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Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with non-erosive reflux disease

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SUMMARY

Background
The proportion of patients who respond to proton pump inhibitor (PPI) therapy is about 20% lower in those with non-erosive reflux disease (NERD) than in those with erosive oesophagitis.

Aim
To assess efficacy and safety of dexlansoprazole MR, a PPI using Dual Delayed Release technology, in NERD patients.

Methods
In this 4-week, double-blind, placebo-controlled study, 947 NERD patients randomly received dexlansoprazole MR 30 mg, 60 mg or placebo once daily (QD). The percentages of 24-h heartburn-free days (primary) and nights without heartburn (secondary) were assessed from patients' daily diaries. Investigators also assessed symptoms. Patients completed validated quality of life and symptom severity questionnaires.

Results
Dexlansoprazole MR provided significantly greater median percentages of 24-h heartburn-free days (54.9% and 50.0% for the 30- and 60-mg doses vs. 17.5% for placebo, $P < 0.00001$) and nights without heartburn (80.8% and 76.9% vs. 51.7%, $P < 0.00001$ vs. placebo). Dexlansoprazole MR also reduced symptom severity. Quality of life improvements in patients receiving dexlansoprazole MR were consistent with clinical efficacy endpoints. Percentages of patients experiencing treatment-emergent adverse events were similar among groups.

Conclusions
Dexlansoprazole MR 30 and 60 mg were superior to placebo in providing 24-h heartburn-free days and nights in NERD patients. Treatment was well tolerated.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is highly prevalent, affecting up to 20% of the adult population in North America.[1] Up to 70% of GERD patients have non-erosive reflux disease (NERD),[2–5] a term used to describe symptoms suggestive of GERD in patients with no endoscopic evidence of erosive oesophagitis (EO). The NERD population is heterogenous. Some patients experience symptoms due to abnormal oesophageal acid exposure, while others are symptomatic due to hypersensitivity to acid associated with normal oesophageal acid exposure.[6, 7] NERD patients also have been found to have a more homogeneous intraoesophageal distribution of acid reflux and are more likely to perceive acid reflux symptoms compared with patients with EO.[8, 9] Some patients with GERD symptoms have no evidence of acid reflux. It has been suggested that such patients may have symptoms as a consequence of non-acid reflux, inflammation, motility abnormalities or visceral hypersensitivity.

Treatment of NERD can be a challenge for clinicians. According to a recent systematic review, the pooled rate for symptomatic response in NERD patients was lower than for EO patients (37% vs. 56% respectively; $P < 0.0001$) after 4 weeks of proton pump inhibitor (PPI) therapy, using complete symptom resolution (defined as no heartburn during the preceding 7 days) as the outcome measure for comparison.[10]

Lansoprazole and its enantiomers are equipotent inhibitors of proton pumps. The *R*-enantiomer, dexlansoprazole, constitutes >80% of circulating drug after oral administration of lansoprazole and has a lower clearance and fivefold greater systemic exposure than the *S*-enantiomer.[11] These pharmacokinetic advantages, much like the development of esomeprazole from omeprazole[12, 13] were important considerations for the development of dexlansoprazole MR (TAK-390MR; Takeda Global Research & Development Center, Inc., Deerfield, IL, USA), a novel modified-release formulation of dexlansoprazole that employs a Dual Delayed Release technology designed to prolong the dexlansoprazole concentration–time profile and provide extended duration of acid suppression.[14] This technology uses two types of granules with different pH-dependent dissolution profiles designed to release drug in the proximal small intestine initially and, several hours later, in the distal small intestine. The two separate timings of drug-release produce a distinctive two-peaked pharmacokinetic profile that extends the duration of drug exposure by prolonging mean residence time (the average time a drug molecule spends in the systemic circulation). To maintain pharmacologically active plasma dexlansoprazole concentrations, a higher daily dose of dexlansoprazole MR is required compared with conventional single-release drug delivery systems commonly used in PPI formulations.[15] Preliminary data from phase 1 trials in healthy subjects have shown that dexlansoprazole MR 30–90 mg provides an increased pharmacodynamic effect and that dexlansoprazole MR generally produced significantly greater acid suppression than standard doses of lansoprazole.[15] An exposure–response analysis of data from the phase 1 trials has suggested that doses lower than 30 mg would produce less therapeutic effect.[15]

Therefore, the present study was designed to evaluate the efficacy and safety of dexlansoprazole MR 30 and 60 mg once daily (QD) for 4 weeks compared with placebo for relief of heartburn in patients with NERD. Placebo is a standard comparator that has been used in previous trials of similar design.[16–22]

METHODS

Study design

This was a phase 3, randomized, double-blind, multicentre, placebo-controlled, parallel-group, three-arm study of 4 weeks duration (ClinicalTrials.gov No. NCT00321984). The study was conducted in patients with NERD who displayed normal mucosa (no EO) at the screening endoscopy. The primary objectives were to assess efficacy and safety of dexlansoprazole MR 30 and 60 mg administered QD compared with placebo for the relief of heartburn for 24 h as recorded in a daily electronic diary. The secondary objective was to assess relief of nighttime heartburn.

