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Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results

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SUMMARY

Aim: To compare the efficacy of esomeprazole, 20 mg once daily, vs. lansoprazole, 15 mg once daily, for the maintenance treatment of patients with healed reflux oesophagitis.

Methods: During the initial open healing phase, 1391 patients with endoscopically verified reflux oesophagitis and a history of heartburn, with or without acid regurgitation, received esomeprazole 40 mg for 4–8 weeks. Patients who were healed (identified by endoscopy at 4 or 8 weeks) and symptom free were then randomized to receive 6 months of treatment with esomeprazole, 20 mg once daily, or lansoprazole, 15 mg once daily.

Results: Esomeprazole, 20 mg once daily, maintained a significantly higher proportion of patients in remission than lansoprazole, 15 mg once daily, over 6 months [83% (95% CI, 80–86%) of esomeprazole recipients compared with 74% (95% CI, 70–78%) of lansoprazole recipients; $P < 0.0001$; life table estimates]. When data were analysed according to baseline Los Angeles grade classification, esomeprazole, 20 mg once daily, achieved consistently higher remission rates across all grades of disease severity, whereas the efficacy of lansoprazole decreased to a greater extent with increasing severity of reflux oesophagitis.

Conclusion: Esomeprazole, 20 mg once daily, is more effective than lansoprazole, 15 mg once daily, in maintaining remission in patients with healed reflux oesophagitis.

INTRODUCTION

Reflux oesophagitis is a chronic, recurring disease that requires initial healing and symptom resolution, followed by effective continuous maintenance therapy to prevent relapse. Reflux oesophagitis can lead to complications, such as peptic stricture and ulcer, if not successfully managed in the long term.[1] Significant morbidity associated with oesophagitis has been observed in approximately 75% of patients followed up for 10 years after the initial diagnosis.[2]

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Furthermore, studies in healed reflux oesophagitis patients have reported relapse rates of up to 80–90% within 6–12 months after withdrawal of drug therapy.[3–5]

Proton pump inhibitors provide highly effective maintenance therapy, significantly reducing relapse rates,[6–9] and are therefore recommended as first-line treatment for the maintenance of healed oesophagitis.[9–11]

Esomeprazole, the *S*-isomer of omeprazole, is highly effective for the treatment of gastro-oesophageal reflux disease. Pharmacodynamic studies have demonstrated significantly greater intragastric acid control when the standard dose of esomeprazole (40 mg) is compared with standard doses of all other proton pump inhibitors in patients with gastro-oesophageal reflux disease and healthy volunteers.[12–15] Furthermore, esomeprazole 20 mg has been shown to provide more effective intragastric acid control than lansoprazole 15 mg in healthy volunteers.[16]

This pharmacodynamic profile may translate into clinical benefits over other proton pump inhibitors in the management of gastro-oesophageal reflux disease. Esomeprazole is the first proton pump inhibitor to demonstrate greater efficacy than both omeprazole and lansoprazole for the healing of reflux oesophagitis and the resolution of heartburn.[17–19] Furthermore, placebo-controlled clinical studies have demonstrated that esomeprazole is a highly effective treatment for the maintenance of patients with healed reflux oesophagitis.[20, 21]

For the maintenance therapy of reflux oesophagitis, guidelines published by the National Institute of Clinical Excellence in the UK[22] and the Genval Guidelines[9] both recommend that treatment should be stepped down to the lowest effective dose of proton pump inhibitor that controls symptoms. The licensed dose of esomeprazole for the healing of reflux oesophagitis is 40 mg once daily (od) (20 mg is also a licensed dose for the healing of reflux oesophagitis in the USA). In line with these treatment guidelines, esomeprazole, 20 mg od, is the commonly recommended maintenance dose. Similarly, lansoprazole, 30 mg od, is the recommended dose for the healing of reflux oesophagitis, but it is recommended that this dose is reduced to 15 mg od when prescribed for maintenance therapy.[23, 24]

This study was designed to compare the remission rates (assessed by endoscopy and symptom evaluation) during 6 months of treatment with maintenance doses of esomeprazole (20 mg od) or lansoprazole (15 mg od) in patients with healed reflux oesophagitis.

