Relationship between esomeprazole dose and timing to heartburn resolution in selected patients with gastroesophageal reflux disease

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Objective: To increase response rates to therapy by increasing the dosage of proton pump inhibitor (PPI) therapy in patients with gastroesophageal reflux disease (GERD) whose symptoms are predominantly associated with acid reflux.

Methods: In this double-blind, randomized, proof-of-concept study, 369 patients with GERD and moderate heartburn lasting ≥ three days/week, a history of response to antacids/acid suppression therapy, and a positive esophageal acid perfusion test result were randomized to esomeprazole 20 or 40 mg once daily, or to 40 mg twice daily for four weeks. Heartburn symptom relief/resolution was subsequently evaluated.

Results: In this study population, no relationship was apparent between esomeprazole dosage and efficacy variables for sustained heartburn resolution (seven days without symptoms) at week 4 (48.0%, 44.0%, and 41.4% for esomeprazole 20 mg once daily, 40 mg once daily, and 40 mg twice daily, respectively). Nocturnal heartburn resolution with esomeprazole 40 mg twice daily showed a numeric improvement trend versus esomeprazole 20 and 40 mg once daily, but this was not statistically significant.

Conclusions: Heartburn resolution rates at four weeks were similar for all esomeprazole dosages and comparable with rates reported previously, suggesting a plateau effect in terms of clinical response to acid suppression with PPI therapy in this population of selected GERD patients.

Keywords: acid suppressive therapy, GERD, proton pump inhibitor

Introduction

Gastroesophageal reflux disease (GERD) manifests as heartburn and/or acid regurgitation at least once weekly, and occurs in 10% to 20% of people in the Western world.¹ Several approaches can be used to evaluate a patient for GERD. A diagnosis of GERD can be assumed in patients with classic symptoms who respond to appropriate antacid therapy,² but not all patients with GERD respond to standard treatment.³,⁴ A pooled meta-analysis of 15 studies showed that symptom resolution with proton pump inhibitors (PPIs) has a sensitivity of 78% and a specificity of 54% for GERD, as determined by 24-hour pH monitoring.⁴ Additionally, the esophageal acid perfusion test result,⁵ which presumptively links clinical symptoms to esophageal acid exposure when elicited by acid infusion, demonstrates a clinical correlation with GERD symptoms.⁶,⁷ However, a lack of association exists between esophageal acid perfusion-induced symptoms and symptoms that follow spontaneous reflux in the same individuals.⁸

PPIs are recommended as first-line therapy for GERD⁹ when acid suppression is required because they provide rapid symptomatic relief of GERD and more frequently heal esophagitis than other classes of acid suppressants.³ However, studies suggest that 30% of patients with GERD still experience symptoms despite standard treatment...
with a PPI. Inadequate control of gastric acid secretion may be one explanation for the persistence of GERD symptoms in these patients, and an alteration in the dosing regimen may be warranted to optimize the PPI effect. In patients who do not respond to once-daily dosing, expert opinion recommends an increase in dosage to twice daily for symptom relief, even though supporting clinical data are limited. In a study of patients with Barrett’s esophagus, esomeprazole 40 mg twice daily, 40 mg three times daily, and 20 mg three times daily, yielded significantly improved, dose-dependent intragastric pH values without a comparable effect on esophageal pH values. Alternative regimens designed to optimize the effectiveness of PPI therapy include split-dose regimens, increased doses, and alternative timing of dose administration.

Due to the variety of pathophysiologic mechanisms that may result in heartburn or other esophageal symptoms, treatment with a PPI may not provide complete symptom resolution. Some patients may fail to respond optimally to PPIs because of differences in disease or patient clinical characteristics or because they lack “true” acid-induced, GERD-associated heartburn. Patients with nonerosive reflux disease are reported to have a lower symptom response rate than those with erosive esophagitis. Furthermore, patients may be treated with a PPI without having acid-induced, GERD-associated heartburn because they misunderstand the meaning of heartburn and use the term to describe epigastric pain.

If heartburn symptoms could be objectively characterized as acid-associated, the subset of patients who would most benefit from acid suppression therapy could be identified with the objective of possibly increasing their symptomatic response with increased dosages. Therefore, the aim of this proof-of-concept study was to investigate the relationship between esomeprazole dose and symptom resolution in patients with GERD-associated heartburn, as determined by a history of response to antacids or acid suppression therapy and a positive esophageal acid perfusion test result.