Patients were randomized after a screening period (minimum 7 days, maximum 21 days), during which patients must have met all inclusion criteria and none of the exclusion criteria. Patients received drug beginning on day 1 and returned for visits at weeks 2 and 4 (or final visit) to assess GERD symptoms, complete quality of life (QOL) and symptom severity questionnaires, review concomitant medication use and assess adverse events (AEs). Study drug was collected at week 4 and rescue medication was returned at weeks 2 and 4, with new rescue medication again dispensed at week 2. At week 4 (or final visit), all patients underwent a

complete physical examination that included vital signs and blood samples were taken for fasting laboratory evaluations including serum gastrin. Female patients were required to undergo a serum pregnancy test at screening and at week 4 (or final visit).

The study was approved by independent Institutional Review Boards at participating study centres and conducted according to the ethical principles stated in the 1996 Declaration of Helsinki. Each patient signed an informed consent form and completed Health Insurance Portability Accountability Act authorization forms before any study-related procedure was performed.

Patients

Patients were men and women (aged ≥18 years) who identified heartburn as their primary symptom, had a history of heartburn episodes for 6 months or longer, experienced heartburn on at least 4 of the 7 days preceding randomization (as recorded in electronic diaries) and showed normal oesophageal mucosa at the screening endoscopy. Patients were enrolled regardless of *Helicobacter pylori* status (assessed at screening by finger stick or serology for *H. pylori* antibody). Patients were instructed that lifestyle or behaviour should not be altered to treat their GERD symptoms.

Patients were excluded for the following: pregnancy or lactation; Barrett's oesophagus; active gastric or duodenal ulcers within 4 weeks of the first dose of study drug; coexisting diseases affecting the oesophagus or EO shown by endoscopy; history of gastric, duodenal or oesophageal surgery; oesophageal strictures requiring dilatation; use of a PPI, histimine-2 receptor agonist, antacid [except study-supplied Gelusil (aluminium/magnesium hydroxide, simethicone; Pfizer Inc., New York, NY, USA)], anticholinergic, sucralfate or prokinetic agent during screening and throughout the study; known hypersensitivity to PPIs or Gelusil; long-term use (>12 doses/month) of nonsteroidal anti-inflammatory drugs within 30 days before screening and throughout the study [low-dose aspirin (≤325 mg/day) was allowed during the study]; clinically significant abnormal laboratory values or uncontrolled systemic disease.

Treatment assignment/masking

On day −1, patients were randomized using Interactive Voice Response System (IVRS; ClinPhone, Inc., Northbrook, IL, USA) in a 1:1:1 ratio to receive dexlansoprazole MR 30 mg QD, dexlansoprazole MR 60 mg QD or placebo. During the 4-week treatment period, patients self-administered the study drug QD before breakfast from blinded study-drug blister cards. Dexlansoprazole MR and placebo capsules were manufactured and supplied by Takeda Pharmaceutical Company Ltd. (Osaka, Japan) and were packaged and labelled by Fisher Clinical Services Inc. (Allentown, PA, USA). Open-label Gelusil was provided as rescue medication (up to six tablets per day). The investigators, study coordinators and patients remained blinded to the treatments throughout the study.

Efficacy endpoints

The primary efficacy endpoint was the percentage of 24-h heartburn-free days (days with neither daytime nor nighttime heartburn) during treatment as assessed by a daily electronic diary. The secondary efficacy endpoint was the percentage of nights without heartburn. Additional efficacy endpoints included percentage of days without daytime heartburn; mean severity of heartburn; percentage of patients with 24-h heartburn-free days, nights without heartburn, and days without daytime heartburn during the first 3 days of treatment; time to sustained resolution of heartburn (defined as the first occurrence of 7 consecutive 24-h heartburn-free days); percentage of days without rescue medication use; investigator-reported symptom severity at week 4 and patient-reported QOL and symptom severity.

Efficacy assessments

Patients were given an electronic diary (personal digital assistant; Palm Tungsten E2, Palm Inc., and Inventec Appliances Co., Ltd, both of Shanghai, China) on the first day of the screening period for recording the presence and maximum severity of daytime and nighttime heartburn and use of rescue medication. During both the screening and treatment periods, patients documented in the diaries the presence and severity of heartburn twice daily (each evening before bedtime and each morning upon awakening). Patients rated the severity of heartburn according to the following five-point scale: 0 = none, 1 = mild (occasional heartburn that did not influence the patient's daily routine), 2 = moderate (heartburn that could not be ignored; occasionally influenced the patient's daily routine),

3 = severe (heartburn was present for most of the day; regularly influenced patient's daily routine) and 4 = very severe (constant heartburn; markedly influenced patient's daily routine). Similar five-point scales, although not validated, have been used previously in GERD studies.[23–26] Nighttime was defined as time the patient spent asleep. Only patients who recorded heartburn for ≥4 days during the 7 days before day −1 in their electronic diaries were enrolled in the study.

