date, 31 December 2003.

Target subject population and sample size

Up to 31 *H. pylori* positive and 35 *H. pylori* negative patients from the study I-565 (a study including patients with confirmed peptic ulcer or reflux esophagitis refractory to H_2-receptor antagonists) were to be followed in this study. These patients had been treated with omeprazole for 7 years or more before entering the present study.

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

For *H. pylori* positive patients Helicobacter eradication treatment:

- omeprazole 20 mg BID, amoxicillin 1000 mg BID, and clarithromycin 500 mg BID for one week

or in case of hypersensitivity to amoxicillin (or penicillin):

- omeprazole 20 mg BID, metronidazole 400 mg BID and clarithromycin 250 mg BID for one week.

For *H .pylori* negative patients and after successful eradication treatment: omeprazole maintenance dose.

Duration of treatment

Maintenance treatment with omeprazole throughout the study period. One week eradication treatment for *H. pylori* positive patients.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Primary variable:

- Histopathological assessment of gastritis

Secondary variables:

- *H.pylori* status as determined by *H.pylori* serology (antibodies IgG), histopathology, HUT-test and UBT
- Endoscopy

Safety

Recording of Adverse events, serious adverse events and adverse events leading to discontinuation and clinical laboratory data (haematology and clinical chemistry).

Statistical methods

In this non-randomised study only descriptive statistics were used.

Patient population

All patients participating in this study had been treated with omeprazole for a minimum of 7 years before entering this study.

Table S1 Patient population and disposition

		Total	
Population			
N enrolled		53	
Demographic characteristics			
Sex (n and % of patients)	Male	30	(57)
	Female	23	(43)
Age (years)	Mean (range)	59	(32, 82)
Race (n and % of patients)	Caucasian	52	(98)

		Total	
	Asian	1	(2)
Baseline characteristics			
H. pylori status (n and % of patients)	Negative	37	(70)
	Positive	16	(30)
Disposition			
N (%) of patients who	completed	21	
	discontinued	32 [c]	
N analysed for safety[a]		53	
N analysed for efficacy[b]		50	

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
[b] Number of patients with both baseline and last visit histopathological assessment
c 14 patients discontinued due to study cut off in December 2003

16 patients were *H.pylori* positive at baseline, 9 of these patients received eradication treatment (amoxicillin and clarityhromycin) according to the clinical study protocol. Of these 9 patients one patient remained *H.pylori* positive throughout the study whilst the other 8 patients became *H.pylori* negative. Four patients who were *H.pylori* positive at baseline became *H.pylori* negative although not given any *H.pylori* eradication treatment in the study. Of the 37 *H.pylori* negative patients 34 remained *H.pylori* negative and for 3 patients the *H.pylori* status at the last visit is not known. Two patients classified as *H.pylori* negative according to the clinical study protocol received eradication treatment due to positive CLO-test results.

Efficacy and pharmacokinetic results

Long-term treatment with omeprazole (daily dose of 20 mg or more) in patients who were *H.pylori* positive at baseline and *H.pylori* negative at last visit resulted in a general improvement of signs of gastritis and was not associated with any dysplastic changes in the corporal or antral mucosa.

Safety results

Long-term treatment with omeprazole in a patient population including many cases with serious concurrent illnesses did not raise any safety concerns.

Table S2 Number of patients who had an adverse event in any category (safety population)

Category of adverse events[a]	Omeprazole (without eradication treatment) (n=42)	During OAC eradication treatment (n=11)	Omeprazole before and after OAC eradication treatment (n=11)	Total* (n=53)
Any adverse events	21	4	10	31
Serious AEs	18	0	4	22
Serious AEs leading to death	6	0	1	7
Serious AEs not leading to death	15	0	4	19
Discontinuation of study treatment due to AEs	0	1[c]	0	0
Related AEs[b]	1	4	3	4
Severe AEs	3	3	5	8

OAC = omeprazole, amoxicillin, clarithromycin

[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] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

[c] Patient 1010 was treated with OAC when AE started, only the antibiotic was withdrawn, the omeprazole treatment was continued.