Methods

Patients

Adults aged 18–75 years were eligible for study entry if they had a history of heartburn for ≥six months and a prior self-reported symptomatic response to antacids and/or acid suppression therapy, although the time to response to antacid or acid suppression therapy was not determined. Women had to be postmenopausal, surgically sterilized, or using an acceptable form of birth control during the study. Patients were required to have a positive result on esophageal acid perfusion test, and had to test negative for *Helicobacter pylori* infection (determined by a whole blood *H. pylori* test), and had to be able to use an electronic diary (e-diary).

Exclusion criteria included a history of gastric or esophageal surgery (except for closure of perforated peptic ulcer), a history of endoscopically verified erosive esophagitis within the last 16 weeks (unless healing was documented), current high-dose (more than standard approved) PPI treatment, evidence of other major gastrointestinal, cardiovascular, cerebrovascular, pulmonary, renal, pancreatic, or liver disease, malignant disease, or solid organ transplant. Patients were also excluded from the study if they required concomitant therapies, including acid suppression therapy (histamine-2 receptor antagonists or PPIs other than study drug), sucralfate, promotility drugs, benzodiazepines, anticoagulants, anticholinergics, analgesics, prostaglandin analogs, antineoplastic drugs, acetylsalicylic acid (except at a dosage of ≤165 mg/day for cardiovascular disease prophylaxis), corticosteroids, gastrointestinal/esophageal irritants, drugs requiring gastric acid for optimal absorption, narcotics, or human immunodeficiency virus protease inhibitors. The use of any other investigational drug within 28 days of randomization was also prohibited.

Study design

This randomized, parallel-group, double-blind, multicenter, proof-of-concept study (AstraZeneca study code D9612 L00664; ClinicalTrials.gov identifier, NCT00206024) was conducted at 25 US centers (predominantly gastroenterology practices) between November 2004 and July 2005. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and its amendments, and was in compliance with the International Conference on Harmonization/Good Clinical Practice regulations. Patients provided written informed consent before the initiation of any study procedure.

At the initial screening visit, physical examination results, demographic and baseline disease characteristics, and medical histories were obtained. Eligible patients entered a two-week runin period during which they reported daily heartburn symptoms via e-diaries (handheld PHT LogPad®; PHT Corporation, Charlestown, MA). Patients could use antacid tablets (Gelusil®; Wellspring Pharmaceutical Corporation, Sarasota, FL) as rescue medication for up to three consecutive days per week during the runin period. At the end of this period, patients who reported heartburn of at least moderate severity (discomforting symptom sufficient to cause interference with normal activities, including sleep) on ≥three of the previous seven days in their e-diary and who had not used acid suppression...
therapy (eg, PPIs or histamine-2 receptor antagonists) other than the rescue medication (Gelusil tablets) underwent an esophageal acid perfusion test.

The esophageal acid perfusion test was performed on day 0, using a technique based on the Bernstein test with some modifications. The patient was placed in an upright position, and a lubricated, small-bore (≤12-French) catheter was passed transnasally and placed in the distal esophagus, which had been located by esophageal manometry or a pH step-up procedure. The test included a five-minute infusion of normal saline at a rate of 1.5 mL/min and a subsequent infusion of 0.1 N hydrochloric acid at a rate of 1.5 mL/min, and lasting until symptoms appeared or 30 minutes had elapsed. The patient was instructed to indicate whether typical heartburn symptoms occurred during infusions, but the patient was unaware of the content of the infusion. The test result was considered positive only if symptoms were reported during the acid infusion.

Assignment

Patients who had moderate heartburn and a positive esophageal acid perfusion test result were assigned randomly (1:1:1) in a double-blind, double-dummy fashion to four weeks of treatment with esomeprazole magnesium 20 mg once daily, 40 mg once daily, or 40 mg twice daily. The patients were instructed to take their treatment 30 minutes before their morning and evening meals. During the four weeks of treatment, patients assessed their heartburn symptoms before each morning dose of study medication and recorded their assessments via e-diaries.