Investigators also assessed GERD symptoms during the day −1 visit as well as weeks 2 and 4 or final visits. The maximum severity of symptoms (heartburn, acid regurgitation, dysphagia, belching and epigastric pain) was evaluated as none, mild, moderate, severe or very severe during the 7 days before the patient's study visit and throughout the treatment period.

Patient-reported outcomes were assessed using two validated, self-administered questionnaires during the day −1 visit as well as weeks 2 and 4 or final visits. The Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index (PAGI-QOL) assesses health-related QOL in patients with GERD, dyspepsia and gastroparesis (subscales: daily activities, clothing, diet and food habits, relationship, and psychological well-being and distress).[27] The PAGI-Symptom Severity Index (PAGI-SYM) is a brief symptom severity instrument (subscales: nausea/vomiting, fullness/early satiety/bloating, upper and lower abdominal pain and heartburn/regurgitation).

Safety assessments

Safety of the study drugs was determined by systematic assessment of AEs at weeks 2 and 4 as well as by physical examinations, vital signs, clinical laboratory tests, electrocardiogram (planned for a subset of 540 patients), fasting serum gastrin levels and prior and concomitant medication usage.

All AEs, whether observed by the investigator, elicited during study visits, or spontaneously reported by the patient, were collected from the day patients signed informed consent forms and until 30 days after the last day study drug was administered. Investigators evaluated the severity of events and determined whether the event(s) might have been related to study drug therapy. Any clinically significant change in a laboratory parameter was reported by the investigators as an AE. Routine laboratory evaluations (haematology, chemistry and urinalysis), serum pregnancy tests and fasting serum gastrin levels were conducted.

Statistical analysis

A sample size of 240 patients (allowing for 20% drop-out from 300 patients) per treatment group was planned to provide at least 95% power at the 0.00125 level of significance to detect a 30% difference between a dexlansoprazole MR dose (60%) and placebo (30%) for the primary efficacy variable. The use of 0.00125 in the power calculation was conservative to ensure sufficient power while accounting for multiplicity. The SAS/STAT software (SAS Institute Inc., Cary, NC, USA) for the UNIX operating system was used to perform statistical analyses. The overall level of significance was 0.0025 for efficacy variables, for which Hochberg's procedure for multiple comparisons was used to ensure that the overall 0.0025 level of significance was maintained for the two pairwise comparisons with placebo and 0.05 for demographic and safety variables.

All randomized patients who received ≥1 dose of study medication and completed the appropriate diary entry (heartburn, heartburn severity, rescue medication use) on ≥1 day during treatment were included in the efficacy analysis [intent-to-treat (ITT) population] for that variable. All patient diary data from days 1 through 35 and no later than the day of the last dose of study drug were used in the efficacy analyses. Days with missing diary results for each variable were excluded from the numerator and denominator.

The primary efficacy endpoint was calculated as the percentage of 24-h heartburn-free days out of the total number of days for which either a daytime or nighttime result was recorded in diary entries. Pairwise comparisons between each dexlansoprazole MR dose and placebo were made using a Wilcoxon rank-sum test.

Subgroup analyses for the primary efficacy variable were conducted using pairwise comparisons between all treatment groups. The van Elteren test was applied with subgroup as the stratification factor. For analysis of the secondary efficacy endpoint, comparisons between dexlansoprazole MR and placebo were made using Wilcoxon rank-sum test.

For the additional endpoints, comparisons were analysed using Wilcoxon rank-sum tests. Over the first 3 days of treatment, the percentages of patients with 24-h heartburn-free days, nights without heartburn and days without heartburn were calculated and treatment comparisons were performed using Fisher's exact test. The percentage of subjects who achieved

sustained resolution of heartburn, defined as having at least 7 consecutive days of 24-h heartburn-free days by the end of treatment, was obtained from the Kaplan–Meier estimates and summarized by treatment group. Comparisons of the survival functions of the time to first sustained resolution of heartburn between treatment groups were performed using log-rank tests.

Analysis of investigator-assessed GERD symptom severity was performed using a Cochran–Mantel–Haenszel test for ordered responses with baseline severity as the stratum. Analyses of the change from baseline to week 4 in the PAGI-QOL total score and the PAGI-SYM heartburn/regurgitation subscale were performed for the ITT population. Within each treatment group, the significance of the mean change from baseline to week 4 vs. no change was tested with a one-sample paired *t*-test. Pairwise comparisons for the mean change values between the treatment groups were made using contrast statements within the framework of a one-way analysis of covariance model with treatment group as the factor and baseline score as the covariate.

The safety population included all patients who received ≥1 dose of study medication. Treatment-emergent AEs were summarized and comparisons between treatment groups were made using Fisher's exact test.