*Note that patients with an adverse event during eradication treatment could continue to have the same adverse event after the eradication. Thus numbers in the three columns do not necessarily add up to the number provided in the column total.

Table S3 Number of adverse events in any category (safety population)

Category of adverse events[a]	Omeprazole (without eradication treatment) (n=42)	During OAC eradication treatment (n=11)	Omeprazole before and after OAC eradication treatment (n=11)	Total* (n=53)
Any adverse events	41	7	21	62
Serious AEs	37	0	7	44
Discontinuation AEs	0	2[c]	0	0
Other significant AEs	0	0	0	0
Related AEs[b]	1	7	5	6
Severe AEs	4	6	9	13

OAC = omeprazole, amoxicillin, clarithromycin

[a] 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.

[b] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

[c] Patient 1010 was treated with OAC when AE started, only the antibiotic was withdrawn, the omeprazole treatment was continued.

*Note that patients with an adverse event during eradication treatment could continue to have the same adverse event after the eradication. Thus numbers in the three columns do not necessarily add up to the number provided in the column total.

Table S4 Number of patients with the most commonly reported non-serious adverse events recorded up to Visit 5, presented by preferred term in descending frequency, sorted by the summarised total number (safety population)

Preferred term	Omeprazole (without eradication treatment) (n=42)	During OAC eradication treatment (n=11)	Omeprazole before and after OAC eradication treatment (n=11)	Total* (n=53)
Diarrhoea	0	4	5	5
Circulatory collapse[a]	0	2	2	2
Back pain	0	0	1	1
Bronchitis	0	0	1	1
Diabetes mellitus	1	0	0	1
Hepatic enzyme increased	0	0	1	1
Hoarseness	0	0	1	1
Hyperthyroidism	1	0	0	1
Influenza	0	0	1	1
Inguinal hernia	1	0	0	1
Joint swelling	1	0	0	1
Loose stools	0	0	1	1
Weight decreased	0	1	1	1

OAC = omeprazole, amoxicillin, clarithromycin

[a] During the OAC treatment two "circulatory collapse" events were reported as non-serious events. The patients recovered and continued the omeprazole treatment according to the protocol. The events were assessed by the investigator as probably related to the antibiotic treatment.

* Note that patients with adverse event during eradication treatment could continue to have the same adverse event after the eradication. Thus numbers in the three columns do not necessarily add up to the number provided in the column total.

Table S5 Number of patients with reported serious adverse events, presented by system organ class in descending frequency, sorted by the summarised total number (safety population)

System organ class	Omeprazole (without eradication treatment) (n=42)	During OAC eradication treatment (n=11)	Omeprazole before and after OAC eradication treatment (n=11)	Total (n=53)
Cardiac disorders	7	0	1	8
Infections and infestations	3	0	2	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	0	1	4
Nervous system disorders	4	0	0	4
Gastrointestinal disorders	1	0	1	2
Vascular disorders	2	0	0	2

System organ class	Omeprazole (without eradication treatment) (n=42)	During OAC eradication treatment (n=11)	Omeprazole before and after OAC eradication treatment (n=11)	Total (n=53)
Endocrine disorders	1	0	0	1
Reproductive system and breast disorders	1	0	0	1
Surgical and medical procedures	1	0	0	1
Respiratory, thoracic and mediastinal disorders	1	0	0	1
Renal and urinary disorders	1	0	0	1
Injury, poisoning and procedural complications	1	0	0	1
Metabolism and nutrition disorders	1	0	0	1
Psychiatric disorders	0	0	1	1
Musculoskeletal and connective tissue disorders	1	0	0	1

OAC = omeprazole, amoxicillin, clarithromycin

Adverse events (AEs) were recorded up to visit 5. Thereafter, only serious adverse events (SAEs) and discontinuations due to AE were recorded. The most commonly reported serious adverse event was cardiac failure (system organ class cardiac disorders), which was reported for three patients in the omeprazole treatment group. The other SAEs reported were from several different system organ classes.