Masking

Randomized patients received one capsule in the morning and one capsule in the evening, regardless of treatment, and esomeprazole magnesium and placebo capsules were identical in appearance. Treatment codes indicating the treatment randomization for each randomized patient were available to the investigators or pharmacists at the study center. The treatment code was not to be broken except in medical emergencies when the appropriate management of the patient necessitated knowledge of the treatment randomization. All personnel involved in the monitoring or the analysis of the study remained blinded to the allocation schedule until the study was completed. The data were screened, and any protocol violators were identified.

Assessments

At the screening visit, patients received an e-diary to record heartburn and nocturnal heartburn symptoms and instructions for its use. Heartburn was defined as a burning feeling rising from the stomach or lower part of the chest toward the neck. Nocturnal heartburn was defined as heartburn that occurred from the time the patient retired for the evening until the patient rose in the morning to start daily activities.

Using a severity scale (none = 0; mild = 1; moderate = 2; severe = 3), patients responded to the following statement on their handheld e-diary devices: “Please rate the severity of your most intense heartburn episode during the previous 24 hours”. In response to the question, “Did you experience nocturnal heartburn during your normal sleeping hours?” patients also recorded the presence (no = 0; yes = 1) of nocturnal heartburn during nighttime hours.

Efficacy measures assessed in each treatment group were sustained resolution of heartburn (defined as seven consecutive days with a daily e-diary heartburn assessment of “none”) and relief of heartburn during week 4 of treatment and included all patients who had sustained resolution and those who experienced six consecutive days with a daily e-diary assessment of “none” and one day of “mild” (ie, all patients who had six days with a daily e-diary assessment of “none” and one day of “none” or “mild”). The cumulative daily sustained resolution rate through 4 weeks of treatment also was assessed. The times to the first day of the sustained resolution of heartburn and to the first day of relief of heartburn were determined. The percentages of heartburn-free days and nights during week 4 of treatment were calculated.

Patients were required to bring unused rescue medication to the study site on the day of randomization (day 0) and unused study drug to the study site on the final visit. Returned tablets/capsules were counted and documented in the patient’s source documents and case report form. Investigators were responsible for ensuring that accurate accountability records were kept. Treatment compliance was assessed from reviewing accountability records, and patients were considered compliant if they consumed ≥80% of the prescribed study drug.

Safety and tolerability assessments were based on adverse event (AE) reports, laboratory data, vital signs, and physical examination results. AEs were recorded at day 0 and at the end of the study in response to an open question by the investigator. Spontaneously reported AEs also were recorded throughout the study.

Statistical analysis

No hypothesis was made and no statistical comparisons or statistical inferences were drawn for this exploratory study. Sample sizes were based on those used in a previous study.
for which it was calculated that a sample size of 100 patients would have a 95% power to detect a difference in resolution rates of 60% for esomeprazole treatment and 30% for placebo treatment. Thus, allowing for a 10% dropout rate, 330 patients had to be randomized to provide approximately 100 patients per treatment arm. The efficacy variables were summarized in the intent-to-treat population, defined as all patients who took ≥one dose of study drug and had ≥one efficacy measurement. The safety population included all patients who took ≥one dose of study medication.

Results
Of 630 patients screened, 369 were randomly assigned to treatment. The major reasons for study exclusion and discontinuation are summarized in Figure 1. All 369 randomized patients who reported that their heartburn responded to antacids/acid suppression therapy also had a positive esophageal acid perfusion test result except for one. This patient died in a traffic accident and thus was not included in the intent-to-treat population (368 patients) because no data were recorded after the second visit (day 0). All randomized patients received ≥one dose of study drug; data from all randomized patients were analyzed for safety. Patients in this population had a mean age of 45 years, were predominantly white women, and had a mean body mass index of >29 kg/m² (Table 1). All patients had a history of heartburn, tested negative for H. pylori, and had a positive esophageal acid perfusion test result. Thirteen percent of patients had a history of erosive esophagitis. Prior to study enrollment, 31 (8.4%) of the 368 patients were receiving histamine-2 receptor antagonists and 114 (31.0%) were receiving PPI therapy, including 35 (9.5%) patients who were receiving esomeprazole. Most patients were classified as compliant (ie, took ≥80% of their study medication), including 112 (93%) in the 20-mg once-daily and 40-mg once-daily groups, and 113 (90%) in the 40-mg twice-daily groups. No instances of treatment overdose were reported.