RESULTS

Demographic and clinical characteristics

Investigators at 154 US centres enrolled patients and conducted the study from June to December 2006. Nine hundred forty-seven patients were randomized and included in the safety analysis (Figure 1); 929 were included in the ITT efficacy population. Eighteen patients were not included in the ITT population (three, eight and seven patients in the dexlansoprazole MR 30 mg, 60 mg and placebo groups respectively) because they did not complete the appropriate diary entry on ≥1 day during treatment. Six patients were found to have Barrett's oesophagus and three to have EO, and therefore were discontinued from participating

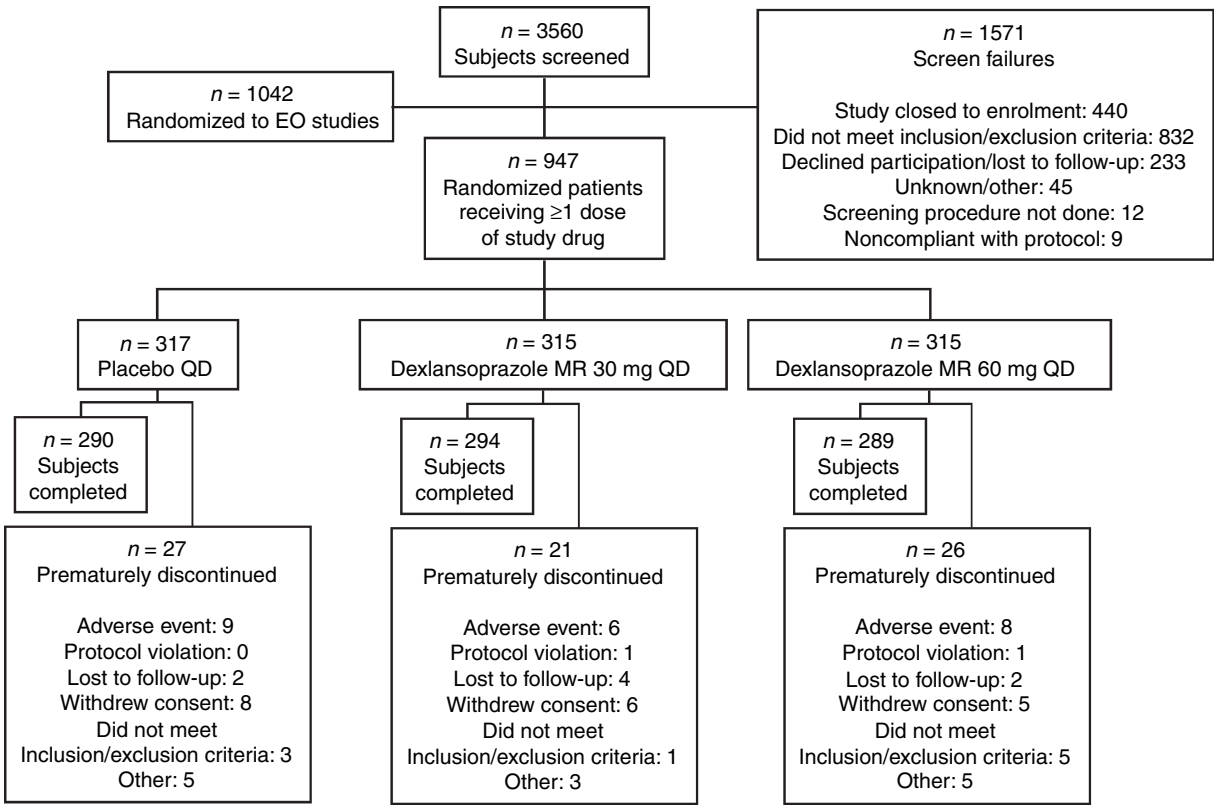

Figure 1. Patient disposition. QD, once daily.

in the study. A total of 74 patients prematurely discontinued: 21 from the dexlansoprazole MR 30-mg group, 26 from the dexlansoprazole MR 60-mg group and 27 from the placebo group. No significant differences in reasons for premature discontinuation were noted between treatment groups.

No statistically significant differences were observed among the three groups in any baseline demographic characteristic (Table 1). There was a statistically significant difference among treatment groups in the number of days with baseline daytime/nighttime heartburn ($P < 0.05$). A greater percentage of patients in the placebo and dexlansoprazole MR 30-mg groups had 6–7 days with daytime/nighttime heartburn compared with the dexlansoprazole MR 60-mg group (80% and 76% vs. 68% respectively), while a greater percentage of patients in the dexlansoprazole MR 60-mg group had 4–5 days of daytime/nighttime heartburn compared with the placebo and dexlansoprazole MR 30-mg groups (30% vs. 17% and 21% respectively). At baseline, the median mean severity of heartburn on a five-point scale ranged from 1.57 to 1.60 for patients with daytime heartburn and from 1.21 to 1.36 for patients with daytime/nighttime heartburn. All groups reported a median mean severity for nighttime heartburn of 1.14 on a five-point scale. The three treatment groups were similar with respect to mean number of days on study drug and extent of compliance with diary completion.