MATERIALS AND METHODS

Study design, patients and treatments

This was a multi-centre ($n = 148$), parallel-group, two-phase study consisting of an initial open-label healing phase, followed by a randomized, double-blind, double-dummy, maintenance phase, conducted in sites throughout Europe and South Africa. The study was undertaken according to the principles of the Declaration of Helsinki and local ethics committee approval was obtained before the start of the study. Written, informed consent was obtained from all patients before study entry.

Patients over 18 years of age, with a history of heartburn (with or without acid regurgitation) and with endoscopically verified reflux oesophagitis (Los Angeles grade A–D),[25] were eligible for inclusion in the healing phase of the study. After 4 weeks of treatment with esomeprazole, 40 mg od, asymptomatic patients (defined as the absence of heartburn and acid regurgitation during the 7 days prior to the clinic visit) underwent endoscopy. Those with healed oesophagitis were randomized to receive maintenance treatment with either esomeprazole, 20 mg od, or lansoprazole, 15 mg od, for 6 months. Symptomatic and unhealed patients continued treatment for a further 4 weeks and were then endoscoped. Asymptomatic, healed patients at 8 weeks were randomized to receive maintenance treatment; those who were unhealed or healed with persistent symptoms ($n = 63$) were discontinued from the study at this stage. Randomization was performed by computer in a 1 : 1 ratio for esomeprazole and lansoprazole. Blinding was maintained using double-dummy capsules, identical in appearance and taste to the corresponding esomeprazole or lansoprazole capsules.

Patients were excluded if they had a history of gastrointestinal surgery; evidence of Zollinger–Ellison syndrome, upper gastrointestinal malignancy, abnormal absorption or motility disorders; gastric or duodenal ulcer and/or duodenal erosions within the last 3 months; oesophageal stricture; Barrett's oesophagus (> 3 cm); or any sign indicating serious or malignant disease. Female patients were required to have a negative pregnancy test, be non-lactating or using a medically acceptable form of birth control. In addition, patients using a proton pump inhibitor for more than 10 days during the 28 days before baseline, patients with contra-indications to the study drugs and those requiring continuous concomitant therapy with

medication that might affect the interpretation of the treatment outcome [anticholinergics, cisapride, prostaglandin analogues, non-steroidal anti-inflammatory drugs or aspirin (except for ≤ 165 mg/day for cardiovascular prophylaxis)] were excluded from the study. In addition, histamine-2 receptor antagonists, prokinetics and *Helicobacter pylori* eradication therapy were not allowed during the study period.

A full medical history and physical examination were carried out prior to the start of the healing phase, together with an upper endoscopy, including a biopsy to assess the *H. pylori* status. All patients were tested for the presence of *H. pylori* at baseline using the HUT test (Helicobacter urease test) and were entered into the study regardless of subsequent *H. pylori* status. Laboratory safety measurements, which included haematology, clinical chemistry and urinalysis, were performed at baseline, week 4 (only for healed patients entering the maintenance phase), week 8 and at months 3 and 6.

Patients were instructed to take study medication in the morning before breakfast with a glass of water. Treatment compliance was assessed by counting all unused medication.

Efficacy measurements and variables

The primary efficacy variable was the remission rate during the 6-month maintenance phase, based on endoscopy and/or symptom evaluation. Remission rates were calculated by assessing the time to relapse in patients during the maintenance phase. The secondary efficacy variables were the remission rate during maintenance treatment based on endoscopic criteria only, healing and symptom resolution during the initial healing phase and assessment of symptoms during the maintenance phase.

