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# *Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial*

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## SUMMARY

*Background*: The pharmacologic profile of the new proton pump inhibitor esomeprazole has demonstrated advantages over omeprazole that suggest clinical benefits for patients with acid-related disease.

*Methods*: 1960 patients with endoscopy-confirmed reflux oesophagitis (RO) were randomized to once daily esomeprazole 40 mg ($n = 654$) or 20 mg ($n = 656$), or omeprazole 20 mg ($n = 650$), the standard recommended dose for RO, for up to 8 weeks in a US, multicentre, double-blind trial. The primary efficacy variable was the proportion of patients healed at week 8. Secondary variables included healing and heartburn resolution at week 4, time to first resolution and sustained resolution of heartburn, and per cent of heartburn-free days and nights. Safety and tolerability were also evaluated.

*Results*: Significantly more patients were healed at week 8 with esomeprazole 40 mg (94.1%) and 20 mg (89.9%) vs. omeprazole 20 mg (86.9%), using cumulative life table estimates, ITT analysis (each $P < 0.05$). Esomeprazole 40 mg was also significantly more effective than omeprazole for healing at week 4 and for all secondary variables evaluating heartburn resolution. The most common adverse events in all treatment groups were headache, abdominal pain and diarrhoea.

*Conclusion*: Esomeprazole was more effective than omeprazole in healing and symptom resolution in GERD patients with reflux oesophagitis, and had a tolerability profile comparable to that of omeprazole.

## INTRODUCTION

Significant advances have been made over the past decade in understanding the epidemiology and symptomatology of gastro-oesophageal reflux disease (GERD) with and without oesophagitis. Reflux symptoms are common in the general adult population. Recent US surveys indicate that more than 60 million adult Americans suffer from heartburn at least once a month, and 25 million adults experience heartburn on a daily basis.[1] Of patients presenting with GERD symptoms, it is now estimated that 40–60% or more have reflux oesophagitis (RO).[2–4] Irrespective of the presence or absence of oesophagitis, GERD patients generally report decreases in produc-

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tivity, quality of life and overall well-being.[5, 6] Many rate their quality of life to be lower than that reported by patients with untreated angina pectoris or heart failure.[7]

The severity of GERD is directly correlated with the degree and duration of oesophageal exposure to acid refluxate.[8–10] Chronic exposure has been associated with serious complications including oesophageal stricture in 4–20% of patients[8] and Barrett's oesophagus in up to 15% of patients with GERD.[8–11] Healing of RO has been directly correlated with the amount of time intragastric pH is > 4.0.[12, 13]

While knowledge about GERD is accelerating, advances in pharmacotherapy to treat this disease have not progressed since the first proton pump inhibitor, omeprazole, revolutionized the treatment of GERD over a decade ago.[14–16] Since that time, no proton pump inhibitor has surpassed the clinical efficacy of omeprazole in the treatment of GERD.[17–22] Early pharmacokinetic and pharmacodynamic trials with the novel proton pump inhibitor esomeprazole, the *S*-isomer of omeprazole, have yielded some promising findings. Compared with omeprazole, esomeprazole is subject to less first-pass hepatic metabolism and lower plasma clearance. This results in high systemic bioavailability. The area under the plasma concentration–time curve (*AUC*) for esomeprazole 20 mg has been shown to be 70% higher than that of omeprazole 20 mg, and repeated administration of esomeprazole has resulted in greater inhibition of pentagastrin-stimulated acid secretion as compared with omeprazole (90% vs. 79%).[23] In a separate study of patients with GERD symptoms, the *AUC* has been shown to be 2-fold higher for esomeprazole vs. omeprazole after a 20-mg dose of each compound, and 5-fold higher for esomeprazole 40 mg vs. omeprazole 20 mg (each $P < 0.0001$). Furthermore, esomeprazole 40 mg and 20 mg maintained intragastric pH > 4 for 16.8 and 12.7 h, respectively, vs. 10.5 h for omeprazole 20 mg ($P < 0.001$ and $P < 0.01$). Esomeprazole was also associated with less interpatient variability in both intragastric pH and *AUC* than was omeprazole.[24]

These findings prompted further study to evaluate the efficacy (healing and symptom resolution) and tolerability of once-daily doses of esomeprazole 40 mg and 20 mg, compared to omeprazole 20 mg in a large population of patients with RO.