Table 1. Baseline demographic characteristics

Variable	Placebo (n = 317)	Dexlansoprazole MR 30 mg QD (n = 315)	Dexlansoprazole MR 60 mg QD (n = 315)	All patients (N = 947)
Gender, *n* (%)				
Men	84 (26.5)	84 (26.7)	106 (33.7)	274 (28.9)
Women	233 (73.5)	231 (73.3)	209 (66.3)	673 (71.1)
Ethnicity, *n* (%)				
Hispanic or Latino	62 (19.6)	67 (21.3)	53 (16.8)	182 (19.2)
Not Hispanic or Latino	255 (80.4)	248 (78.7)	262 (83.2)	765 (80.8)
Race, *n* (%)				
American Indian or Alaskan Native	3 (0.9)	0	2 (0.6)	5 (0.5)
Asian	5 (1.6)	4 (1.3)	7 (2.2)	16 (1.7)
Black	45 (14.2)	37 (11.7)	48 (15.2)	130 (13.7)
Native Hawaiian or other Pacific Islander	3 (0.9)	1 (0.3)	0	4 (0.4)
White	255 (80.4)	267 (84.8)	251 (79.7)	773 (81.6)
Multiracial	4 (1.3)	3 (1.0)	6 (1.9)	13 (1.4)
Unknown	2 (0.6)	3 (1.0)	1 (0.3)	6 (0.6)
Age (years)				
Mean (s.d.)	47.6 (14.4)	47.6 (13.6)	47.5 (13.8)	47.5 (13.9)
Weight (kg)				
n	317	315	314	946
Mean (s.d.)	80.5 (20.2)	80.8 (20.0)	83.3 (20.5)	81.5 (20.3)
BMI (kg/m^2)				
n	317	314	313	944
Mean (s.d.)	29.1 (6.7)	29.0 (6.8)	29.6 (7.0)	29.2 (6.8)
Helicobacter pylori status, *n* (%)				
Positive	89 (28.1)	95 (30.2)	90 (28.6)	274 (28.9)
Alcohol use, *n* (%)				
Drinker	182 (57.4)	162 (51.4)	181 (57.5)	525 (55.4)
Smoking status, *n* (%)				
Smoker	52 (16.4)	72 (22.9)	57 (18.1)	181 (19.1)

All baseline demographics $P > 0.05$.
BMI, body mass index; MR, modified release; QD, once daily.

Relief of daytime/nighttime heartburn

The median percentage of 24-h heartburn-free days was significantly greater in both the dexlansoprazole MR 30- and 60-mg treatment groups compared with the placebo group (54.9% and 50.0% vs. 18.5% respectively; $P < 0.00001$; Figure 2). There was no statistically significant difference in treatment response between the two dexlansoprazole MR treatment groups. Dexlansoprazole MR 30- and 60-mg QD remained significantly greater than placebo in controlling heartburn over 24 h after adjusting for the various subgroup factors (age, gender, BMI, alcohol, tobacco, *H. pylori* status and baseline symptom severity). There were no differences in efficacy between *H. pylori*-positive and *H. pylori*-negative patients after 4 weeks of treatment with dexlansoprazole MR 30 or 60 mg. The percentage of patients who had neither daytime nor nighttime (24-h) heartburn is presented by each study day in Figure 3.

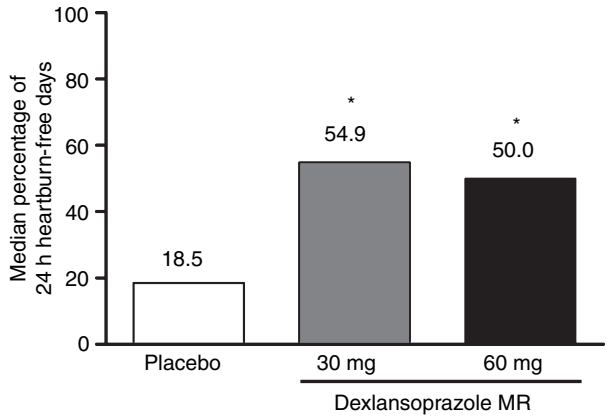

Figure 2. Median percentage of 24-h heartburn-free days. *$P < 0.00001$.

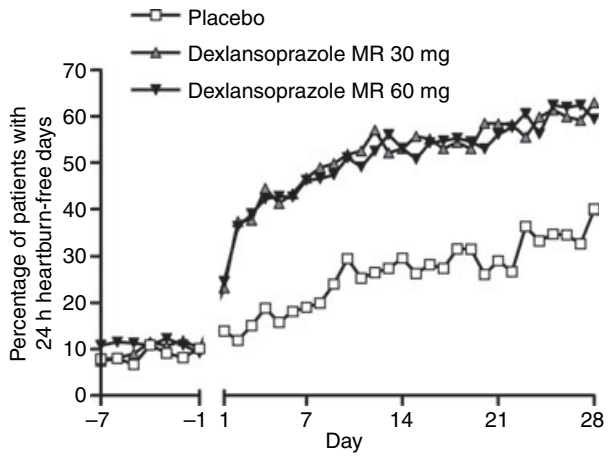

Figure 3. Percentage of patients with 24-h heartburn-free days by each study day. (Note: there was no comparison made for each study day and hence no statistical significance is reported.)