Endoscopy was performed at baseline (within 7 days of visit 1), at week 4 and/or week 8 of the healing phase and at 3 and 6 months during the maintenance phase, or between clinic visits in the case of symptom relapse. Symptoms (heartburn, acid regurgitation, dysphagia and epigastric pain) were assessed retrospectively by the investigator at each visit during the healing phase (baseline, week 4 and week 8) and during the maintenance phase (months 1, 3 and 6). Symptoms were classified as none, mild (awareness of symptoms, but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities) and severe (incapacitating, with inability to perform normal activities). For the determination of endoscopic and symptomatic relapse, patients were instructed to report any moderate or severe heartburn and/or acid regurgitation persisting over three consecutive days. Additional endoscopy was performed in these patients and, if oesophagitis (Los Angeles grade A–D) was found, or if the patient was not willing to continue in the study because of reflux symptoms, this was classified as a relapse and the patient was discontinued from the study.

Statistical analysis

The SAS System (version 8.1) was used to analyse and produce all summary tables and descriptive and inferential statistics.

Intention-to-treat analyses were performed for both the primary and secondary efficacy variables of the 6-month remission rates. A per protocol analysis was also performed for the primary variable. Patients were excluded from the intention-to-treat analysis if they had not received any dose of the study drug in the maintenance phase, if they had received unknown study drug during the maintenance phase or if they had persistent oesophagitis at entry into the maintenance phase. For the primary analysis of the remission rates, the treatments were compared for time to relapse using life table methods, and were statistically analysed using the log rank test. Data were censored for patients discontinuing for reasons other than relapse, including patients discontinuing due to reflux symptoms with no endoscopic relapse. Adverse event data were presented descriptively.

Sample size calculations assumed a remission rate at 6 months of 75% for lansoprazole and 85% for esomeprazole. It was calculated that 500 patients would be required in each treatment group (1000 patients in total) during the maintenance phase to detect this difference using a two-sided log rank test with a 5% significance level and a 95% power, allowing for 15% of patients being excluded from the per protocol analysis. To ensure that the required minimum of 1000 patients were randomized to receive maintenance treatment, 1391 patients were recruited into the healing phase.

RESULTS

Patient characteristics and disposition

In total, 1391 patients were enrolled into the 4–8-week healing phase. The cumulative 8-week endoscopic