## METHODS

### *Study design and patient selection*

This double-blind, randomized, multicentre, parallel-group trial was conducted at 140 centres in the United States. All patients provided written informed consent prior to being enrolled in the trial. At baseline screening, patients with symptoms of GERD underwent esophagogastroduodenoscopy (EGD). Mucosal breaks were graded according to the Los Angeles (LA) Classification (Table 1).[25] Patients with confirmed RO (LA grades A–D) were eligible for inclusion in the study. Given the multicentre nature of this trial, the LA Classification was chosen because it offers a high degree of interobserver reliability among experienced endoscopists.[26] Patients were excluded if they tested positive for *Helicobacter pylori* at serology screening to eliminate a potentially confounding variable in assessing the efficacy of study medications. Final determination of *H. pylori* status was made by evaluation of the gastric biopsy samples obtained from the antrum and corpus. Patients found to be *H. pylori* positive based on the subsequent biopsy results were allowed to remain in the study.

Patients were not included if they had any bleeding disorder or signs of gastrointestinal (GI) bleeding within 3 days prior to randomization, or had a history of gastric or oesophageal surgery. Patients were also

Table 1. Los Angeles Classification of Oesophagitis (adapted from reference 25)

| | |
|---|---|
| Not present | No breaks (erosions) in the oesophageal mucosa (oedema, erythema or friability may be present). |
| Grade A | One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length. |
| Grade B | One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of two mucosal folds. |
| Grade C | Mucosal breaks that are continuous between the tops of two or more mucosal folds, but which involve less than 75% of the oesophageal circumference. |
| Grade D | Mucosal breaks which involve at least 75% of the oesophageal circumference.<br>The presence of absence of strictures, ulcers and/or Barrett's oesophagus must be noted separately, e.g. 'Grade B with stricture'. |

excluded if they had evidence of Zollinger–Ellison syndrome, primary motility disorders, oesophageal stricture, Barrett's oesophagus (> 3 cm), evidence of upper GI malignancy, severe concomitant disease, or if they were pregnant or lactating. Additionally, patients who had received either proton pump inhibitor therapy within 28 days of the baseline visit or an $H_2$-receptor antagonist on a daily basis during the 2 weeks prior to baseline endoscopy, patients taking nonsteroidal anti-inflammatory drugs or other concomitant medication that might affect the interpretation of the treatment outcome (e.g. diazepam, quinidine, Dilantin, warfarin, anticholinergics, prostaglandin analogs, or sucralfate), and those with a known hypersensitivity to omeprazole or aluminium/magnesium hydroxide (Gelusil; Parke Davis, NJ), were excluded. Other medication considered necessary for the patient's welfare could be given at the discretion of the investigator.

Eligible patients were randomized to receive once-daily therapy with esomeprazole 40 mg, esomeprazole 20 mg, or omeprazole 20 mg (Figure 1), which is the usual recommended dose of omeprazole for patients with RO and accompanying symptoms. Patients were instructed to take the study medication in the morning. Compliance was assessed through unused capsule count. Patients were permitted to use an aluminium/magnesium hydroxide antacid preparation as a rescue medication throughout the study. To ensure blinding, all three study drugs and bottles had the same appearance. Investigators were provided with individually sealed and blinded randomization envelopes indicating the treatment allocation for each patient.