Relief of nighttime heartburn

The median percentage of nights for which patients did not report having heartburn was significantly greater for the dexlansoprazole MR 30- and 60-mg treatment groups compared with the placebo group (80.8% and 76.9% vs. 51.7%, respectively; $P < 0.00001$; Figure 4). There was no significant difference between the two dexlansoprazole MR treatment groups.

Additional efficacy variables

The median percentage of days for which patients did not report having daytime heartburn was significantly greater in both dexlansoprazole MR treatment groups compared with the placebo group (63.0% for both doses of dexlansoprazole MR vs. 26.9% for placebo, $P < 0.00001$). The mean severity of heartburn was significantly reduced in both dexlansoprazole MR treatment groups compared with the placebo group for daytime/nighttime heartburn (0.66 and 0.69 vs. 1.04 respectively), nighttime heartburn (0.56 and 0.60 vs. 0.90) and daytime heartburn (0.74 and 0.76 vs. 1.15)

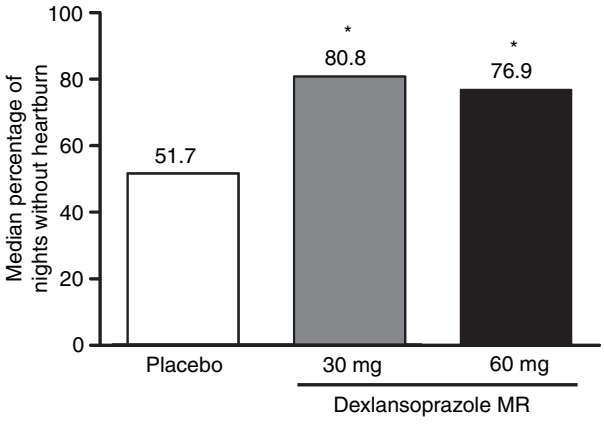

Figure 4. Median percentage of nights without heartburn. *$P < 0.00001$.

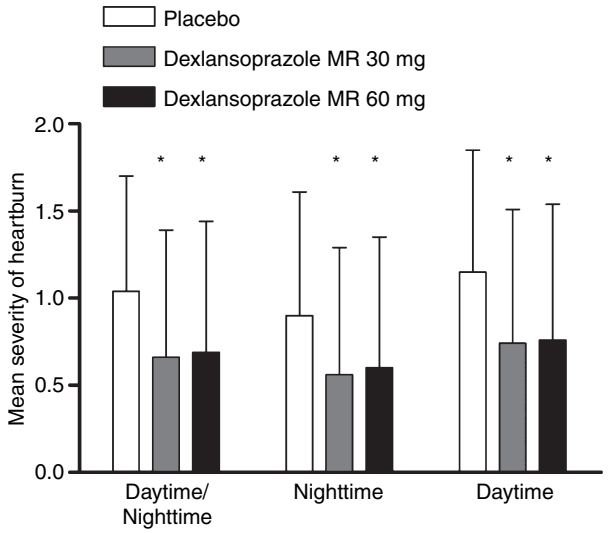

Figure 5. Mean severity of heartburn during treatment. *$P < 0.00001$.

($P < 0.00001$ for all; Figure 5). There were no significant differences between the two dexlansoprazole MR treatment groups.

Over the first 3 days of treatment, dexlansoprazole MR 30 and 60 mg were both significantly greater than placebo in terms of the percentage of patients who experienced 24-h heartburn-free days (13.9% and 16.2% vs. 2.2% respectively; $P < 0.00001$), nights without heartburn (38.0% and 39.8% vs. 17.3%; $P < 0.00001$) and days without heartburn (18.5% and 19.8% vs. 8.7%, $P < 0.01$). There were no significant differences between the two dexlansoprazole MR treatment groups.

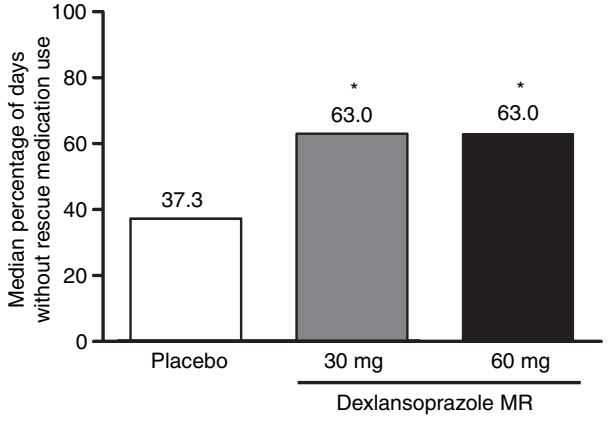

Figure 6. Mean percentage of days without rescue medication use. *$P < 0.00001$.