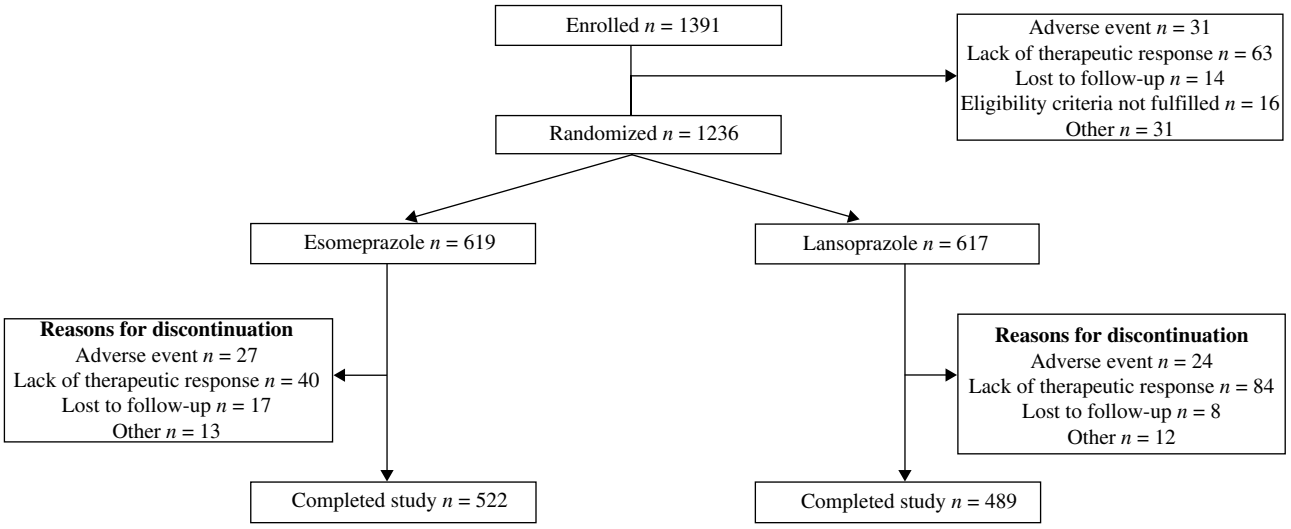

Figure 1. Overall study design and patient disposition.

healing rate in these patients was 96.5% (life table estimate). Heartburn and acid regurgitation were resolved in 90.6% of patients at week 8. Hence, following the initial healing phase, 1236 patients, who were both healed (determined by endoscopy) and asymptomatic (no heartburn or acid regurgitation during the 7 days prior to the clinic visit), were randomized to receive maintenance treatment with esomeprazole, 20 mg od ($n = 619$), or lansoprazole, 15 mg od ($n = 617$), and 1011 completed the study (esomeprazole, $n = 522$; lansoprazole, $n = 489$). The main reasons for study discontinuation were a lack of therapeutic response, adverse events and loss to follow-up (Figure 1). The two treatment groups were similar with respect to baseline characteristics, Los Angeles grade classification, *H. pylori* status and the frequency and severity of gastro-oesophageal reflux disease symptoms (Table 1). A total of 1224 patients were included in the intention-to-treat population and were analysed for efficacy (esomeprazole, $n = 615$; lansoprazole, $n = 609$; 12 patients were excluded from the randomized population because they did not take the study drug during the maintenance phase or because persistent oesophagitis was present at entry to the maintenance phase).

Table 1. Baseline demographics and disease characteristics (prior to the healing phase) of the intention-to-treat population

	Esomeprazole 20 mg ($n = 615$)	Lansoprazole 15 mg ($n = 609$)
Gender (male)	388 (63.1%)	356 (58.5%)
Race (Caucasian)	599 (97.4%)	595 (97.7%)
Age (mean) (years)	49.3	49.2
Los Angeles grade		
Grade A	232 (37.7%)	229 (37.6%)
Grade B	269 (43.7%)	278 (45.6%)
Grade C	95 (15.4%)	82 (13.5%)
Grade D	19 (3.1%)	20 (3.3%)
History of reflux symptoms (≥ 1 year)	480 (78.1%)	485 (79.7%)
H. pylori status		
Positive	184 (29.9%)	195 (32.0%)
Missing	29 (4.7%)	21 (3.4%)

Remission rates

Esomeprazole, 20 mg od, maintained a significantly higher proportion of patients in remission than did lansoprazole, 15 mg od, over the 6-month course of treatment ($P < 0.0001$; log rank test; intention-to-treat analysis) (Figure 2). Life table estimates indicated that, after 6 months of treatment, 83% [95% confidence interval (CI), 80–86%] of esomeprazole recipients were in remission compared with 74% (95% CI, 70–78%) of lansoprazole recipients.

When the data were analysed according to the baseline Los Angeles grade classification, esomeprazole, 20 mg od, achieved consistently higher remission rates (life table estimates) across all grades of baseline disease severity, whereas the efficacy of lansoprazole, 15 mg od,

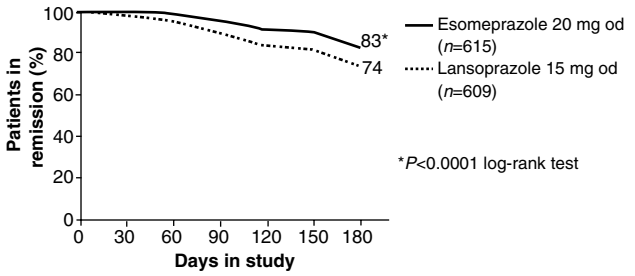

Figure 2. Life table estimates of time to relapse by days in patients randomized to receive esomeprazole, 20 mg once daily, or lansoprazole, 15 mg once daily, for maintenance treatment of healed reflux oesophagitis.