*Efficacy assessments*

The primary efficacy variable was endoscopically confirmed healing of RO after 8 weeks' treatment. Following the baseline visit, patients were evaluated 4 and 8 weeks after starting study medication. At both the 4- and 8-week visits an EGD was performed by the investigator. Patients with normal endoscopic appearance (absence of mucosal breaks per protocol using the LA Classification Grading system) during either the week 4 or week 8 visit were considered to be healed. If healing was observed at week 4, the patient was discharged from the study. If RO was still present at this time, the patient received an additional 4 weeks of treatment. Secondary efficacy variables included complete resolution of heartburn as assessed by the

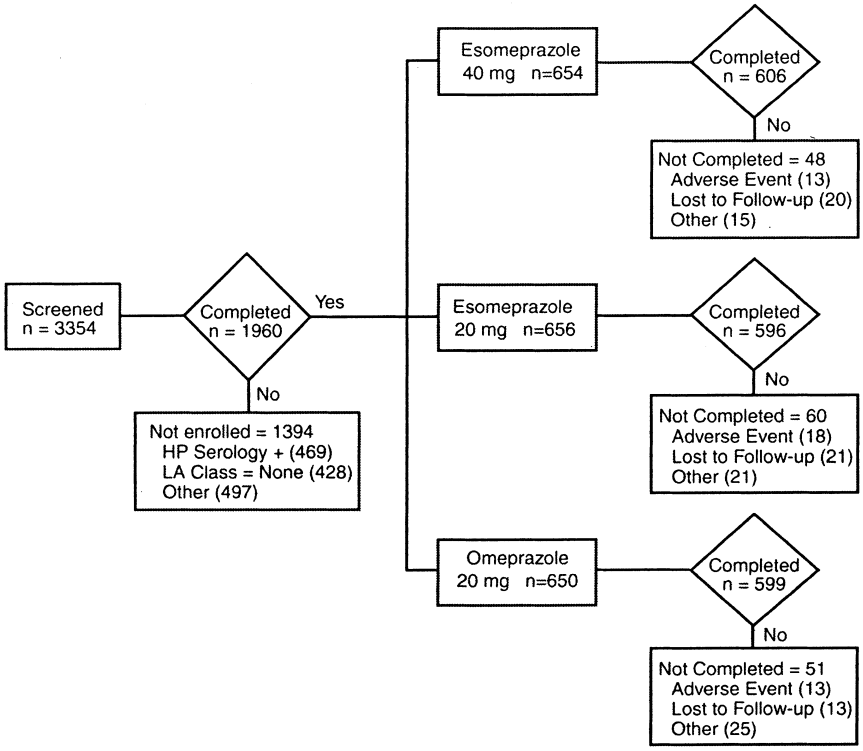


Figure 1. Trial profile.

investigator at week 4 and 8. Heartburn was graded on a 4-point scale: none, mild (awareness of heartburn but easily tolerated), moderate (discomfort sufficient to interfere with normal activities, including sleep), and severe (incapacitating with inability to perform normal activities, including sleep). Investigators also evaluated the use of antacids. Patients used daily diary cards during the first 4 weeks of the study to record episodes of heartburn experienced during the previous 24 h, as well as the presence of nocturnal heartburn. Patients graded heartburn using the same 4-point grading scale as the investigators. Percentage of heartburn-free days and nights, time to first resolution of heartburn, and time to sustained resolution of heartburn (defined as the first day of the heartburn-free period) were evaluated using diary card data. Resolution was defined as heartburn recorded as 'none' and sustained resolution was defined as 7 consecutive days with heartburn recorded as 'none'.

### *Adverse event assessment*

During each follow-up visit, investigators questioned the patients about the occurrence of adverse effects. All adverse events were recorded, regardless of likely causal association with study medication. The relationship of an adverse event to the study drug was classified by the investigator as probable, possible or unlikely and the intensity as mild, moderate or severe. Sub-analyses were conducted to evaluate the incidence of adverse events in terms of gender, age and race.

### *Statistical analysis*

The primary efficacy variable was analysed on an intention-to-treat basis. The results from patients who were healed at week 4 were carried over to week 8, based on the assumption that the patients who were healed would remain healed if they had continued the same therapy for the full 8 weeks. A log-rank test was used to evaluate between-group differences with respect to the percentage of patients healed at 8 weeks, applying the Hochberg procedure to correct for multiple comparisons (each esomeprazole treatment group compared to omeprazole) and maintain the level of significance at $\alpha = 0.05$. The percentage of patients healed adjusted for baseline RO severity (LA Classification) was evaluated using the Cochran-Mantel-Haenszel (CMH) test. All patients with missing (i.e. no postbaseline endoscopy results) or inappropriate data were considered treatment failures for the CMH analysis.