A significantly greater percentage of patients in both the dexlansoprazole MR 30- and 60-mg treatment groups achieved sustained resolution of heartburn by the end of treatment compared with the placebo group (59% and 42% vs. 14% respectively; $P < 0.00001$). Patients in both the dexlansoprazole MR 30- and 60-mg treatment groups had a significantly greater percentage of days without rescue medication use compared with placebo-treated patients (median, 63.0% for both dexlansoprazole MR groups vs. 37.3% for placebo; $P < 0.00001$; Figure 6).

For the investigator-assessed GERD symptoms, patients receiving dexlansoprazole MR had significantly less severe heartburn and acid regurgitation compared with those receiving placebo. A greater percentage of patients in the dexlansoprazole MR 30- and 60-mg treatment groups had ≥1 category improvement in investigator-assessed heartburn severity at week 4 compared with the placebo group (76.9% and 80.4% vs. 56.6% respectively; $P < 0.00001$). In addition, for acid regurgitation at week 4, more patients showed improvement from baseline in the dexlansoprazole MR 30- and 60-mg groups than in the placebo group (67.4% and 62.6% vs. 58.4% respectively), but this difference did not reach statistical significance.

The PAGI-SYM total score, as well as the subscale scores for fullness/early satiety and heartburn/regurgitation, was significantly better for the dexlansoprazole MR treatment groups compared with the placebo group at all patient visits ($P < 0.005$). For the PAGI-QOL, the total score and score for the diet and food habits subscale were significantly greater for both dexlansoprazole MR treatment groups compared with the placebo group at all visits ($P < 0.001$).

Safety

The incidence of treatment-emergent AEs (a majority of which were mild-to-moderate in severity) was 35% for the dexlansoprazole MR 30-mg group, 32% for the dexlansoprazole MR 60-mg group and 32% for the placebo group. Diarrhoea, headache, and nausea and vomiting were the most frequently reported (≥5% of patients in any treatment group) treatment-emergent AEs. There were no statistically significant differences across treatment groups in the percentages of patients who experienced ≥1 treatment-emergent AE.

Six patients receiving dexlansoprazole MR 30 mg (1.9%), eight patients receiving dexlansoprazole MR

60 mg (2.5%) and 11 patients receiving placebo (3.5%) experienced ≥1 AE that may have led to withdrawal from the study; there was no statistically significant difference between any treatment group in the percentage of patients whose primary reason for discontinuation was an AE. Four patients experienced eight serious AEs (SAEs) during treatment (one who received placebo, two who received dexlansoprazole MR 30 mg and one who received dexlansoprazole MR 60 mg). The SAEs were coronary artery occlusion secondary to diabetes, hypertension and hypercholesterolemia in the placebo-treated patient; myocardial infarction (MI) in two patients with arteriosclerosis who received dexlansoprazole MR 30 mg (as well as a postsurgical cerebrovascular accident in one patient and post-MI cardiogenic shock and sepsis in the other) and lower abdominal pain and haematochezia in the patient treated with dexlansoprazole MR 60 mg following polyp removal. There was no pattern to these events and all were assessed by the investigator as not related to study drug.

Increases in serum gastrin values from baseline to week 4 were significantly greater ($P < 0.001$) in both dexlansoprazole MR treatment groups (103.6 pg/mL and 97.0 pg/mL in the dexlansoprazole MR 30- and 60-mg groups respectively) compared with placebo (0.9 pg/mL); no statistically significant difference was observed between the two dexlansoprazole MR treatment groups ($P = 0.545$). The increases in serum gastrin levels were similar to those expected in patients receiving PPI therapy and not clinically concerning. No other clinically significant differences were observed between the dexlansoprazole MR and placebo treatment groups in clinical laboratory or vital signs results.

DISCUSSION

This trial demonstrated that treatment with dexlansoprazole MR 30 and 60 mg QD was significantly better than placebo in providing 24-h heartburn-free days in patients with NERD. Dexlansoprazole MR 30 and 60 mg were superior to placebo for the secondary endpoint evaluating the percentage of nights without heartburn. Heartburn relief occurred as early as the first 3 days of dosing with dexlansoprazole MR and was maintained throughout treatment; significantly more patients achieved sustained heartburn resolution by the end of treatment. Patients receiving dexlansoprazole MR experienced significant improvements in the incidence and severity of heartburn in both patient and investigator assessments and they used less rescue medication. The decreases in symptom severity in patients treated with dexlansoprazole MR probably contributed to the improved scores patients achieved on both symptom severity and QOL questionnaires. There were no statistically significant differences between dexlansoprazole MR 30 and 60 mg in any clinical efficacy variables.