As shown in Table 2, no apparent relationship existed between the dosage of esomeprazole and any of the efficacy variables, including sustained resolution and relief rates at week 4, cumulative daily sustained resolution rate at day 28, time to first day of sustained resolution or relief, and percentage of heartburn-free days during week 4. However, a nonsignificant trend was seen toward improved nocturnal heartburn.

Figure 1 Patient disposition.
resolution with esomeprazole 40 mg twice daily compared with esomeprazole 20 mg once daily and 40 mg once daily in terms of heartburn-free nights during week 4 (Table 2).

All three esomeprazole dosage regimens were well tolerated (Table 3). Three serious AEs were observed: pulmonary abscess, atypical chest pain, and death in a traffic accident. However, none of these events were attributed to esomeprazole treatment. The incidence of AEs was slightly higher with esomeprazole 40 mg twice daily (21%) compared with esomeprazole 20 mg once daily (17%) and 40 mg once daily

Table 2 Efficacy of esomeprazole 20 mg once daily, 40 mg once daily, or 40 mg twice daily in the treatment of acid-related heartburn

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Esomeprazole 20 mg once daily (n = 121)</th>
<th>Esomeprazole 40 mg once daily (n = 121)</th>
<th>Esomeprazole 40 mg twice daily (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained HB resolution rate during week 4, n/N (%)</td>
<td>47/98 (48.0)</td>
<td>40/91 (44.0)</td>
<td>41/99 (41.4)</td>
</tr>
<tr>
<td>HB relief rate during week 4, n/N (%)</td>
<td>58/98 (59.2)</td>
<td>47/91 (51.7)</td>
<td>53/99 (53.5)</td>
</tr>
<tr>
<td>Cumulative daily sustained HB resolution rate at day 28, n/N (%)</td>
<td>27/43 (62.8)</td>
<td>26/50 (52.0)</td>
<td>31/50 (62.0)</td>
</tr>
<tr>
<td>Time to first day of first sustained HB resolution, n days</td>
<td>121</td>
<td>121</td>
<td>126</td>
</tr>
<tr>
<td>Mean (SEM), days</td>
<td>14.7 (1)</td>
<td>14.0 (1)</td>
<td>15.5 (1)</td>
</tr>
<tr>
<td>Time to first day of first HB relief, n days</td>
<td>121</td>
<td>121</td>
<td>126</td>
</tr>
<tr>
<td>Mean (SEM), days</td>
<td>12.1 (1)</td>
<td>12.5 (1)</td>
<td>12.9 (1)</td>
</tr>
<tr>
<td>HB-free days during week 4, n</td>
<td>120</td>
<td>112</td>
<td>121</td>
</tr>
<tr>
<td>Mean (SEM), %</td>
<td>66.5 (4)</td>
<td>62.4 (4)</td>
<td>67.8 (3)</td>
</tr>
<tr>
<td>HB-free nights during week 4, n</td>
<td>120</td>
<td>112</td>
<td>121</td>
</tr>
<tr>
<td>Mean (SEM), %</td>
<td>80.8 (3)</td>
<td>78.0 (3)</td>
<td>88.2 (2)</td>
</tr>
</tbody>
</table>

Notes: Last observation carried forward was used in the analyses of sustained resolution and relief rates during week 4 for patients whose last diary data were from days 26 or 27. This approach was necessary because of the limited number of patients with data for day 28.

Abbreviations: HB, heartburn; SEM, standard error of the mean.
Table 3 Number of patients (%) with most commonly reported adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Esomeprazole 20 mg once daily (n = 122)</th>
<th>Esomeprazole 40 mg once daily (n = 121)</th>
<th>Esomeprazole 40 mg twice daily (n = 126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4 (3.3)</td>
<td>7 (5.8)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (3.3)</td>
<td>5 (4.1)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (2.5)</td>
<td>4 (3.3)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1 (0.8)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>4 (3.3)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (1.6)</td>
<td>2 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (2.5)</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Note: Events with a total frequency $\geq$1% across treatment groups.