Severity of heartburn was recorded by both investigator and patient. The analysis of the investigators' assessments of heartburn was stratified by baseline severity and analysed using the Cochran-Mantel-Haenszel test. The number of days until the first heartburn-free day and the number of days until sustained resolution of heartburn based on patient diary data were analysed using a log-rank test. Between-group differences with respect to the proportion of heartburn-free days (24-h period) and nights were compared using analysis of variance.

With 95% power to detect at least a 10% difference in RO healing rate between omeprazole and esomeprazole, a sample size of 560 patients in each group was required. A two-sided test using arcsine transformation and Bonferroni correction for the comparison of each esomeprazole dose with omeprazole was assumed for sample size calculation.

Incidence rates of adverse events were assessed throughout the 8-week study period, and expressed as the number of patients experiencing at least one adverse event for those who received at least one dose of study drug.

## RESULTS

### *Patient characteristics*

A total of 3354 patients who presented with symptoms of GERD were screened for possible inclusion in the trial, and a total of 1960 patients were randomized to study medication. Patient demographics and baseline characteristics were comparable among the treatment groups (see Table 2). The primary reasons for exclusion from the trial were similar across all treatment groups (Figure 1). Forty-four patients did not complete the study due to an adverse event and 115 for other reasons included being lost to follow-up and withdrawal of consent. Overall patient medication compliance rates during the study were similar across treatment groups, and approached 90%.

### *Efficacy*

Both once-daily doses of esomeprazole, 40 mg and 20 mg, were significantly superior to omeprazole 20 mg once daily after 8 weeks of treatment. Esomeprazole

Table 2. Patient demographics and baseline characteristics

| | Esomeprazole | | Omeprazole |
|---|---|---|---|
| | 40 mg o.d. ($n$ = 654) | 20 mg o.d. ($n$ = 656) | 20 mg o.d. ($n$ = 650) |
| Gender | | | |
| Male | 384 (58.7%) | 391 (59.6%) | 399 (61.4%) |
| Female | 270 (41.3%) | 265 (40.4%) | 251 (38.6%) |
| Age (Years) | | | |
| Mean (± s.d.) | 44.8 (13.0) | 45.3 (13.3) | 46.5 (13.5) |
| <65 years (%) | 597 (91.3%) | 587 (89.5%) | 574 (88.3%) |
| LA Classification | | | |
| Grade A | 235 (35.9%) | 217 (33.1%) | 203 (31.2%) |
| Grade B | 253 (38.7%) | 274 (41.8%) | 265 (40.8%) |
| Grade C | 119 (18.2%) | 119 (18.1%) | 137 (21.1%) |
| Grade D | 47 (7.2%) | 46 (7.0%) | 45 (6.9%) |
| GERD History | | | |
| Unknown | 1 (0.2%) | 0 (0.0%) | 0 (0.0%) |
| <1 years | 32 (4.9%) | 30 (4.6%) | 39 (6.0%) |
| 1–5 years | 316 (48.3%) | 317 (48.3%) | 300 (46.2%) |
| >5 years | 305 (46.6%) | 309 (47.1%) | 311 (47.8%) |
| Heartburn | | | |
| None | 14 (2.1%) | 20 (3.0%) | 17 (2.6%) |
| Mild | 71 (10.9%) | 60 (9.1%) | 69 (10.6%) |
| Moderate | 282 (43.1%) | 309 (47.1%) | 296 (45.5%) |
| Severe | 286 (43.7%) | 267 (40.7%) | 268 (41.2%) |