tended to decrease to a greater extent with increasing severity of oesophagitis. In milder grades of disease severity (Los Angeles grades A and B) and in more severe disease (Los Angeles grades C and D), esomeprazole achieved significantly higher remission rates than lansoprazole ($P < 0.01$ for both; Figure 3). Remission rates for baseline Los Angeles grades A, B, C and D for esomeprazole and lansoprazole were 87% vs. 84%, 83% vs. 72% ($P < 0.01$), 75% vs. 61% ($P < 0.05$) and 77% vs. 50% ($P < 0.05$), respectively.

The remission rate in *H. pylori*-positive patients was 80% and in *H. pylori*-negative patients was 78% ($P = 0.6432$; log rank test stratified by treatment group). Therefore, the presence or absence of *H. pylori* had no effect on the remission rates in these patients.

Esomeprazole was also significantly more effective than lansoprazole for the secondary end-point of relapse according to endoscopic criteria only; 84% of patients remained healed with esomeprazole compared with 76% for lansoprazole (life table estimates; $P < 0.0002$).

Symptom control

At 6 months, a significantly greater proportion of esomeprazole recipients were free from heartburn, acid regurgitation and epigastric pain compared with lansoprazole recipients ($P < 0.01$, $P < 0.001$ and $P < 0.05$, respectively; chi-square test) (Figure 4). Furthermore, at the earlier time points of 1 and 3 months, the proportion of patients free from heartburn was also significantly higher in the esomeprazole group than in the lansoprazole group (89.3% vs. 83.6%, $P < 0.01$ and 83.1% vs. 78.5%, $P < 0.05$, respectively).

Safety and tolerability

Of the 1236 patients randomized to receive maintenance treatment, five were excluded from the safety analysis as they had not received study medication ($n = 1$), had received unknown study medication ($n = 2$) or had received medication, but with no subsequent data ($n = 2$). The safety population assessed during the maintenance phase therefore consisted of 1231 patients. Both esomeprazole and lansoprazole were well tolerated over the 6-month maintenance treatment period and were found to have similar adverse event profiles. The most frequently reported adverse events in both treatment groups were diarrhoea and flatulence (Table 2).

Three patients receiving lansoprazole, 15 mg od, and none receiving esomeprazole, 20 mg od, reported serious adverse events that were considered by the investigator to be related to the study drug. These serious adverse events included rash, arthralgia and confusion with hallucination (the last two were both experienced by the same patient). Three fatalities

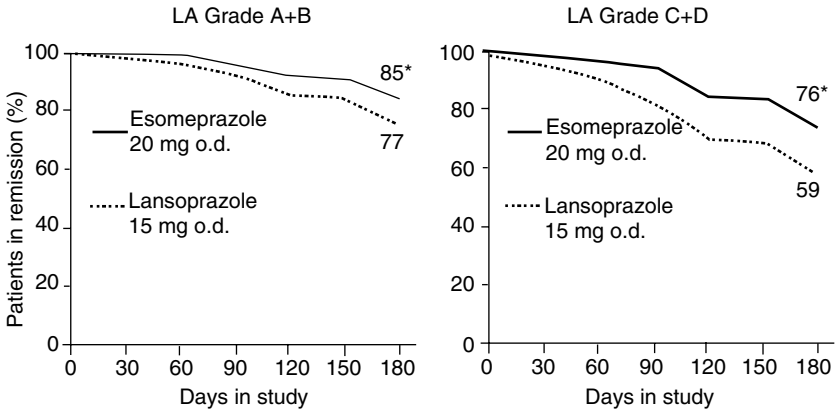

Figure 3. Life table estimates of time to first relapse after treatment with esomeprazole, 20 mg once daily, or lansoprazole, 15 mg once daily, in patients with baseline Los Angeles grade A and B ($n = 501$ for esomeprazole; $n = 507$ for lansoprazole) and Los Angeles grade C and D ($n = 114$ for esomeprazole; $n = 102$ for lansoprazole) in the intention-to-treat population. *$P < 0.01$, log rank test.