(18%). Study medication was discontinued because of AEs in three patients who received esomeprazole 40 mg once daily: one patient with severe symptoms of fatigue, arthralgia, myalgia, hyperhidrosis, and blurred vision; one patient with mild nausea and diarrhea; and one patient with moderate diarrhea. Two patients who received esomeprazole 40 mg twice daily also discontinued study medication; one of these patients discontinued due to moderate noncardiac chest pain and one due to severe injury resulting from trauma.

Discussion

The present study reports resolution of GERD symptoms after treatment with different dosages of esomeprazole and assesses the possible value of tailoring a PPI dosage to achieve heartburn relief/resolution in individual patients. In this study, esomeprazole was an effective treatment for heartburn in a selected patient population with symptomatic GERD based on history of heartburn and relief by antacids/acid suppression therapy and a positive esophageal acid perfusion test result. Sustained heartburn resolution rates for esomeprazole ranged from 41% to 48%, and heartburn relief rates ranged from 52% to 59% at week 4.

To assess the effect of increasing esomeprazole dosage in patients with acid-induced GERD-associated heartburn, we attempted to enrich the population for study entry with possible responders to esomeprazole by requiring a history of relief with antacids and/or acid suppression therapy and a positive esophageal acid perfusion test result. We hypothesized that these requirements would identify patients who were more likely to respond to acid suppression therapy, allowing us to determine better the effects of PPI dosage on symptom control. However, rates of sustained response to esomeprazole 20 mg once daily and 40 mg once daily were similar to those reported in other esomeprazole studies of similar design that did not attempt to enrich the population.

Several reasons may explain why this enrichment technique failed in our study. First, as a result of selecting our patient population in this manner, we may have selected a highly responsive subpopulation of patients for whom variations in symptom response to different doses and timing frequency of PPIs may not be detectable. PPIs do not abolish acid secretion, so the remaining “weakly acidic” reflux episodes may continue to be effective in provoking heartburn or, alternatively, heartburn may be provoked by nonacidic components in meals or refluxates in patients with symptomatic GERD. Additionally, although the esophageal acid perfusion test result has been reported by some investigators to have a good clinical correlation with a GERD diagnosis, a weak association has been observed between a positive esophageal acid perfusion test result and symptom index. Therefore, although the test may identify individuals whose heartburn may be induced by high degrees of intraesophageal acidity, it does not exclude individuals who experience spontaneous episodes of heartburn caused by weakly acidic or nonacidic refluxates. Furthermore, the positive esophageal acid perfusion test result does not establish symptomatic responsiveness to acid suppressant therapy. In this regard, one limitation of this study is that pH monitoring was not performed to confirm pharmacodynamic variations in efficacy of different esomeprazole dosages on suppressing gastric acidity or decreasing esophageal acid exposure. Also, in a previous study of patients with Barrett’s esophagus, esomeprazole treatment yielded significantly improved, dose-dependent suppression of intragastric acidity without comparable effect on esophageal pH values in patients.

In the present study, selecting patients with a history of positive response to acid suppression therapy does not appear to have enriched the study population for an increased symptomatic response with increased esomeprazole dosages based on comparisons with previously reported response rates in studies of patients whose heartburn had not been determined to be acid-related. However, a comparison of the present results with those of previous studies is limited because of differences in study designs and analysis methods. In addition, the highly stringent criteria for gauging success in the relatively short four-week treatment period may not have allowed therapeutic effect to be achieved fully in the large number of patients with nonerosive reflux disease in this study. A four-week treatment period may not sufficiently heal the potential underlying lesions in symptomatic GERD.
(eg, dilated intercellular spaces), thereby limiting the rates of symptom resolution. Healing of dilated intracellular spaces, which parallels heartburn resolution, can take as long as 3–6 months of PPI therapy.28,29