40 mg provided the greatest life table estimate healing rate, 94.1%, vs. 89.9% for esomeprazole 20 mg and 86.9% for omeprazole 20 mg ($P < 0.001$ for E40 vs. O20 and $P < 0.05$ for E20 vs. O20). A significantly higher proportion of patients were healed at week 4 during esomeprazole 40 mg therapy compared with omeprazole 20 mg (Table 3). This greater efficacy for esomeprazole 40 mg vs. omeprazole 20 mg was seen consistently when adjusting for baseline oesophagitis grade and remained statistically significant after 8 weeks' treatment based on crude rates (Figure 2). At week 4, the difference between the esomeprazole 20 mg vs. omeprazole 20 mg group was not statistically significant ($P = 0.09$). There were no differences in

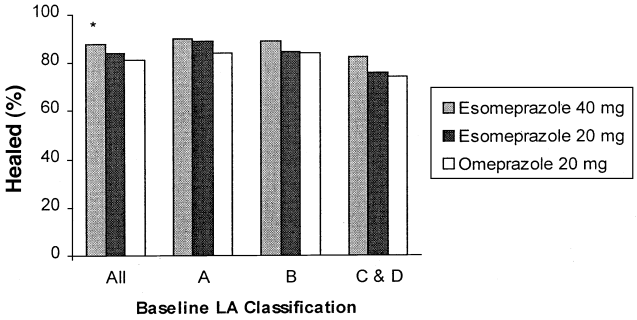


Figure 2. Comparison of RO healing rates at week 8 by baseline severity grade using crude rates (LA Classification). * $P < 0.05$ for CMH test, esomeprazole 40 mg vs. omeprazole 20 mg.

healing at week 8 between the three groups with respect to age or gender.

One of the criteria for exclusion from the study was a positive serology for *H. pylori.* On subsequent biopsy analysis 189 patients (9.6%) had histological evidence of *H. pylori* infection. The study was not powered to detect a statistical difference by *H. pylori* status, however efficacy in healing was tabulated separately for these patients. The proportion of patients healed at week 4 was 81.5% and 73.2% for esomeprazole 40 mg and 20 mg, respectively, in the *H. pylori* positive groups vs. 69.9% and 65.7% in the *H. pylori* negative groups. At week 8, healing was observed in 89.2% and 85.7% of *H. pylori* positive patients on esomeprazole 40 mg and 20 mg, respectively, vs. 87.3% and 83.6% in the *H. pylori* negative groups.

Esomeprazole 40 mg produced significantly greater results for all secondary variables that evaluated heartburn resolution (see Table 4), including complete heartburn resolution, time to first resolution of heartburn, time to sustained resolution of heartburn, and percentage of heartburn-free days. Both dosages of esomeprazole, 40 mg and 20 mg, achieved a significantly greater proportion of heartburn-free nights than omeprazole therapy. The cumulative percentage of patients experiencing sustained resolution of heartburn was consistently higher with E40 and E20 vs. O20 over the 4-week

Table 3. Healing rates of reflux oesophagitis in the intention-to-treat population

| | | Esomeprazole | | Omeprazole |
|---|---|---|---|---|
| | Statistic | 40 mg o.d. | 20 mg o.d. | 20 mg o.d. |
| Week 4 | Cumulative life table rate | 75.9% | 70.5% | 64.7% |
| | 95% life table CI | 72.5–79.3% | 66.9–74.1% | 60.9–68.5% |
| Week 8 | Cumulative life table rate | 94.1% | 89.9% | 86.9% |
| | 95% life table CI | 92.2–96.0% | 87.5–92.3% | 84.2–89.6% |