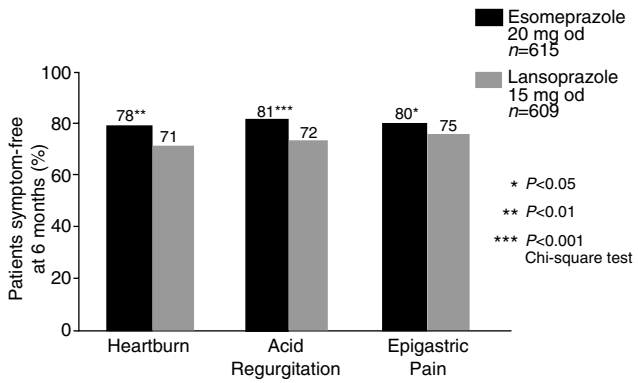

Figure 4. The proportion of patients free from symptoms after 6 months of treatment with esomeprazole, 20 mg once daily, or lansoprazole, 15 mg once daily, for maintenance treatment of healed reflux oesophagitis.

Table 2. Most common adverse events reported after 6 months of daily treatment with esomeprazole 20 mg or lansoprazole 15 mg (patient incidence at least 2% in either treatment group at month 6)

	Esomeprazole 20 mg ($n = 617$)	Lansoprazole 15 mg ($n = 614$)
Diarrhoea	35 (5.7)	42 (6.8)
Flatulence	33 (5.3)	23 (3.7)
Respiratory infection	29 (4.7)	23 (3.7)
Headache	26 (4.2)	22 (3.6)
Abdominal pain	21 (3.4)	14 (2.3)
Nausea	18 (2.9)	17 (2.8)
Bronchitis	16 (2.6)	10 (1.6)
Pharyngitis	9 (1.5)	16 (2.6)
Constipation	7 (1.1)	22 (3.6)
Dry mouth	6 (1.0)	12 (2.0)

occurred in the esomeprazole group, but none was considered to be related to the study drug. One subject died of colon carcinoma, another of pulmonary embolism and a third was found dead at home with no cause of death obtainable.

Drug treatment was discontinued due to adverse events in 29 (4.7%) and 32 (5.2%) patients in the esomeprazole and lansoprazole treatment groups, respectively. There were no clinically meaningful differences in laboratory safety test results during the course of the study.

DISCUSSION

This study has shown that, in patients with healed reflux oesophagitis, 6 months of maintenance treatment with esomeprazole, 20 mg od, maintained significantly more patients in remission than treatment with lansoprazole, 15 mg od. In addition, esomeprazole was more effective in maintaining patients free from heartburn, acid regurgitation and epigastric pain than lansoprazole. These findings are in line with those of a previous study, in which esomeprazole (40 mg od) demonstrated significantly greater efficacy than lansoprazole (30 mg od) in healing patients with reflux oesophagitis (92.6% vs. 88.8%; $P = 0.0001$; life table estimate) and in resolving accompanying gastro-oesophageal reflux disease symptoms.[19] Similarly, healing studies comparing esomeprazole with omeprazole have reported that esomeprazole, 40 mg od, healed a significantly greater proportion of patients with reflux oesophagitis than did omeprazole, 20 mg od, over 8 weeks. Life table estimates of healing rates at 8 weeks with esomeprazole 40 mg were 94.1% and 93.7% compared with 86.9% and 84.2% for omeprazole 20 mg ($P < 0.001$ for both studies).[17, 18] Furthermore, a systematic review of proton pump inhibitors in the acute treatment of reflux oesophagitis has found that esomeprazole 40 mg is the only proton pump inhibitor to provide significantly higher healing rates than omeprazole.[26]