Nocturnal heartburn is common in patients with heartburn and may negatively affect their ability to sleep well, potentially impacting daytime functioning.30 Studies suggest that PPIs improve sleep quality in patients with GERD-related sleep disturbance.31–34 In the present study, a numeric trend was seen toward improvement in nocturnal heartburn resolution with esomeprazole 40 mg twice daily versus esomeprazole 20 mg once daily and esomeprazole 40 mg once daily, but this difference was not statistically significant. The study did not clarify whether patients on once-daily esomeprazole with persistent nocturnal heartburn may benefit from a day increase to twice-daily esomeprazole or whether the possible trend toward improvement may be due to the increase in dose or the effect of split dosing. Neither pH monitoring nor biopsies were performed in the present study. Therefore, other etiologies characterized by heartburn symptoms, such as eosinophilic esophagitis, were not addressed.3 Such etiologies may confound the responses observed during esophageal acid perfusion testing. However, patients with a history of endoscopically verified erosive esophagitis within the last 16 weeks before randomization were excluded from the study unless healing had been documented.

Apart from a trend toward improved nocturnal heartburn resolution, this study did not support a dose response in the other endpoint measures, a finding reported in other studies of PPIs in patients who had symptomatic GERD.24,25,35–37 The present findings suggest that a plateau effect exists in terms of clinical response to acid suppression with PPI therapy with respect to day-long heartburn resolution. However, this result does not exclude the possibility of a dose or timing frequency response for nighttime heartburn.

Similar observations were made in studies investigating heartburn resolution in patients with erosive esophagitis.38,39 In a study by Kahrilas et al,38 no differences were seen in heartburn resolution even though esomeprazole 40 mg was superior to omeprazole 20 mg for acid suppression. Specifically, esomeprazole at doses of 40 and 20 mg was superior to omeprazole 20 mg in achieving heartburn-free nights. Only the 40-mg dose of esomeprazole was superior to omeprazole in heartburn-free days. Moreover, these improvements in heartburn resolution were associated with improved healing.38 Katz et al39 similarly demonstrated that greater intragastric acid control (ie, mean percentage of time with pH >4) with esomeprazole 40 mg once daily did not correlate with resolution of heartburn symptoms in patients with endoscopically verified erosive esophagitis. Increased intragastric acid control had a positive correlation with healing status of erosive esophagitis and with the severity of daytime and nighttime heartburn symptoms.39 However, no significant correlation was found between intragastric acid control and changes in symptom severity from baseline to the conclusion of the 28-day study.39

Although results from the two previously described studies were similar to those in the present study, the previous two study populations consisted of patients with erosive esophagitis, whereas the present study specifically excluded patients with erosive esophagitis. Therefore, the underlying mechanisms influencing response to therapy in these two patient populations may have differed from those seen in the present study. However, on the basis of the previous studies, symptoms do not appear to be sensitive to modest changes in the degree of acid suppression achievable with PPIs. These results, along with findings of the present study, raise the question of whether an increase in PPI dose or modification in the timing of PPI administration can lead to clinical improvements in GERD symptoms, subject to possible clinical variations in different subpopulations of GERD patients. Additionally, these findings suggest the possibility that optimal symptom resolution in patients with GERD may require the management of other factors besides acid suppression.

In summary, the results of this study showed that four weeks of esomeprazole therapy achieved a reasonable rate of success in providing sustained heartburn resolution. Although the study failed to demonstrate a clinically significant effect after enrichment of the population based on history of relief by antacids/acid suppression therapy and esophageal acid perfusion testing, a numeric but nonsignificant trend toward improvement in nocturnal heartburn resolution with esomeprazole 40 mg twice daily was observed. Additional research into the dose, timing of administration, and split-dosing regimens in different subpopulations of GERD patients is warranted to understand further the possible value of tailoring PPI dose and timing of administration to achieve clinically meaningful symptom improvements in the individual patient. However, a ceiling effect appears to exist for clinical response with acid suppression in the overall population of patients with GERD. Future areas of research may include dose titration studies in patients who are unresponsive to standard PPI doses and the identification and management of other disease components of GERD to optimize treatment in other selected subpopulations.
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Disclosures
Dr Orlando has or has had in the recent past financial relationships (consulting, lecture bureau, research support, and stock ownership) with Amicus Therapeutics, AstraZeneca LP, Boston Scientific, Merck, Novartis, Pfizer, Procter and Gamble, Santarus, and Sirna. Drs Illueca and Liu are employees of AstraZeneca. The authors report no conflict of interest in this work. Dr Orlando was employed by Tulane University Medical School, New Orleans, LA, USA, at the time of the study.

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