Table 4. Heartburn resolution rates

| Variable | Esomeprazole 40 mg o.d. | Esomeprazole 20 mg o.d. | Omeprazole 20 mg o.d. |
|---|---|---|---|
| *n* | 621 | 626 | 624 |
| Resolution at week 4 | 64.7% (402) | 61.0% (382) | 57.2% (357) |
| *P*-value vs. O20 | 0.005* | 0.143 | |
| Time to first resolution† | | | |
| *n* | 621 | 620 | 626 |
| % (*n*) by day 1 | 46.6% (290) | 37.9% (235) | 37.0% (232) |
| % (*n*) by day 7 | 83.2% (517) | 81.4% (505) | 79.8% (500) |
| Median (days) | 2 | 2 | 2 |
| *P*-value vs. O20 | 0.013* | 0.310 | |
| Time to sustained resolution‡ | | | |
| *n* | 621 | 620 | 626 |
| % (*n*) by day 1 | 29.9% (186) | 21.7% (135) | 23.0% (144) |
| % (*n*) by day 28 | 74.2% (461) | 70.1% (435) | 66.6% (417) |
| Median (days) | 5 | 8 | 9 |
| *P*-value vs. O20 | 0.0006* | 0.143 | |
| % Heartburn-free days | 72.7% | 69.3% | 67.1% |
| *P*-value vs. O20 | 0.002* | 0.227 | |
| % Heartburn-free nights | 84.7% | 83.6% | 80.1% |
| *P*-value vs. O20 | 0.001* | 0.013* | |

O = omeprazole.
* $P < 0.05$.
† First day of heartburn recorded as 'none' on patient diary cards.
‡ Defined as 7 consecutive days without heartburn.

period (Figure 3). A cumulative analysis at week 8 was not done because patients could complete the study at week 4 with healed RO, even if symptoms were present.

There was a statistically significant correlation between symptom resolution and oesophageal healing in this study. Patients whose heartburn was resolved at week 4 were healed 83.2% of the time with esomeprazole 40 mg and 73.1% of the time with omeprazole 20 mg ($P < 0.001$ for E40 vs. O20).

### *Safety and tolerability*

Of the 1960 patients randomized to study medication, 1957 received at least one dose of a study drug and were therefore included in the tolerability analysis. Overall, the incidence and profile of adverse events were comparable between treatment groups (see Table 5). No serious drug-related adverse events were reported. The percentage of patients who discontinued therapy due to an adverse event were comparable among the three treatment regimens at 2.0%, 2.6% and 2.0% for esomeprazole 40 mg and 20 mg, and omeprazole 20 mg, respectively. One fatality occurred in the esomeprazole 20 mg group (myocardial infarction), but this was considered not to be drug related. No clinically relevant differences in the number of patients experiencing adverse events were observed when evaluated according to gender, age or race.

## DISCUSSION

This is the first head-to-head clinical trial to demonstrate significantly greater healing rates of a proton pump inhibitor vs. omeprazole 20 mg once daily in the treatment of RO and related symptoms. A review of the literature shows that comparative trials with lansoprazole 30 mg once daily,[27–32] rabeprazole 20 mg once daily,[33–35] or pantoprazole 40 mg[32–38] demonstrate healing rates comparable to omeprazole 20 mg at 4 and 8 weeks. The present study demonstrates that both doses of esomeprazole, 40 mg and 20 mg, were significantly more effective than omeprazole 20 mg in healing RO at week 8. Esomeprazole 40 mg provided the highest healing rates. Furthermore, more patients were healed in a shorter period of time with esomeprazole 40 mg as evidenced by significantly higher healing rates at week 4.