The therapeutic gains of 36.4 and 31.5 percentage points respectively for dexlansoprazole MR 30 and 60 mg for 24-h heartburn-free days are somewhat higher than the therapeutic gain achieved with other PPIs in earlier trials; however, it is difficult to compare results across trials because study designs and endpoints vary widely. Dean *et al.*[10] performed a systematic review of seven placebo-controlled trials published between 1980 and 2002 to compare the efficacy of PPIs with placebo.[16–22] Using defined endpoint criteria to enable comparisons of symptom relief in NERD patients treated with PPIs vs. placebo, the authors estimated therapeutic gains for PPI treatment that were similar to those reported in the current study [from 30% to 35% for patients who achieved sufficient heartburn control (defined as <1 day of moderate heartburn during the preceding 7 days of treatment) and from 25% to 30% for patients who achieved complete symptom resolution (defined as no heartburn during the preceding 7 days of treatment)]. Placebo is a standard comparator for pivotal trials of this kind;[16–22] however, future trials with active comparators would be required to evaluate fully the efficacy of dexlansoprazole MR relative to other PPIs.

The increase in response to dexlansoprazole MR over time in this study suggests that 28 days may not be sufficient to evaluate the full symptomatic response of NERD patients to PPI therapy. This finding is consistent with a meta-analysis performed by Dean *et al.*,[10] which noted that symptom improvement in NERD patients continues to increase from weeks 1 to 2 assessments and again at the week 4 assessment. The authors speculated that patients with NERD may take longer to achieve complete symptom response and suggested that the duration of future studies in NERD patients should be extended beyond the usual 1-month time frame to observe the possibility of continued symptom improvement.[10]

Symptom response rates in the current trial of dexlansoprazole MR were lower than those achieved in trials evaluating dexlansoprazole MR in patients with

EO, in which the median percentage of 24-h heartburn-free days ranged from 80.7% to 84.2% for dexlansoprazole MR 60 and 90 mg (vs. 80.7% for lansoprazole 30 mg) after 4–8 weeks of treatment.[28] It is typical that the rate of symptom relief would be lower (approximately 20%) in patients with NERD compared with those with EO.[10] This may be attributed, in part, to the fact that pH testing is generally not performed at screening in NERD studies; therefore, the percentage of patient population with symptoms that were not acid-related is uncertain (i.e. those patients with functional heartburn). Additionally, the proportion of those with borderline reflux disease who may also demonstrate a reduced response to a PPI remains unknown.[20] Patients with non-acid-related symptoms would probably experience lower response rates. Not excluding these patients from the trial better reflects the heterogeneity of the overall NERD population and treatment results that may be observed in clinical practice. The absence of a dose response to dexlansoprazole MR for most outcomes suggests that further increasing the level of gastric acid suppression in the NERD population offers little incremental value, which may relate to the heterogeneity of this population. The placebo response rate of 52% observed in this study for the secondary endpoint, percentage of nights without heartburn, was somewhat higher than results seen in previous studies of GERD patients. The lower prevalence of nighttime heartburn compared with daytime heartburn in patients enrolled in this study may have contributed to the high placebo response rate. Additionally, nighttime symptoms were not a requirement during screening in the current trial. Other data also suggest that the placebo response can be relatively high in patients with GERD and varies across endpoints.[29–31] The pattern of increase in placebo response over time observed in the current trial has also been observed in trials of patients with functional bowel disorders.[32] In this trial, the phenomenon may be driven by patients with functional heartburn, who may account for a significant proportion of the study population.

Both dexlansoprazole MR 30 and 60 mg were well tolerated by patients in the current trial. The majority of AEs were mild or moderate and no dose-related trends were observed for treatment-emergent AEs. Additionally, increases in serum gastrin seen in patients treated with dexlansoprazole MR were similar to those seen in earlier trials with lansoprazole, which has a well-established safety profile.[33]

There were some limitations to the current study. Similar to all previous studies evaluating the efficacy of medical therapy for NERD, this trial relied upon self-reported symptom-based endpoints to assess the efficacy of dexlansoprazole MR. Some have criticized such endpoints because of their lack of objectivity and potential for recall bias. At present, symptom-based endpoints are the accepted standard for treatment trials in patients with NERD. We attempted to limit recall bias through the use of electronic diaries, which allowed timely capture of symptom data.

Additionally, assessing pH and oesophageal manometry prior to randomization would have better characterized the study population. As these assessments are not routinely performed in trials of this type or in clinical practice, the findings of the current trial may be more generalizable than they would have been had these procedures been performed. Finally, the impact of the availability of over-the-counter PPIs on the current study population remains uncertain. Use of over-the-counter PPIs is more common today than in earlier trials of other PPIs. Patients who fail to obtain relief from over-the-counter PPIs may be more likely to seek participation in current trials, potentially biasing the study sample with more difficult-to-treat patients.

In conclusion, NERD patients treated with dexlansoprazole MR 30 and 60 mg QD experienced a significantly higher percentage of 24-h heartburn-free days than those treated with placebo. Furthermore, dexlansoprazole MR provided faster, more prolonged symptom relief, less frequent and severe symptoms as reported by patients and investigators and improved QOL. Both doses of dexlansoprazole MR were well tolerated in this study. Dexlansoprazole MR demonstrated a favourable safety profile, similar to that seen in previous trials evaluating lansoprazole.

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