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NAME OF COMPANY **ASTRA HÄSSLE AB** TRADE NAME(S) NAMES OF ACTIVE INGREDIENT(S) INN Omeprazole Ranitidine	**Clinical Study Synopsis** REFERENCE IN THE DOSSIER VOLUME REF. NUMBER PAGE	(FOR NATIONAL AUTHORITY USE ONLY) STUDY CODE I-665 REPORT NO.

TITLE OF THE STUDY

EFFECTS OF ELIMINATION OF GASTRO-OESOPHAGEAL REFLUX BY OMEPRAZOLE ON PARAMETERS OF PREMALIGNANT CHANGE AND DEDIFFERENTIATION (I.E. CELL KINETICS AND PLASMINOGEN ACTIVATORS), ON CLASSICAL HISTOLOGICAL CRITERIA, AND FURTHER ON THE EXTENT OF BARRETT'S EPITHELIUM

A synopsis referring to demography, safety of treatment and extent of Barrett's epithelium before and at the end of treatment

STUDY CENTRES: Multicentre study including three centres in The Netherlands.

PUBLICATION (REFERENCE): Peters FTM, Ganesh S, Kuipers EJ et al. Gastroenterology 1995;108:A525.

STUDY PERIOD: 26 February 1992 - 3 April 1996

CLINICAL PHASE: IIIb/IV

OBJECTIVES: Primary aim: To compare the effects of the different treatments on the histological parameters (i.e. dysplasia, metaplasia, inflammation) and the parameters of premalignant change (i.e. cell kinetics and plasminogen activators) in Barrett's epithelium and relate these to the degree of acid gastro-oesophageal reflux.

Secondary aim: To compare the effects of the different treatments on the extent of the Barrett's epithelium.

N.B. This synopsis addresses only the secondary aim. The primary aim will be addressed in a future clinical report.

STUDY DESIGN: This study was performed using a randomised, double-blind, double-dummy, parallel-group design, as shown in Figure 1. Patients were randomised in the proportion 1:1 to treatment with either omeprazole 40 mg b.i.d. or ranitidine 150 mg b.i.d. for up to two years. Patients who at screening were requiring acid reducing drugs in doses stronger than the equivalent to ranitidine 150 mg b.i.d. entered a run-in period of three months on ranitidine 150 mg b.i.d., if medically justified.

Patients who were judged to be unfit to change their acid reducing drugs and who had unacceptable reflux symptoms during ongoing treatment were given open label omeprazole 40 mg b.i.d. for up to two years. Patients who at any time during the double-blind treatment presented with unacceptable oesophageal symptoms were transferred to the open treatment with omeprazole 40 mg b.i.d. Visits were scheduled quarterly and a summary of the assessments performed at each visit is given in Figure 1.

NUMBER OF PATIENTS: A total of 72 patients were enrolled (48 males and 24 females, mean age 56 years), of which 33 were randomised to omeprazole 40 mg b.i.d. and 35 to ranitidine 150 mg b.i.d. Four patients commenced open treatment with omeprazole 40 mg b.i.d. at enrolment.

DIAGNOSIS AND CRITERIA FOR INCLUSION: Outpatients of either sex, aged >18 years and <75 years, who had endoscopically and histologically proven diagnosis of Barrett's oesophagus extending 3 cm or more proximal to the gastro-oesophageal junction. Patients should also have a documented acid reflux (defined as oesophageal pH <4 for >1% of the 24-hour period), measured by 24-hour intra-oesophageal pH-metry during ongoing anti-reflux treatment within a month prior to visit 1. Patients should also give their written or witnessed verbal consent.

INVESTIGATIONAL THERAPY: Omeprazole 40 mg b.i.d. The 40 mg capsules used in the study were produced by Astra AB, Sweden, and the batch numbers were: H 743-2-1-3, H 743-2-1-4 and H 743-2-1-5.

REFERENCE THERAPY: Ranitidine 150 mg b.i.d. The 150 mg tablets used in the study were produced by Glaxo, Italy, and the batch numbers were: H 538-5-1-6, H 538-5-1-7, H 538-5-1-8, H 538-5-1-9, H 538-5-1-10, H 538-5-1-11 and H 538-5-1-12.

DURATION OF TREATMENT: 24 months.

ASSESSMENT METHODS: Endoscopic examination of the oesophagus and stomach was performed at entry, before commencement of study medication, and was repeated at the 3, 9, 15 and 24-month visits. The extent of Barrett's epithelium was determined by

measuring the distance between the squamocolumnar junction or Z-line and the gastro-oesophageal junction.