In previous maintenance therapy studies, esomeprazole 20 mg has been compared with placebo in patients with healed reflux oesophagitis. The estimated endoscopic remission rates (life table estimates) at 6 months were 93%[20] and 79%[21] of patients receiving esomeprazole 20 mg, compared with 29% of placebo recipients in both studies. Data from the current study, which showed that 84% of esomeprazole recipients remained in remission at 6 months (according to endoscopic criteria), are consistent with the two previous studies. As in the earlier trials, both esomeprazole and lansoprazole were well tolerated.

Lansoprazole 15 mg was used in this study because it is the recommended dose for the maintenance therapy of healed reflux oesophagitis[24] and, in line with guidelines recommending the use of the lowest effective maintenance dose, no significant benefit has been observed by increasing the dose to 30 mg.[27–29] Although it is difficult to directly compare results across studies because of differences in the definition of relapse, patient numbers and in the grading of oesophagitis and symptoms, it is of interest to look at data from the current study in the context of other maintenance studies with lansoprazole. Six-month endoscopic remission rates of 76–81% have been observed with

lansoprazole 15 mg,[27–29] which is comparable to the 76% endoscopic remission rate reported in the current study.

The analysis of remission rates based on the Los Angeles classification at baseline demonstrated that esomeprazole maintained patients in remission more consistently across all grades of reflux oesophagitis, whereas the efficacy of lansoprazole decreased to a greater extent with increasing severity of disease (from Los Angeles grade A to D), a trend consistent with the results observed in previous trials with lansoprazole.[30] The consistency of response to esomeprazole across all grades of disease may be of particular importance for primary care physicians, who often treat patients on the basis of their clinical symptoms without the advantage of an endoscopic assessment to determine disease severity.[31] Symptom severity does not correlate directly with disease severity,[32] and a consistent response to proton pump inhibitor therapy across all grades of baseline disease severity is therefore important in predicting optimal outcomes during both acute and long-term treatment.

The difference between treatment groups with regard to the absence of any particular symptom ranged from 5% to 9%. The study used a composite primary end-point, defining relapse as the presence of oesophagitis grade A–D and/or unwillingness to continue in the study due to reflux symptoms. This study was neither primarily designed nor powered to test any specific difference in the proportion of symptoms between the treatment groups at any particular time point. Some patients were asymptomatic when they were withdrawn on the basis of recurrence of endoscopically verified oesophagitis. We believe that this composite primary end-point represents a more clinically meaningful end-point. In everyday clinical practice, the agent of choice should maintain as many patients as possible in endoscopic and symptomatic remission to avoid other possible clinical complications in the longer term, such as stricturing, in particular amongst patients with Los Angeles grade C or D disease.[33–35]

Taken together, these clinical findings are supported by earlier pharmacodynamic studies that demonstrated an improved efficacy of esomeprazole vs. omeprazole for intragastric acid control in gastro-oesophageal reflux disease patients,[12] and improved intragastric acid control of esomeprazole vs. lansoprazole at both healing and maintenance doses in healthy volunteers.[13, 16] The greater acid control with esomeprazole compared with lansoprazole appears to translate into improved clinical efficacy and predictability in both the acute and maintenance treatment of patients with reflux oesophagitis.

These data are particularly important when related to the Genval Guidelines[9] and the UK National Institute of Clinical Excellence guidelines,[22] both of which clearly recommend that the lowest effective dose of a proton pump inhibitor should be prescribed for maintenance therapy. In conclusion, esomeprazole, 20 mg od, provides higher remission rates than lansoprazole, 15 mg od, in patients with healed reflux oesophagitis during 6 months of maintenance treatment.

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