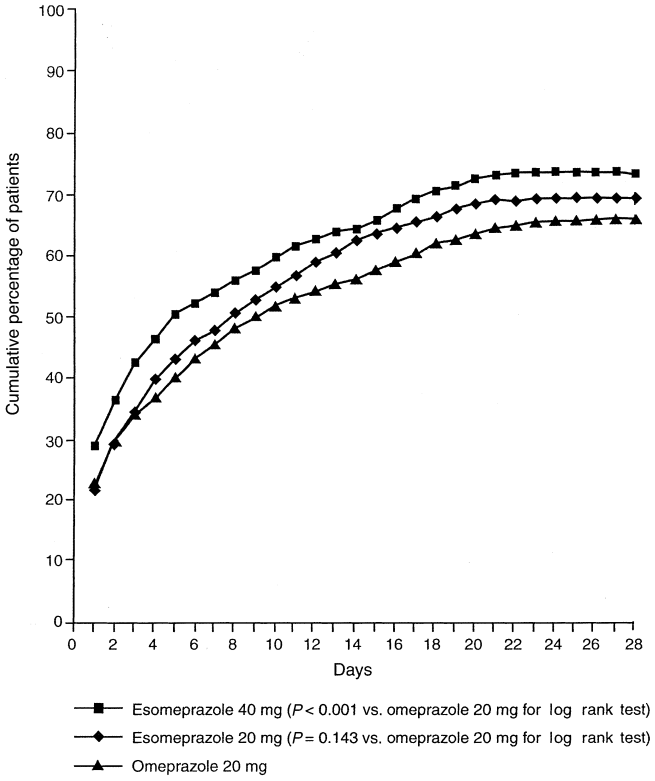


Figure 3. Cumulative percentage of patients experiencing sustained resolution of heartburn in the intention-to-treat population.

Table 5. Adverse events occurring in ≥ 3% of patients receiving any study drug during the 8-week study period

| | Esomeprazole | | Omeprazole |
|---|---|---|---|
| | 40 mg ($n$ = 653) | 20 mg ($n$ = 655) | 20 mg ($n$ = 649) |
| Central nervous system | | | |
| Headache | 56 (8.6%) | 57 (8.7%) | 45 (6.9%) |
| GI system | | | |
| Abdominal pain | 24 (3.7%) | 24 (3.7%) | 27 (4.2%) |
| Diarrhoea | 30 (4.6%) | 31 (4.7%) | 25 (3.9%) |
| Flatulence | 12 (1.8%) | 23 (3.5%) | 26 (4.0%) |
| Gastritis | 16 (2.5%) | 23 (3.5%) | 16 (2.5%) |
| Nausea | 25 (3.8%) | 19 (2.9%) | 20 (3.1%) |
| Respiratory system | | | |
| Respiratory infection | 28 (4.3%) | 35 (5.3%) | 30 (4.6%) |

Esomeprazole 40 mg continued to produce a significantly higher proportion of healed oesophageal lesions compared with omeprazole when adjusting for baseline grade of severity. This trial also demonstrated that esomeprazole treatment resulted in faster and more sustained resolution of heartburn compared with omeprazole. Of particular note, a significantly higher percentage of heartburn-free nights were observed in patients treated with esomeprazole vs. omeprazole. Lind *et al.*[24] had demonstrated that intragastric pH is maintained above 4.0 for 6 h longer with esomeprazole 40 mg vs. omeprazole 20 mg and that the difference was most apparent between 12 and 20 h after a morning dose.

The significant correlation between symptom resolution and oesophageal healing with esomeprazole in this study is consistent with data in a meta-analysis by Carlsson et al.,[39] which evaluated the relationship between symptoms, endoscopic findings and treatment outcome in 3242 RO patients treated short-term with omeprazole or ranitidine. In that trial, patients whose heartburn was resolved at week 4 were healed 73.3% of the time with omeprazole 20 mg. The investigators concluded that absence of symptoms with omeprazole closely predicted endoscopic healing. Data from the current trial indicates that heartburn was resolved in 73.1% of patients on omeprazole 20 mg and 83.2% of patients on esomeprazole 40 mg.

The correlation between symptom resolution and health-related quality of life (HRQL) was not assessed in the current trial. Published data on this subject are sparse, despite the fact that the negative impact of GERD is well established. A new study by Revicki et al.[40] does provide a summary of the findings of three HRQL trials assessing 1406 symptomatic GERD patients. The authors conclude that sustained heartburn resolution, i.e. 7 consecutive heartburn-free days, was consistently associated with statistically significant improvements in patients' HRQL compared with patients who continued to experience GERD symptoms while on therapy. Reaching the rigorous end-point of complete symptom resolution does appear to offer HRQL benefits to GERD patients.

## CONCLUSIONS

The present study demonstrates that esomeprazole is more effective than omeprazole in healing across all grades of oesophagitis and in heartburn resolution, and that esomeprazole had a tolerability profile comparable to that of omeprazole.

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