STATISTICAL METHODS: An all-patients-treated analysis was performed. The mean extent (cm) of Barrett's epithelium was calculated for each treatment at visit 1 and at the last visit. For patients who were transferred from double-blind to open treatment the last measurement on double-blind treatment was used. The confidence intervals (95%) for the true mean of the extent of Barrett's epithelium were calculated for each treatment at visit 1 and at the last visit as the observed mean ± the standard error of the observed mean multiplied by the 2.5 % t-quantile with the appropriate degrees of freedom. The confidence intervals (95%) for the mean change from visit 1 to the last visit were calculated for each treatment in a similar way as described above. A two sample *t*-test for testing the hypothesis that there is no difference between omeprazole 40 mg b.i.d. and ranitidine 150 mg b.i.d. with respect to the change from baseline to the last visit was also performed.

SUMMARY OF RESULTS: A flow chart of the numbers of patients entering, completing or discontinuing the study is shown in Figure 2. One patient who was randomised to double-blind treatment with omeprazole 40 mg b.i.d. did not take any study medication and was therefore excluded from the statistical analyses. Five patients who were randomised to double-blind treatment did not enter the run-in period despite they were on a too high dose of acid reducing drugs at screening. These patients were included in the all-patients-treated analysis.

A summary of the patients' baseline characteristics is shown in Table 1. No major differences were noted between the two double-blind treatment groups with regard to baseline characteristics.

The mean extent of Barrett's epithelium at baseline was 6.0 and 5.6 cm for the randomised patients in the omeprazole and ranitidine groups, respectively (Table 2). The statistical analysis showed that there was a significant decrease in the length of the Barrett's epithelium from the first to the last investigation in the randomised omeprazole group but not in the ranitidine group (-0.7 cm vs +0.1 cm; Table 3). Furthermore, the two sample t-test showed that this difference between omeprazole and ranitidine was statistically significant ($p = 0.004$). The mean duration of treatment for the randomised omeprazole group (690 days) was comparable to the ranitidine group (670 days), as shown in Table 4.

Safety in terms of adverse events, serum gastrin and histology of gastric body mucosa is reported in appendices 1 and 2.

APPENDICES:

Appendix No. 1

Adverse Event Report
Study Code: I-665
Dated: 1997-03-13

Appendix No. 2

Analysis of gastric biopsies and serum gastrin
Study Code: I-665
Dated: 1997-03-14

Table 1. Summary of patients' baseline characteristics by treatment.

		Double-blind treatment		Open treatment
		Omeprazole	Ranitidine	Omeprazole
		N	N	N
		32	35	4
Sex				
	Male	24	23	1
	Female	8	12	3
Ethnic origin				
	Unknown	1	0	0
	Caucasian	31	35	4
Smoking (cigarettes per day or equivalent)				
	None	24	24	2
	1-10	4	6	0
	10-20	4	5	2
Duration of reflux disease				
	Unknown	1	0	0
	< 5 years	7	15	2
	> 5 years	24	20	2
Age (years)				
	Mean	57.0	55.0	54.9
	SD	11.7	12.8	13.0
	Min	21	23	35
	Max	73	74	63
Weight (kg)				
	Mean	76.9	76.1	65.5
	SD	9.3	13.7	4.9
	Min	55	49	60
	Max	98	109	72

Table 2. Estimates and 95 % confidence intervals for the true mean of the extent of Barrett's epithelium (B.E.) at baseline for all patients treated (including those patients with no last measurement on double-blind treatment).

Treatment	Parameter	N	Mean extent of B.E. (cm)	Lower	Upper
Omeprazole	Baseline	32	6.00	4.95	7.05
Ranitidine	Baseline	35	5.56	4.69	6.42
Omeprazole (Open treatment)	Baseline	4	4.75	1.47	8.03

Table 3. Estimates and 95% confidence intervals for the true mean of the extent of Barrett's epithelium (B.E.) at baseline and at the last visit.

Treatment	Parameter	N	Mean extent of B.E. (cm)	Lower	Upper
Omeprazole	Baseline	29	5.96	4.86	7.07
	Last visit	29	5.31	4.23	6.39
	Last visit - Baseline	29	-0.66	-1.01	-0.37
Ranitidine	Baseline	32	5.67	4.74	6.61
	Last visit	32	5.75	4.83	6.67
	Last visit - Baseline	32	0.08	-0.27	0.43
Omeprazole	Baseline	4	4.75	1.47	8.03
(Open treatment)	Last visit	4	4.25	1.53	6.97
	Last visit - Baseline	4	-0.50	-2.55	1.55

Table 4. Mean duration of treatment (number of days) for patients with a measurement of Barrett's epithelium both at baseline and at the last visit.

Treatment	N	Mean (days)	SD	Min	Max
Omeprazole	29	690	168.1	90	794
Ranitidine	32	670	194.5	85	826
Omeprazole (Open treatment)	4	630	237.2	274	761